UNIVERSITA' DEGLI STUDI

DI MILANO-BICOCCA

SCUOLA DI DOTTORATO DI SCIENZE

Facoltà di Scienze Matematiche , Fisiche e Naturali

Corso di Dottorato di Ricerca in Scienze Chimiche XXII Ciclo

Sustainable procedures in organic synthesis

Tutor: **Prof Bruno Rindone**

Ricardo Suarez Bertoa

Dipartimento di Scienze Ambientali

A miña nai

Index

1. Green Chemistry

Green chemistry, also known as sustainable chemistry, is a chemical philosophy that encourages the design of products and processes that reduce or eliminate the use and generation of hazardous substances[1]. While environmental chemistry is the chemistry of the natural environment, and of polluting chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. The green chemistry was born in USA in the 90's, when scientist realized that anti-pollution laws such as "clean air act" [2], 1970 or "toxic substances control act" (TSCA)[3], 1976 had not achieved the expected results in both, environmental and economic field.

In 1990 the Pollution Prevention Act[4] was passed in the United States. This act helped create a *modus operandi* for dealing with pollution in an original and innovative way. It aims to avoid problems before they happen. The environmental protection agency (EPA) starts

---

[1] http://www.epa.gov/greenchemistry;

[2] *www.**epa**.gov/**air**/caa/*

[3] *www.epa.gov/agriculture/lsca.html*

[4] *www.epa.gov/p2/*

to focus on green chemistry in the 1991. EPA defined green chemistry as the design of chemical products and processes which reduce or eliminate the use or formation of dangerous substances, decreasing or eliminating risks for humans and environment.

The institution of the green chemistry as a plausible approach to the chemistry will be further confirmed by the increasing number of congresses and conferences focus on Eco-sustainability and also for the rising interest shown in the research at universities and industries. Finally, the importance of this sort of approach was highlighted by the creation of awards and journals aimed to promote and favor chemical process towards this direction. Hence, Bill Clinton's administration created the green chemistry challenge award in 1995[5], while the green chemistry journal was founded in the 1999[6]. Furthermore, the Organization for Economic Co-operation and Development (OCSE)[7],

---

[5] "The Presidential Green Chemistry Awards". *United States Environmental Protection Agency*. http://www.epa.gov/greenchemistry/pubs/pgcc/presgcc.html. Retrieved on 2006-07-31

[6] www.rsc.org/Publishing/**Journals**/gc/

[7] *www.oecd.org/*

sustaining a proposal made by EPA, instituted a guide committee for the sustainable chemical activity.

Paul Anastas, then of the United States Environmental Protection Agency, and John C. Warner developed 12 principles of green chemistry[8], which help to explain what the definition means in practice. The principles cover such concepts as:

the design of processes to maximize the amount of raw material that ends up in the product;

the use of safe, environment-benign substances, including solvents, whenever possible;

the design of energy efficient processes;

the best form of waste disposal: do not create it in the first place.

---

[8] "The 12 Principles of Green Chemistry”. *United States Environmental Protection Agency*. http://www.epa.gov/greenchemistry/pubs/principles.html. Retrieved on 2006-07-31

1.1. The 12 principles of the green chemistry

Prevent waste: Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

Design safer chemicals and products: Design chemical products to be fully effective, yet have little or no toxicity.

Design less hazardous chemical syntheses: Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

Use renewable feedstock: Use raw materials and feedstock that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstock are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

Use catalysts, not stoichiometric reagents: Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

Avoid chemical derivatives: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals. If a solvent is necessary, water is a good medium as well as certain eco-friendly solvents that do not contribute to smog formation or destroy the ozone.

Increase energy efficiency: Run chemical reactions at ambient temperature and pressure whenever possible.

Design chemicals and products to degrade after use: Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

Analyze in real time to prevent pollution: Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.

Minimize the potential for accidents: Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

This pHd thesis was developed following this philosophy and principles. Hence, new methods of sustainable organic synthesis such as the preparation of oxadolidinediones using TEMPO and using CO_2 and DBU instead of CrO_3 or the preparation of carbamates and ureas via cobalt-catalyzed oxidative carbonylation of aromatic or aliphatic primary amines avoiding the use of phosgene were carried out successfully. Furthermore, oxidations of unactivated carbons using ozone, an important green oxidant, were study in its whole complexity. Hence, the different reactivity of ozone towards different carbons groups (tertiary, secondary) was studied, and how different heteroatoms influence the regioselectivity of the oxidation. The mechanisms of such reactions were deeply studied.

2. Green oxidations. Ozonation reactions and mechanisms

2.1. Introduction

Ozone has always been known to be formed in electrical storms. Its first identification as a distinct chemical compound was due to Christian Friedrich Schönbein[1], Professor of Chemistry at the University of Basel from 1828. He dominated the study of ozone

---

[1] Christian Friedrich Schönbein, 1799-1868. Professor at the University of Basel from 1828. For biographical information see R. E. Oesper, *J. Chem. Educ.*, **1929**, *6*, 432-40. This author has also given an overview of Schönbein's research work, *J. Chem. Educ.*, **1929**, *6*, 677-85. A much more extensive early source is the book by E. Hagenbach, *Christian Friedrich Schönbein, Programm fur die Rectoratsfeier der Universität,* Basel, 1868. A biography of Schönbein has appeared recently in honor of the 200th anniversary of his birth: P. Nolte, *Christian Friedrich Schönbein. Ein Leben für die Chemie 1799-1868,* Arbeitskreis Stadtgeschichte der Volkshochschule Metzingen-Ermstal e.V., 1999. ISBN 3-9802924-6-0. The Basler Magazine of the Basler Zeitung dated Saturday, October 16, 1999, also features a cover photograph of Schönbein and a long article with photographs on the man and his work;

chemistry until his death in 1868. The molecular formula of ozone was determined by Soret in 1865 and confirmed by Soret himself in 1867, shortly before Schönbein's death. It is interesting to note that at least 13 citations of Schönbein's work on ozone have appeared in the chemical literature during the period 1988-98.

2.1.1. Discovery

On March 13, 1839, Schönbein reported to the local Naturforschung Gesellschaft in Basel that the electrolysis of water produced an odor at the positive electrode which was the same as the odor produced by an arc between electrodes[2]. This odor had existed since the occurrence of lightning in the presence of an oxygen atmosphere on earth. Much later, when static electricity machines were developed, van Marum[3] attributed the odor accompanying operation of the machine in air or oxygen to the electricity itself and it became known as the odor of electricity. His results were largely

---

[2] C. F. Schönbein, *Ber. Verh. Nat. Ges. Basel*, **1838-40,** *4*, 58, from a lecture on March 13, 1839. Author's translation: Prof. S.;

[3] Ann. Phys. [Gilberts Annalen], **1801**, 7, 107);

ignored except for the term “odor of electricity.” Schönbein had acquired a Grove cell, paid for by popular subscription in Basel, after attending a conference in Manchester during the preceding summer. This cell provided a much more powerful current than the equipment he had used previously in his studies of passivation of metals and van Marum’s “odor of electricity” was very pronounced in his poorly ventilated laboratory.

The suggestion that the odor was due to a distinct chemical substance was formally proposed in 1840 in a lecture to the Bavarian Academy of Science and to a wider audience when a letter to Faraday was read before the Royal Society[4] and one to Arago[5] before the

---

[4] C. F. Schönbein, “On the Odour Accompanying Electricity and on the Probability of its Dependence on the Presence of a New Substance,” *Philos. Mag.* (III), **1840**, *17*, 293-4. Also: *München Abhandl.*, **1837-43**, 587; also: “Beobachtungen über den bei der Elektrolysation des Wassers und dem Ausströmen der ewöhnlichen Elektricität aus Spitzen sich entwickelnden Geruch,”

Ann. Phys. Chem., **1840**, *50*, 616-635;

French Academy of Science. In this latter paper Schönbein proposed the name ozone[6] for the new substance.

2.1.2. Ozone Production

Because ozone is an unstable molecule, it should be generated at the point of application for use in Organic synthesis[7]. It is generally formed by, combining an oxygen atom with an oxygen molecule

(O_2) (equation 1):

$$3O_2 \rightleftharpoons 2O_3 \qquad (1)$$

---

[5] C. F. Schönbein, “Recherches sur la nature de l’odeur, qui se manifeste dans certaines actions chimiques,” *C. R. Hebd. Seances Acad. Sci., Ser. C*, **1840**, *10*, 706-10;

[6] “Aelteste Nachricht über Ozon und seine Benennung,” *Ann. Phys. Chem.*, **1854**, *91*, 625-627

[7] www.**epa**.gov/. Alternative Disinfectants and Oxidants - Guidance Manual

This equilibrium reaction is endothermic and requires a considerable input of energy.

Schönbein first discovered synthetic ozone through the electrolysis of sulfuric acid. Ozone can be produced in several ways, although one method, corona discharge, predominates in the ozone generation industry. Ozone can also be produced by irradiating an oxygen-containing gas with ultraviolet light, electrolytic reaction and other emerging technologies as described by Rice (1996)[8].

Corona discharge, also known as silent electrical discharge, consists of passing an oxygen-containing gas through two electrodes separated by a dielectric and a discharge gap. Voltage is applied to the electrodes, causing an electron flow through across the discharge gap. These electrons provide the energy to decompose oxygen molecules, leading to the formation of ozone. Figure 1 shows a basic ozone generator.

---

[8] Rice, R.G. 1996. Ozone Reference Guide. Electric Power Research Institute, St. Louis, MO;

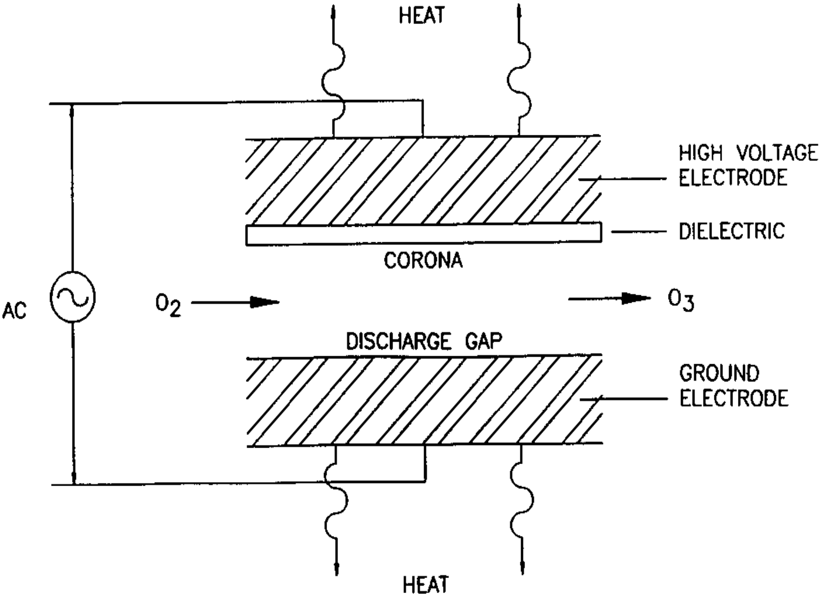


Figure 1 Ozone generator

2.1.3. Ozone Chemistry

Ozone exists as a gas at room temperature. The gas is colorless with a pungent odor readily detectable at concentrations as low as 0.02 to 0.05 ppm (by volume), which is below concentrations of health concern. Ozone gas is highly corrosive and toxic.

Ozone is a powerful oxidant, second only to the hydroxyl free radical treatment. Therefore, it is capable of oxidizing many organic and inorganic compounds in water. These reactions with organic and inorganic compounds cause an ozone demand in the water treated, which should be satisfied during water ozonation prior to developing a measurable residual.

Ozone is sparingly soluble in water. At 20 ºC, the solubility of 100 percent ozone is only 570 mg/L[9]. Basic chemistry research[10] [11] [12] has shown that ozone decomposes spontaneously when dissolved in water by a complex mechanism that involves the generation of hydroxyl free radicals. The hydroxyl free radicals are among the most reactive

---

[9] Kinman, R.N. 1975. "Water and Wastewater Disinfection with Ozone: A Critical Review." *Crit. Rev. Environ. Contr.* 5:141-152;

[10] Hoigné J., and H. Bader. 1983b. "Rate Constants of Reaction of Ozone with Organic and Inorganic Compounds in Water - II. Dissociating Organic Compounds." *Water Res.* 17:185-194;

[11] Hoigné J., and H. Bader. 1983a. "Rate Constants of Reaction of Ozone with Organic and Inorganic Compounds in Water - I. Non-dissociating Organic Compounds." *Water Res.* 17:173- 183;

[12] Glaze, W.H., et al.1987. "The Chemistry of Water Treatment Processes Involving Ozone, Hydrogen Peroxide, and Ultraviolet Radiation." *Ozone Sci. Engrg.* 9(4):335;

oxidizing agents in water, with reaction rates on the order of 10^{10} - 10^{13} M^{-1} s^{-1}, approaching the diffusion control rates for solutes such as aromatic hydrocarbons, unsaturated compounds, aliphatic alcohols, and formic acid[13]. Furthermore, the half-life of hydroxyl free radicals is on the order of microseconds, therefore concentrations of hydroxyl free radicals never reach levels above 10 –12 M[14].

As shown in Figure 2 ozone reacts in both modes in aqueous solution[15]:

· Direct oxidation of compounds by molecular ozone (O_3(aq)).

· Oxidation of compounds by hydroxyl free radicals produced during the decomposition of ozone.

---

[13] Hoigné J. and H. Bader. 1976. Role of Hydroxyl Radical Reactions in Ozonation Processes in Aqueous Solutions, *Water Res.* 10: 377;

[14] Glaze, W.H., and J.W. Kang. 1988. “Advanced Oxidation Processes for Treating Groundwater Contaminated with TCE and PCE: Laboratory Studies.” *J. AWWA.* 88(5):57- 63;

[15] Hoigné J., and H. Bader. 1977. “The Role of Hydroxyl Radical Reactions in Ozonation Processes in Aqueous Solutions.” *Water Res.* 10:377-386;

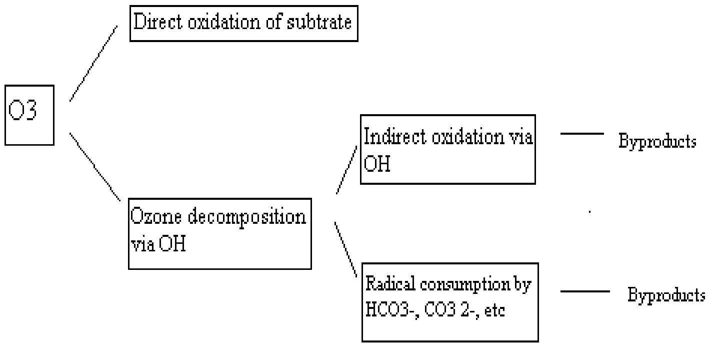


Figure 1. Oxidation Reactions of Compounds (Substrate) During Ozonation of Water

The two oxidation pathways compete for substrate (i.e., compounds to oxidize). The oxidation with aqueous ozone is relatively slow compared to hydroxyl free radical oxidation, but the concentration of aqueous ozone is relatively high. However, the hydroxyl radical reaction is fast, but the concentration of hydroxyl radicals, under normal ozonation conditions, is relatively small. Hoigné and Bader (1977)[16] found that:

---

[16] Hoigné J., and H. Bader. 1977. "The Role of Hydroxyl Radical Reactions in Ozonation Processes in Aqueous Solutions." *Water Res.* 10:377-386;

□Under acidic conditions, the direct oxidation with molecular ozone is of primary importance; and under conditions favoring hydroxyl free radical production, such as high pH, exposure to UV, or addition of hydrogen peroxide, the hydroxyl oxidation starts to dominate.

The spontaneous decomposition of ozone occurs through a series of steps. The exact mechanism and reactions associated have not been established, but mechanistic models have been proposed[17].

Ozone use is associated with the following:

Reactions with natural organic matter (NOM) in water. The oxidation of NOM leads to the formation of aldehydes, organic acids, and aldo- and ketoacids[18].

□Organic oxidation byproducts. Organic oxidation byproducts are generally more amenable to biological degradation and can be

---

[17] Glaze, W.H., et al.1987. “The Chemistry of Water Treatment Processes Involving Ozone, Hydrogen Peroxide, and Ultraviolet Radiation.” *Ozone Sci. Engrg.* 9(4):335;

[18] Singer P.C. 1992. “Formation and Characterization of Disinfection Byproducts.” Presented at the First International Conference on the Safety of Water Disinfection: Balancing Chemical and Microbial Risks;

measured as assimilable organic carbon (AOC) or biodegradable dissolved organic carbon (BDOC).

- Synthetic organic compounds (SOCs). Some SOCs can be oxidized and mineralized under favorable conditions. To achieve total mineralization, hydroxyl radical oxidation should usually be the dominant pathway, such as achieved in advanced oxidation processes.
- Bicarbonate or carbonate ions, commonly measured as alkalinity, will scavenge the hydroxyl radicals and form carbonate radicals[19] [20]. These reactions are of importance for advanced oxidation processes where the radical oxidation pathway is predominant.

2.1.4. Organic Reactions

Progress in the investigation of reactions of ozone with organic compounds was much slower. Early work was of a purely qualitative

---

[19] Staehelin, J., R.E. Bühler, and J. Hoigné. 1984. “Ozone Decomposition in Water Studies by Pulse Radiolysis. 2 OH and HO4 as Chain Intermediates.” *J. Phys. Chem.* 88:5999-6004;

[20] Glaze, W.H., and J.W. Kang. 1988. “Advanced Oxidation Processes for Treating Groundwater Contaminated with TCE and PCE: Laboratory Studies.” *J. AWWA.* 88(5):57- 63;

nature. In spite of an avowed fear[21] of the complexity of organic chemistry, Schönbein reported[22] in 1845 that the ozone odor disappeared in the presence of straw, humus, humuscontaining earth, sawdust, flour, potato starch, egg white, etc. One year later he added[23] wood alcohol, guaiacum, and ethylene gas to the list and later the reactions of mushrooms and cyanine dye[24], and in 1868 additional

---

[21] C. F. Schönbein, "On Ozone and Ozonic Actions in Mushrooms," *Philos. Mag.* IV, **1856**, *11*, 137. *Ann. Phys. Chem.*, **1856**, *67*, 496

[22] C. F. Schönbein, "Uber die Einwirkung des Ozons auf organische Substanzen," *Ann. Phys. Chem.*, **1845**, *65*, 196-9;

[23] C. F. Schönbein, "Das Ozon als Oxydationsmittel," *Ann. Phys. Chem.*, **1846**, *67*, 89-97;

[24] C. F. Schönbein, "Uber das Verhalten des Ozons und Wasserstoffsuperoxyds zum Cyanin," *J. Prakt. Chem.*, **1865**, *95*, 385-9

natural materials[25]. He noted[26] the important fact that organic substances were not converted to the highest oxidation state of carbon (CO_2) but instead to aldehydes, and carboxylic acids. In this paper he also commented that the product(s) of reaction of ethylene are similar to those obtained upon slow oxidation of diethyl ether in the presence of phosphorus[27] without going into detail. These products were

---

[25] C. F. Schönbein, "Ueber des Verhalten einiger organischer Materien zum Ozon," *J. Prakt. Chem.*, **1868**, *105*, 230-2;

[26] C. F. Schönbein, "Ueber die langsame Verbrennung des Aethers," *Ber. Verh. Nat. Ges. Basel*, **1847**, *7*, 4-6; C. F. Schönbein, "Ueber das Verhalten des Ozons zum oelbildenden Gas," *Ber. Verh. Nat. Ges. Basel*, **1847**, *7*, 7-9;

[27] C. F. Schönbein, "Ueber die bei der langsamen Verbrennung des Aethers entstehende oxidierende Materie," *Ber. Verh. Nat. Ges. Basel,* **1851**, *9*, 23;

identified only much later[28] as formic and acetic acid and formaldehyde. A noteworthy sidelight of this work is the fact that he also observed peroxidic material from the ethylene reaction. Gorup-Besanez[29] explored a variety of organic reactions[30] and reported that uric acid is converted rapidly into allantoin, urea, and CO_2; amyl alcohol to valeraldehyde and valeric acid; tannic acid to oxalic acid and CO_2; potassium cyanide to potassium cyanate; albumin and casein undergo complex reactions, and tyrosine was rapidly converted to a red-brown product. He reported that urea, creatin, alloxan, allantoin,

---

[28] C. F. Schönbein, "Ueber die Erzeugnisse der langsamen Verbrennung des Aethers," *J. Prakt. Chem.*, **1868**, *105*, 232-9;

[29] Eugen Franz Cajetan von Gorup-Besanez, M.D.,1817-1878;

[30] E. von Gorup-Besanez, "Fortgesetzte Untersuchungen über die Einwirkung des Ozons auf organische Stoffe," *Ann. Chem. Pharm.*, **1863**, *125*, 207-9; also *Ann. Chem. Pharm.*, **1854**, *90*, 86; *Ann. Chem. Pharm.*, **1861**, *118*, 232;

leucine, inositol, starch, fibrin, a number of acids (hippuric, acetic, butyric, palmitic, lactic, and tartaric), and glycerol failed to react. In all the above, ozone was generated by the phosphorus reaction, the gas being collected in glass vessels and washed with water before addition of the substrate. The reaction with rubber was first reported by Soret in 1853[31] and noted by a number of other workers. Soret reported that when ozone was generated electrolytically at low temperature, the rubber connections of his apparatus were rapidly attacked but that this did not happen at room temperature. He correctly attributed the difference to the higher concentration of ozone formed at lower temperature. Much later this reaction became the basis of a simple method for determining when a solution bubbled with ozone had become saturated. The only reaction of an organic compound with ozone which is clearly documented is the reaction with indigo.

---

[31] J. L. Soret, "Note sur la production de l'ozone para la décomposition de l'eau à de basses temperatures," *C. R. Hebd. Seances Acad. Sci., Ser. C*, **1853**, *38*, 445-8; also *J. Prakt. Chem.*, **1854**, *62*, 40

Schönbein described[32] the decoloration of indigo by ozone (from phosphorus) in 1851 and stated baldly that it is known that indigo is converted to isatin. However, Erdmann[33] reported full details of an experiment in which an aqueous suspension of indigo was treated with ozone from phosphorus and the product isatin was isolated and characterized by its melting point.

2.1.5. Ozonation of carbon-hydrogen bonds

One of the first organic substances ever ozonized, and possibly the first relatively pure, simple compound, was diethyl ether[34] [35]. This

---

[32] C. F. Schönbein, "Ueber den Einfluss des Phosphors auf die chemische Thätigkeit des gewöhnlichen Sauerstoffgases," *J. Prakt. Chem.*, **1851**, *53*, 501-6;

[33] O. L. Erdmann, "Isatinbildung durch Ozon," *Ann. Phys. Chem.*, **1857**, *71*, 209; also *J. Prakt. Chem.*, **1857**, *61*,209;

[34] P.S. Bailey. "Ozonation in Organic Chemistry" Voll II. Pp 257-258. Academic Press. 1982;

[35] C.F Schonbein. J. Prak. chem. [1] 66, 270. 1855;

was followed by ozonation of simple alcohols[36], simple alkanes[37] [38] [39], and other saturated substances. Harries[40] [41] [42] investigated the breadth of the oxidizing power of ozone with both saturated and unsaturated compounds, including hexane, alkyl halides, alcohols, ethers, and aldehydes. These early studies are discussed in greater detail in several reviews[43] [44] [45] [46].

---

[36] E. Von Gorup-Besannez, Liebigs Ann. Chem. 110, 86. 1859;

[37] M. Otto Ann. CHim. Phys [7] 13, 106. 1898;

[38] W. A. Bone and J. Drugman, Proc. Chem. Soc. , London20, 127. 1904;

[39] J. Drugman, J. Chem. Soc. 89, 939. 1906;

[40] C.D. Harries, Liebigs Ann. Chem. 343, 311. 1905;

[41] C.D. Harries, Liebigs Ann. Chem. 36, 1933. 1903;

[42] C.D. Harries, Liebigs Ann. Chem. 374, 288. 1910;

[43] L. Long, Jr., Chem. Rev. 27, 437. 1940;

[44] E. Fonrobert, “Das Ozon” Enke, Stuttgart, 1916;

During several years ozone became a reagent to cleave double-bonds. The rediscovery of the versatility of ozone as an oxidising agent occurred in 1939[47].

The paper of Durland and Adkins[47] revived interest in the attack of ozone on carbon-hydrogen bonds, and this interest has continued for both substances possessing “unactivated” carbon- hydrogen bonds and those having “activated” methylene or methine groups. “Activated” refers to carbon-hydrogen bonds or groups in which the transition state in ozonation is strongly stabilized through electron donation by an adjacent group such as hydroxyl, alkoxyl, or amino. This includes alcohols and ethers, amines, and aldehydes. “Unactivated” methylene and methine groups include those in alkanes, cycloalkanes.

---

[45] E. Fonrobert, in “Die Methoden der Organischem Chemie” 3rd ed. Vol III. Pp. 406-467. Thieme, Leipzig, 1930;

[46] E. Fonrobert, in “Die Methoden der Organischem Chemie” 3rd ed. Vol III. Pp. 406-467. Thieme, Leipzig, 1930;

[47] J. R. Durland and H. Adkins, J. Am Chem. Soc. 61, 429. 1939;

2.1.6. General Survey

2.1.6.1. Alkanes

Houzeau and Renard[48] appear to have been the first to attempt a reaction between methane and ozone, but they found that it did not occur at ordinary temperatures. However, Otto[49] reported the partial conversion of methane to formaldehyde and formic acid by means of ozone, both at room temperature and at 100 ºC.

Ozonation of C_1-C_{10} alkanes has been carried out[50] [51] [52] [53] [54] along with that of tetradecane and octadecane[55]. Shorter chain alkanes are

---

[48] A Houzeau and A. Renard, C.R. Hebd Seances Acad. Sci. 76, 572. 1873;

[49] M. Otto Ann. CHim. Phys [7] 13, 106. 1898;

[50] T.S. Wheeler and E.W. Blair, J. Soc. Chem. Lnd. London 41, 3117. 1922;

[51] C.C. Schubert and R. N. Pease. J. Am.Chem. Soc. 78, 2044. 1956;

[52] N.A. Keimenov, I.N. Antonova, A.M. Markench and A.B. Nalbandian. J. Chim. Phys 54, 321. 1957;

[53] S.D. Razumovkii, A.A. Kefel, G.R. Trubnikov and G.E. Zainov. Dokl. Akad. Nauk SSSR 192, 1313. 1970;

generally ozonated in the vapour phase, while longer chain alkanes are ozonated in the liquid phase.

Ozonation in liquid phase of long chain alkanes produces alcohols, ketones, carboxylic acis, esters and peroxides. Furthermore, tertiary carbon-hydrogen bonds are more reactive and primary the least reactive[56]. Nevertheless, alkanes react considerably more slowly than alcohols and much more slowly than alkenes[52].

2.1.6.2. Cycloalkanes

Several studies have dealt with the liquid-phase ozonation of cycloakanes[57], but just a few consider long chain cycloalkanes. Obtained products were the corresponding cycloalkanols, cycloalkanones and cycloalkyl hydroperoxides and peroxides.

---

[54] A.A. Vikhorev, A.M. Syroezhko, V.A. Proshiryakov and A.S. Yakovlev, Zh. Priki. Khim. Leningrad 51, 2568. 1978;

[55] G. Geisler, F. Asinger and H. Wien, Chem. Ber 92, 958. 1959;

[56] D.J. Williamson and R.J. Cveranovic, J. Am. Chem. Soc. 92, 2944. 1970;

[57] S.K. Rakovski, A.A. Popov, S.D. Razumovskii, D.M. Shapov and G.E. Zaikov, Izv. Khim. 8, 544. 1975;

Secondary products arose from further reactions producing ring-cleavage products[58] [59] [60].

---

[58] V. Caprio, A. Di Lorenzo, A. Insola. Chim. Ind (Milan) 51, 983. 1969;

[59] S .D. Razomovskii and G.E. Zaikov, Neftekhimiya 13, 565. 1973;

[60] L.V. Rubanm S.K. Rakovski, S.D Razumouskii and G.E. Zaikov, Izv. Akad. Nauk SSSR, Ser. Khim. Pp 2104. 1976;

2.2. Oxidation of alkanes, cycloalkanes and ethers via ozonation

2.2.1. *Introduction*

From ethylene, ethylene oxide is produced with the catalysis of Ag, acetaldehyde with the catalysis of Cu and Pd, aldehydes with carbon monoxide and the catalysis of Co. From propylene, acrolein is produced with the catalysis of Cu and Si. Aromatics are produced from reforming with the catalysis of Pt and Re. From benzene or naphthalene, maleic anhydride or phthalic anhydride are produced with the catalysis of V [1]. Recycle or disposal of the spent metal catalyst is a major problem in these cases[2].

The selective oxidation of alkanes is particularly difficult. Co is used as the catalyst for the oxidation of cyclohexane to cyclohexanone

---

[1] Weissermel, Arpe, H. J., *Industrial Organic Chemistry,* (VCH, Weinheimn, 1993);

[2] Matlack, A.S., *Introduction to Green Chemistry*, (Markel Dekker, New York, Basel, 2001);

and cyclohexanol with dioxygen[3]. Metal centered systems which mimic monooxygenases such as cytochrome P-450 and methanemonoxygenase mimics are also used[4].

Metal free alternatives use dioxiranes as oxidising agents[5], the oxidation of alkanes in superacidic media[6], the oxidation of cycloalkanes with ozone[7].

---

[3] Kochi, J., Sheldon, R., *Metal Catalysed Oxidations of Organic Compounds* (New York, Academic Press,.1981);

[4] Arends, I.W.C.E., Mac Faul, P.A., Snelgrove, D.W., Wayer D.D.M, Ingold K.U. in Minisci, F. ed. *Free Radicals in Biology and Environment* (New York, Kluver Academic Publishers, 1997) p.79-90

[5] Reiser, O., "Oxidation of Weakly Activated C-H Bonds", Angew. Chem. Int. Ed., 33,_69-72 (1994); Minisci, F., Zhao, L.H., Fontana, F., Bravo, A."Free-radicals in the oxidation and halogenation of alkanes by dimethyldioxirane: An oxygen rebound mechanism", Tetrahedron Lett, 1697-1700 (1995); Bravo, A., Fontana, F., Fronza, G., Mele, A., Minisci, F., "Induced homolysis of dimethyldioxirane by alkanes and alkyl radicals in oxidation processes. The dramatic role of molecular oxygen and radical inhibitors", J. Chem. Soc. Chem. Commun., 1573-1574 (1995); Vanni, R., Garden, S.J., Banks, J. T., Ingold, K.U., "Mechanism of hydroxylation of alkanes by dimethyldioxirane. A radical-clock

Ozone has been used in the iron porphyrin-catalyzed oxygenation of alkanes[8]. Moreover, the ozonation of ethers in acidic buffer forms

---

study", Tetrahedron Letters, 7999-8002 (1995); Asensio, G., Mello, R., Gonzalez Nunez, M.E., Boix, C., Royo, C.J., "The oxidation of alkanes with dimethyldioxirane; A new mechanistic insight", Tetrahedron Letters, 2373-2376 (1997); Adam,W., Curci, R., D'Accolti, L., Dinoi, A., Fusco, C., Gasparrini, C., Kluge, R., Paredes, R., Schulz, M., Smerz, A.K., Veloza, L. A., Weinkotz, S., Winde, R., "Epoxidation and oxygen insertion into alkane CH bonds by dioxirane do not involve detectable radical pathways", Chemistry - A European Journal, 3, 105-109 (1997)

[6] Jacquesy, J. C., Jouannetaud, M. P., Martin, A., "Functionalisation of nonactivated bonds in superacidic media", Bulletin de la Societe Chimique de France, 134, 425-438 (1997);

[7] Bailey, P.S., *Ozonation in Organic Chemistry*, (New York, Academic Press, 1981,) p. 255;

[8] Gross, Z., Simkhovich, L., "Ozone as primary oxidant in iron(III) porphyrin catalyzed hydroxylation of hydrocarbons", Journal of Molecular Catalysis -A - Chemical -, 117, 243-248, (1997);

esters[9], and the ozonation of amines forms amides and N-dealkylation products[10].

The formation of hydrotrioxides in the reactions of acetals with ozone has been reviewed[11].

---

[9] Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., “Reactivity of two models of non ionic surfactants with ozone”, Water Research, 31, 1839-1846 (1997);

[10] Brambilla, A., Rindone, B., Polesello, S., Galassi, S., Balestrini, R., “The fate of triazine pesticides in river Po water”, The Science of the Total Environment, 132, 339-348 (1993); .Bolzacchini, E., Brambilla, A., Orlandi, M., Polesello, S., Rindone, B., “Oxidative Pathways in the degradation of triazine herbicides: A mechanistic approach”, Wa. Sci. Tech., 30, 129-136 (1994); Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., “, Reactivity of organic micropollutants with ozone: a kinetic study”, Life Chemistry Reports, 13, 79-84, (1995);

[11] Houben Weyl, *Methoden der Organische Chemie* Vol E13, (Stuttgart, New York, George Thieme Verlag 1988) p. 1118; Plesnicar, B., Cerkovnik, J., Tekavec, T., Koller, J., Chem. Eur. J., 6, 809-819, (2000); Plesnicar, B., Cerkovnik, Tuttle, T., Kraka, E., Cremer, D., J. Amer. Chem. Soc., 124, 11260-11261, (2002); Wu, A., Cremer, D., Plesnicar, B., J. Amer. Chem. Soc., 125, 9395-

Ethers are often used as organic solvents owing to their low reactivity in most conditions.

Here we report the functionalization of the unactivated carbon-hydrogen bond with ozone to give oxygenated products.

2.2.2. Oxidation of alkanes

Cyclodecane (1) and cyclododecane (7), having several equivalent methylenic groups, and n-decane (11), having two equivalent methyl groups and four couples of equivalent methylenic group were ozonated.

2.2.2.1. Cyclodecane (1)

Three different reaction media were used for the ozonation of cyclodecane (1) at 25 °C:

Aqueous suspension pH 3

Dichloromethane solution

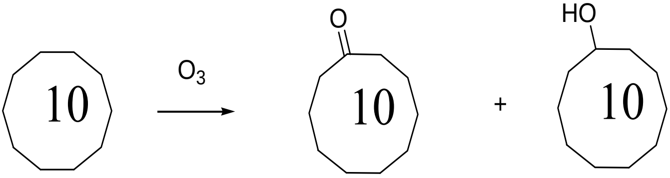
Pure liquid

In all these procedures the main reaction product was cyclodecanone (2), arising from the oxygenation of a methylenic group. Small amounts of cyclodecanol (3) were observed in all but

---

9402, (2003); Tuttle, T., Cremer, D., Plesnicar, B., Cerkovnik, J. Amer. Chem. Soc., 126, 16093-16104, (2004);

one case (the reaction in water pH 3). Scheme 1 and table 1 show these results.



(1) (2) (3)

Conversions were higher in methylene chloride than in pure liquid. In water pH 3 the conversion was deeply influenced by the amount of substrate suspended.

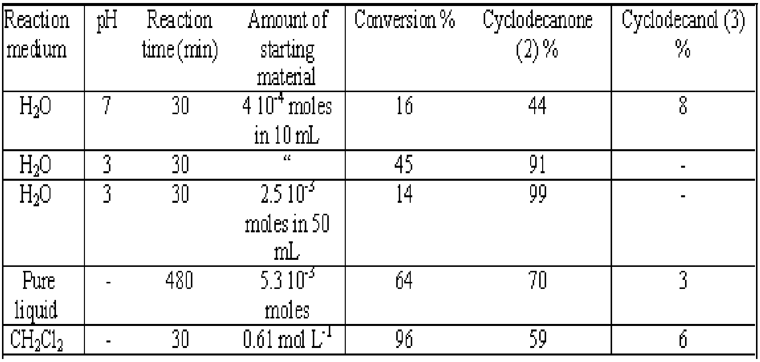
Selectivity in cyclodecanone (2) was highest in water pH 3. Lower selectivity in cyclodecanone (2) was obtained in pure liquid or in dichloromethane. In both cases, byproduct were some acidic products deriving by ring cleavage. In the reaction in dichloromethane byproducts in 18% yield were decanedioic acid (4a), nonanedioic acid (5a) and 8-formyloctanoic acid (6a), determined as their methyl esters (4-6b) (Scheme 1). Also small amounts of cyclodecanol (3) were found.

In order to find the highest conversion and selectivity in cyclodecanone (2) the time course of the reaction in dichloromethane at two different temperatures, 0 °C and 25 °C, was studied for a 0.61

mol L^{-1} initial concentration of cyclodecane (1). Figure 1 shows that after 30 min at 25 °C the conversion was nearly complete and the selectivity in cyclodecanone (2) was ca. 50%. A small amount of cyclodecanol (3) was also present. For longer reaction times the concentration of both reaction products decreased and ring cleavage products increased. This suggests that compounds (2) and (3) were formed by two independent pathways and that they were intermediates in the formation of ring cleavage products.

At 0 °C (Figure 2) the conversion was nearly complete after 60 min and the selectivity in cyclodecanone (2) was higher than in the reaction at 25 °C.

These experiments suggest that a yield in cyclodecanone (2) of ca. 80% may be achieved at °C in a 60 min period. Hence, this reaction has preparative value.



Reaction medium	pH	Reaction time (min)	Amount of starting material	Conversion %	Cyclodecanone (2) %	Cyclodecanol (3) %
H_2O	7	30	$4\ 10^{-4}$ moles in 10 mL	16	44	8
H_2O	3	30	"	45	91	-
H_2O	3	30	$2.5\ 10^{-3}$ moles in 50 mL	14	99	-
Pure liquid	-	480	$5.3\ 10^{-3}$ moles	64	70	3
CH_2Cl_2	-	30	0.61 mol L^{-1}	96	59	6

Table 1 Conversion and yields in the oxidation of cyclodecane (1) with ozone at 25 °C

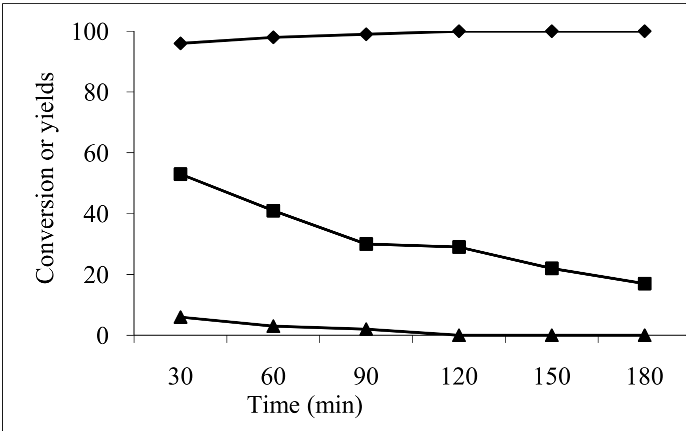


Figure 1.Time course of the ozonation of cyclodecane (1) in dichloromethane at 25 °C, ♦Conersion%, ■ Cyclodecanone (1) %, ▲ Cyclodecanol (5)%.

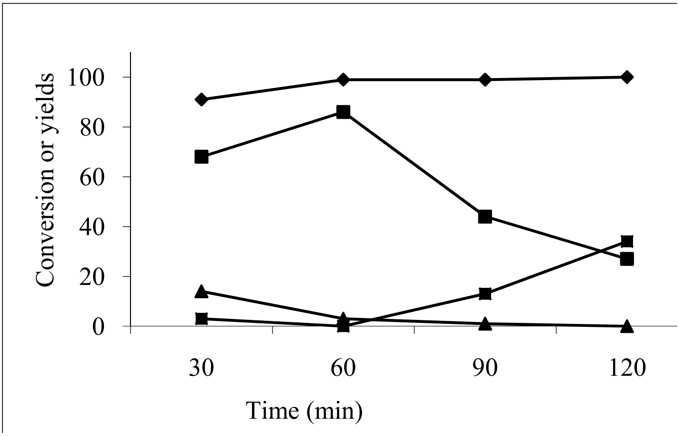
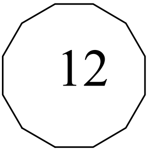


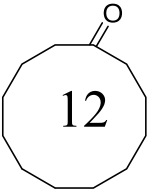
Figure 2 Time course of the ozonation of cyclodecane (1) in dichloromethane at 0°C. ♦Conersion%, ■ Cyclodecanone (1) %, ▲ Cyclodecanol (5)%, ▪ Mixture of acids %.

2.2.2.2. Cyclododecane (7)

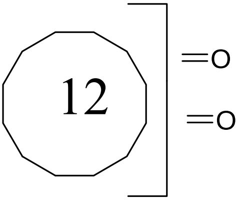
Cyclododecane (7) was also submitted to ozonation in dichloromethane at 25 °C (Table 2). It was less reactive than cyclodecane (1), but more selective into the alkanone cyclododecanone (8). (Scheme 1). Small amounts of cyclododecanediones (9) and cyclododecanol (9) were also present.



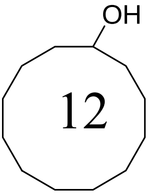
(7)



(8)



(9)



(10)

The time course of the reaction of cyclododecane (7) with ozone at 25 °C in dichloromethane is shown in Figure 3 and shows that after 90 min reaction the yield in cyclododecanone (8) was ca. 65%.

Reaction medium	Reaction time (min)	Amount of starting material	Conversion %	Cyclododecanone (8) %	Cyclododecandiones (9) %	Cyclododecanol (10) %
CH_2Cl_2	30	0.61 mol L^{-1}	24	99	traces	traces

Table 2. Conversion and yields in the oxidation of cyclododecane (7) with ozone at 25 °C

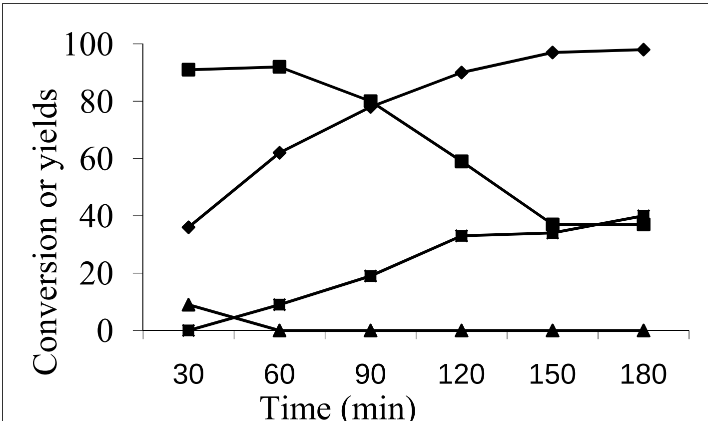


Figure 3. Time course of the ozonation of cyclododecane (7) in dichloromethane at 25 °C. ♦Conersion%, ■ Cyclododecanone (8) %, ▲ Cyclododecanol (9) %, ▪ Cyclododecandiones (10) %.

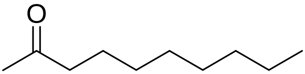
.

2.2.2.3. n-decane (11)

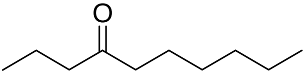
n-decane (11) was also used as a substrate both in dichloromethane and in water pH 3.

Table 3 shows the results thus obtained. In dichloromethane, n-decan-2-one (12), n-decan-3-one (13), n-decan-4-one (14), n-decan-5-one (15) (Scheme 1) were found in similar yields, thus showing that ozone attacks statistically all the non equivalent carbon-hydrogen bonds in the $–CH_2$- groups of n-decane (11). The aldehyde (16), deriving from the attack to the carbon-hydrogen bonds of the $–CH_3$ group was not found. However, n-decanoic acid (17a), is the methyl ester (17b) was found. Hence, the aldehyde (16), deriving from the oxidation of the methyl group was probably rapidly further oxidized to this acid. 11% of the converted substrate was constituted of acids and diacids having ten or less carbon atoms. Also minute amounts of the alcohols n-decan-2-ol (18) and n-decan-3-ol (19) were found.

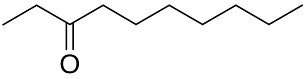
(11)



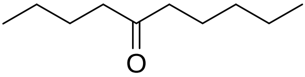
(12)



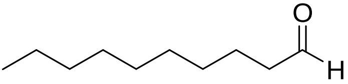
(14)



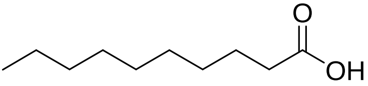
(13)



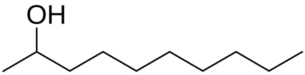
(15)



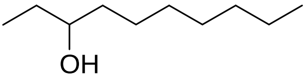
(16)



(17)



(18)



(19)

In water pH 3 the conversion was lower than in dichloromethane, probably because of the low solubility of the substrate, but the selectivity in n-decanones (12)-(15) was very similar to that in dichloromethane. n-decanols were not found.

Also in this case the time course of the ozonation of n-decane (11) in dichloromethane at 25 °C (Figure 4) showed that the highest selectivity into the carbonyl compounds is obtained using short reaction times and low conversion. The reaction is not regioselective, and all the methylenic groups are attached with nearly the same reactivity.

Reaction medium	pH	Reaction time (min)	Amount of starting material	Conversion %	n-decanones (12-15) %	n-decanols (18-19) %
H_2O	3	30	4 10^{-4} moles in 10 mL	28	n-decan-5-one (15) + n-decan-4-one (14): 18% n-decan-3-one (13): 11% n-decan-2-one (12): 10%	
CH_2Cl_2	-	90	0.51 mol L^{-1}	56	n-decan-5-one (15) + n-decan-4-one (14): 26% n-decan-3-one (13): 16%; n-decan-2-one (12): 10%	n-decan-2-ol (18): 3% n-decan 3-ol (19), 2%

Table 3. Conversion and yields in the oxidation of n-decane (11) with ozone at 25 °C.

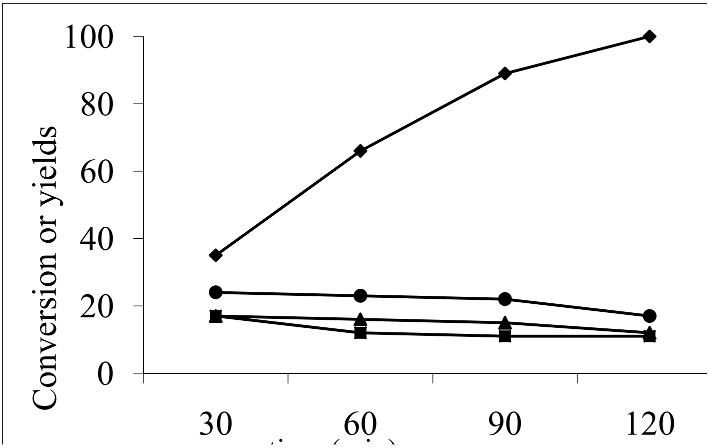


Figure 4. Time course of the ozonation of n-decane (11) in dichloromethane at 25 °C. ♦Conersion%, ● n-decan-5-one (15)+ n-decan-4-one(14) %, ▲ n-decan-3-one (13) %, ■ n-decan-2-one (12)%.

2.2.3. Oxidation of ethers

18-crown-6 (20), a water soluble ether having eight equivalent methylene groups, and dibenzylether (23), a lipophilic ether having two equivalent methylene groups, were ozonated in order to explore the possibility of transforming an ether into an ester.

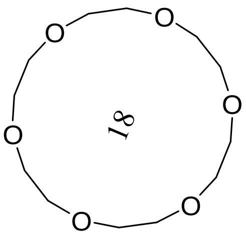
2.2.3.1. 18-crown-6 (20)

Two different reaction media were used for the ozonation of 18-crown-6 (20) at 25 °C:

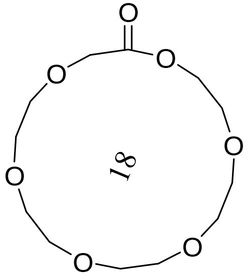
a) Aqueous solution pH 3.

b) Dichloromethane solution

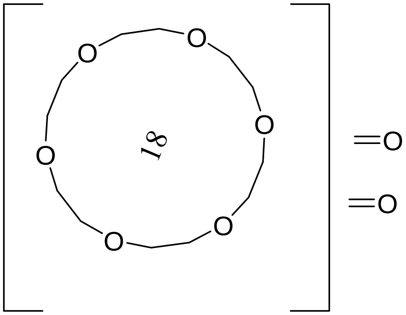
The substrate was completely dissolved in both cases. The conversion was higher in dichloromethane than in water pH 3 and the ester (21), as shown in Table 4 (Scheme 2) was formed in both cases. The selectivity was higher in water. Also minute amounts of a diester (22) appeared in the GLC-MS analysis.



(20)



(21)



(22)

The time course of this reaction in dichloromethane (Figure 5) shows that highest selectivity into the ester (21) is obtained using short reaction times and low conversion. After 75 min reaction in these conditions the yield in the ester (21) was ca. 35%.

Reaction medium	pH	Reaction time (min)	Amount of starting material	Conversion %	Ester (21) %
H_2O	3	30	$4\ 10^{4}$ moles in 10 mL	6	84
CH_2Cl_2	-	90	0.51 mol L^{-1}	95	15

Table 4. Conversion and yields in the oxidation of 18-crown-6 (20) with ozone

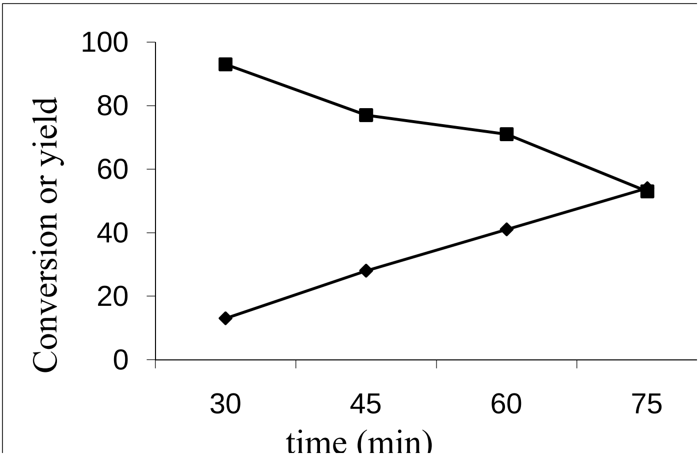


Figure 5. Time course of the ozonation of 18-crown-6 (20) in dichloromethane at 25 °C. ♦Conersion%, ■ Ester (21)

2.2.3.2. Dibenzylether (23)

Dibenzylether (23) was submitted to ozonation to give the ester (24) (Scheme 2) both in dichloromethane and in water pH 3 at 25 °C. Table 5 shows the results thus obtained. The reaction is slower in water, probably for solubility reasons, but the selectivity in the ester (24) is nearly quantitative, thus indicating that the aromatic rings are less reactive than the benzylic methylene groups toward ozone. After 90 min reaction the yield in benzyl benzoate (23) was 98%.

Reaction medium	pH	Reaction time (min)	Amount of starting material	Conversion %	Ester (23) %
H_2O	3	30	$4\ 10^{-4}$ moles in 10 mL	45	95
CH_2Cl_2	-	90	0.51 mol L^{-1}	100	98

Table 5. Conversion and yields in the oxidation of dibenzylether (23) with ozone at 25 °C.

2.2.4. *The proposed reaction mechanism*

A possible reaction mechanism is shown in Scheme 3. Hydride transfer from the methylenic group[12] forms a hydrotrioxide (25). This mechanistic detail has been suggested to account for the oxygenation of some ethers and is in agreement with the fact that oxygen reacts with the methylene group adjacent to the heteroatom both in the oxygenation of ethers to esters [9] and in the oxygenation of amines to amides [10].

This is the key intermediate in the reaction. It may:

Dissociate to a carbonyl compound and hydrogen peroxide (path a)

Dismutate to an alcohol and dioxygen (path b).

Rearrange an aldehyde and a hydroperoxide with further oxidation to carboxylic acids (path c).

With alkanes and ethers path a) is the most important and forms carbonyl compounds which are eventually further oxidized to open-chain products.

The hydrogen which transfers from carbon to oxygen in path a) has the nature of a hydride ion. In fact, a competition experiment performed submitting to ozonation in dichloromethane an

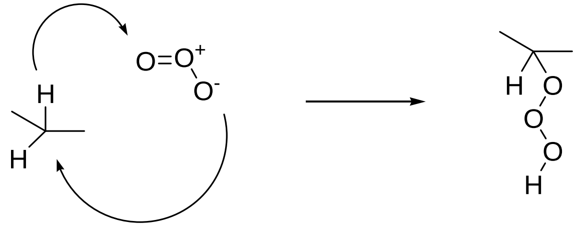
---

[12] Giamalva, D.H., Church, D.F., Pryor, W.A., "Kinetics of ozonation. 5 Reaction of ozone with carbon-hydrogen bonds", J. Am. Chem. Soc., 108, 7678-7681 (1981).

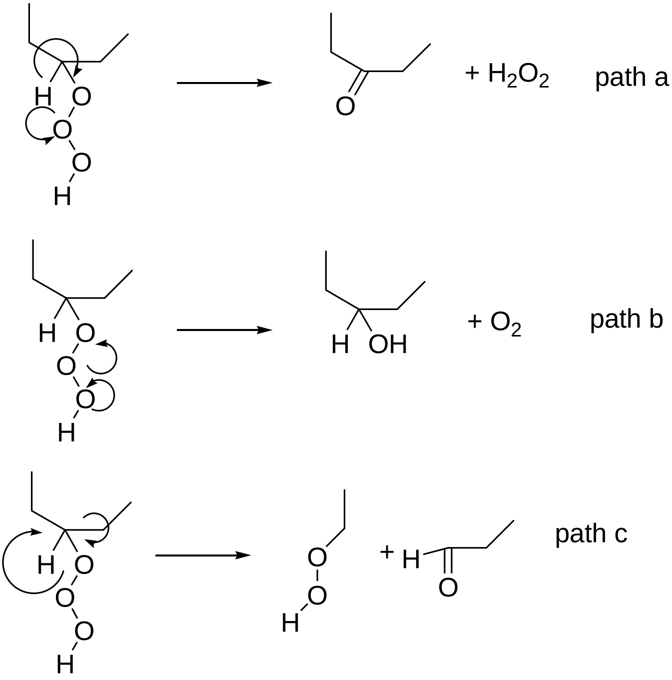
equimolecular mixture of cyclododecane (11) and 18-crown-6 (20), having the same number of carbon-hydrogen bonds (twenty-four) showed that the ether is 3.61 times more reactive than the alkane. This suggests that the positive charge developing on carbon in the transition state derived from a hydride shift (26) (Scheme 3) is stabilized in the ether by one of the lone pairs of the adjacent oxygen atom. This stabilization is not possible when the adjacent atom is a carbon. Hence, the transition state energy is lower with ethers than with alkanes and this result in a major reactivity of ether (20) over alkane (11).

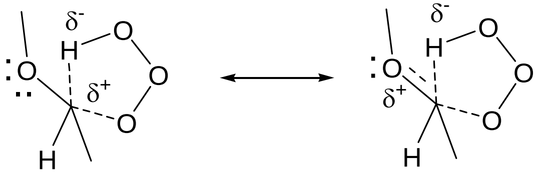
Path b) is much less important and gives minor amounts of the corresponding alcohols. Path c) is probably involved in the formation of shorter carbon chain acids.

Thereby, the ozonation of alkanes and ethers is a mild and selective metal-free method for the oxidation of carbon chains. Many of these reactions have preparative value. This procedure is in the line of sustainability in chemical reactions which is one of the major goals in “green chemistry”[2].



(27)





(28)

2.3. The synthesis of phthalic anhydride via ozonation of naphthalene

2.3.1. Introduction

The selective oxidation of alkanes and arenes at room temperature is one of the more important objectives of synthetic chemistry. Generally these reaction use metal centered systems[1]

The ozonation of naphthalene (1) has been described in a review[2]. Naphthalene (1) in chloroform was ozonized first in 1905[3] and a diozonide (2) was formed (Scheme 1). Hydrolysis of (2) gave phthalic aldehyde (3), 2-formylbenzoic acid (4) and phthalic acid (5)[4] [5]. In

---

[1] Kochi, J., Sheldon, R., *Metal Catalysed Oxidations of Organic Compounds* (New York, Academic Press, (1981);

[2] Bailey, P.S., *Ozonation in Organic Chemistry*, (New York, Academic Press, (1981) p. 255;

[3] Harries, C. D., Over the Effect of Ozone on Organic Compounds, Liebigs Annalen der Chemie, (1905), 343, 311-375;

[4] Seekles, L., o-Phthalaldehyde, Rec. Trav. Chim. Pays Bas, (1923), 42, 706-709;

[5] Wibaut, J. P., Kampschmidt, L. W. F., Ozonization and ozonolysis of naphthalene, 2,3-dimethylnaphthalene, and 1,4-

methanol the emiperacetal (6)[6] and in carbon tetrachloride α-naphthol (7)[7] were formed. In water-acetone phthalic aldehyde (3) was formed after reduction of the reaction mixture[8].

More recently, the preparation of E- and Z 3-phenyl-(2-formyl)-propenal (10-11) was accomplished via ozonation of naphthalene[9], 2-

---

dimethylnaphthalene in connection with the reactivity of the ring system, Rec. Trav. Chim. Pays Bas, (1954), 73, 431-454

[6] Kommissarov V. D., Kommissarova, I. N., Bull Akad Sci: URSS Div. Chem. Sci, (1973), p. 656;

[7] Legube, B., Guyon, S., Sugimitsu, H., Dore, M., Ozonation of some aromatic compounds in aqueous solution: styrene, benzaldehyde, naphthalene, diethyl phthalate, ethyl- and chlorobenzenes, Ozone: Science & Engineering (1984), 5(3), 151-170;

[8] Sturrock, M., Cravy, B. J.; Wing, V. A. , Ozonation of naphthalene with water as participating solvent. Preparation of o-phthalaldehyde, Canadian Journal of Chemistry, (1971), 49(18), 3047-51;

formylbenzoic acid (4), phthalic acid (5) and smaller fragments were obtained in the ozonation of naphthalene in aqueous solution[10]; nitration products were formed if the aqueous solution contained nitrite ion[11].

Studying the reactivity of naphthalene with ozone is important because this compound is a model for the oxidative behaviour of policyclic aromatic compounds and its oxidation may give information about the oxidative removal of these pollutants. Moreover, the oxidation of naphthalene (1) to give phthalic anhydride (8) has been a very important industrial process for the preparation of plastics and dyes. Naphthalene from coal is oxidised with air at 400 °C in the presence of V_2O_5 on SiO_2 as the catalyst and K_2SO_4 as a

---

[9] Larson, R. A., Garrison, W. J., Marley, K. A., Preparation and photoisomerization of 2-formylcinnamaldehyde in solution, Tetrahedron Letters (1986), 27(34), 3987-90;

[10] Legube, B., Guyon, S., Sugimitsu, H., Dore, M., Ozonization of naphthalene in aqueous solution - I. Ozone consumption and reaction products, Water Research (1986), 20(2), 197-208;

[11] Chan, W. F., Larson, R. A., Products of ozonolysis of aromatic compounds in aqueous solution containing nitrite ion, Ozone: Science & Engineering (1995), 17(6), 627-635;

promoter. The conversion of naphthalene is 86% and the selectivity in phthalic anhydride (8) is 90%. Nowadays phthalic anhydride (8) is produced from o-xylene, as long as the price of oil remains low[12].

2.3.2. *Discussion*

Two different reaction media were used for the oxidation of naphthalene (1) with excess ozone at 25 °C:

Dichloromethane solution

Acetonitrile solution

After 0.5 h at 25 °C in dichloromethane the reaction mixture was separated by silica gel chromatography. The conversion was found to be 68%. Isolated reaction products were phthalic aldehyde (3), 2-formyl benzoic acid (4) and phthalic anhydride (8) where two of the ten carbon atoms in naphthalene (1) had been lost. A high amount of the (E)- and (Z)-isomer of 3-phenyl-(2-formyl)-propenal (10) and (11) were also separated. Here, the entire carbon atom skeleton is still present. Table 1 show these results.

---

[12] Weissermerl K., Arpe, H. J., *Industrial Organic Chemistry*, (1993), p. 381-383, VCH;

T (°C)	Solvent	Ozone	Time (h)	Naphthalene (1) %	Phthalic Aldehyde (3) %	2-formylbenzoic acid (4)%	Phthalic Anhydride (8) %	(E)- and (Z)- 3-phenyl-(2-formyl)-propenal (10) + (11) %	Aldehydoacids (12) +(13) %
25	DCM	excess	0.5	32	19	9	8	24	-
25	DCM	excess	4	-	30	-	10	-	-
25	ACN	excess	0.75	-	10	33	36		2
25	ACN	excess	4	-	1	-	30	-	
0	DCM	excess	0.5	28	18	24	8	5	9
0	ACN	excess	0.5	-	40	26	23	-	-
-20	DCM	excess	0.5	-	19	24	22	-	34
-20	ACN	excess	0.5	-	29	-	56	-	14
25	ACN	1:1	1	6	11	-	19	9	-
0	ACN	1:1	1	2	9	-	3	7	-
-25	ACN	1:1	1	39	6	-	-	-	-
25	ACN	2:1	1	2	30	-	7	1	-
0	ACN	2:1	1	3	30	-	7	1	-
-25	ACN	2:1	1	11	39	-	7	-	-

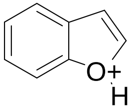
Table 1. Reaction time, temperature and yields in the converted material (DCM = dicloromethane; ACN = acetonitrile)

In acetonitrile at 25 °C for 0.75 h 100% conversion was observed after chromatogrraphic separation. Again compounds (3), (4), and (8) were isolated, together with a small amount of two compounds having in the mass spectrum fragments at m/z = 177, 148, 131, 119, 105, 91, 77. Structures (12) and (13) for R = CHO and R' = COOH or vice versa may be suggested for these compounds. In fact, 177 is the M^++1 fragment, which undergoes two losses of a neutral fragment 29 (CHO) to form an ion at m/z = 119 to which structure (14) may be assigned (Scheme 1). The dialdehydes (10-11) were not found. Under these conditions, the amount of monocyclic compounds was 79%. This gives synthetic value to the reaction, since the dialdehyde (3) and the aldehydoacid (4) may be easily oxidized to phthalic anhydride (8), which is an important commercial product.

Increasing the reaction time to 4 h in both solvents resulted in 100% conversion, but the recovery of material after chromatographic separation was very poor and the yields in compounds (3) and (8) were much lower, indicating that these primary reaction products react further degraded by ozone.

The reaction was then repeated at the temperatures of 0 °C for 0.5 h in both solvents. In dichloromethane the conversion was 72 % and the distribution of isolated reaction products was similar to that observed at 25 °C in the same solvent. In acetonitrile a 100% conversion was observed and the preparative value of the reaction was apparent again from the total yield of 89% in the mixture of monocyclic compounds.

At -20 °C for 0.5 h the conversion was 100% in both solvents. In dichloromethane the yields in monocyclic compounds were similar to the other reactions, but a high amount of the mixture (12-13) was observed. In acetonitrile 56% of phthalic anhydride (8) was obtained, together with phthalic aldehyde (3).



(14)

These data show that:

Mass balance is very high in all the runs performed for short reaction times (0.5-0.75 h). A much poorer mass balance is observed in reactions performed for 4 h.

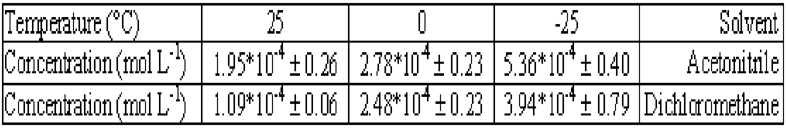
Naphthalene (1) is 100 % converted in acetonitrile at all the temperatures.

In dichloromethane partial conversion is observed at 25 °C and 0 °C. At -20 °C complete conversion is observed.

(E)- and (Z)-3-phenyl-(2-formyl)-propenal (10) and (11) and compounds (12-13), having the same number of carbon atoms than naphthalene (1) itself, are found only in reaction in which some unreacted naphthalene (1) is still present.

The yield in compounds such as phthalic aldehyde (3), 2-formyl benzoic acid (4), phthalic anhydride (8), which derive from the loss of two carbon atoms, is higher in runs where naphthalene (1) has been completely converted.

The solubility of ozone in dichloromethane or acetonitrile at the temperatures of this study is shown in table 2. This was accomplished by bubbling ozone in the solvent for 15 min and measuring its concentration via iodometric titration. Measurements were performed in triplicate[13].



Temperature (°C)	25	0	-25	Solvent
Concentration (mol L^{-1})	$1.95*10^{-4} \pm 0.26$	$2.78*10^{-4} \pm 0.23$	$5.36*10^{-4} \pm 0.40$	Acetonitrile
Concentration (mol L^{-1})	$1.09*10^{-4} \pm 0.06$	$2.48*10^{-4} \pm 0.23$	$3.94*10^{-4} \pm 0.79$	Dichloromethane

Table 2. Solubility of ozone in dichloromethane or acetonitrile at different temperatures

Some other experiments were performed limiting the concentration of ozone in acetonitrile using a 1:1 or a 1:2 ratio naphthalene (1): ozone in acetonitrile for 1 h reactions in experiments performed in triplicate. Acids, including 2-formylbenzoic acid (4), were not determined in these experiments.

The conversion was very high in all the cases, with the exception of the reaction at -25 °C with a 1:1 ratio. The selectivity in phthalic dialdehyde (3) was higher in runs performed with 2:1 stoichiometry.

---

[13] Gordon, S. A,. Chughtai, A. R., Smith, D. M., Revisiting iodometric estimation as a reference method for ozone in laboratory gas streams, American Laboratory (2000), 32(9), 12-13;

The selectivity into phthalic anhydride (8) was low, except in the reaction at 25 °C with a 1:1 stoichiometry.

The results of all these experiments, taken together, suggest that:

The reactivity of naphthalene (1) with ozone is higher in acetonitrile than in dichloromethane for all temperatures. This is the result of the higher solubility of ozone in acetonitrile than in dichloromethane. The rate law for the ozonation of naphthalene (1) in water has been determined[14] as:

$$v = k\,[\text{naphthalene}][\text{ozone}] \qquad (1)$$

If this relationship holds also in organic solvents, an increase in the concentration of ozone results in an increase in the second order

---

[14] Hoigne, J., Bader, H., Ozonation of water: selectivity and rate of oxidation of solutes, Ozone: Science & Engineering (1979), 1(1), 73-85; Rate constants of reactions of ozone with organic and inorganic compounds in water. I. Nondissociating organic compounds, Water Research (1983), 17(2), 173-83; Wang, P. C., Matta, H. B., Kuo, C. H., Kinetics of ozonation of naphthalene and anthracene, Journal of the Chinese Institute of Chemical Engineers (1991), 22(6), 365-71;

reaction rate and hence in the conversion of naphthalene (1) in our experiments.

A reaction time longer than 0.5-0.75 h results in a drastic decrease in mass balance, probably due to the formation of further fragmentation of the primary reaction products which are not recovered after the chromatographic separation.

The conversion of naphthalene (1) is higher at -20 °C than at higher temperature in both solvents. This is probably due to the higher solubility of ozone in the solvent when lowering the temperature. Again, an increase in the concentration of ozone, such as that resulting from the lower temperature experiments, results in an increase in the second order reaction rate and hence in the conversion of naphthalene (1).

The formation of compounds having the same number of carbon atoms as naphthalene (1) such as compounds (10-13) suggests the intermediate formation of the monoozonide (9). Then, both this monoozonide (2) and the diozonide (9) undergo hydrolysis. The former forms dialdehydes (10-11) and hydrogen peroxide; the latter gives phthalic aldehyde (3), glyoxal (CHO-CHO) and hydrogen peroxide.

Compounds (3), (10) and (11) may be oxidized by hydrogen peroxide or by dioxygen to give the corresponding monoacids (4), (12) and (13). These compounds are revealed in GLC-MS because they are in equilibrium with the corresponding acetalic forms such as

(15) for 2-formylbenzoic acid (4). Further oxidation of (15) generates phthalic anhydride (8), which may be hydrolyzed to phthalic acid (5) if excess water is present.

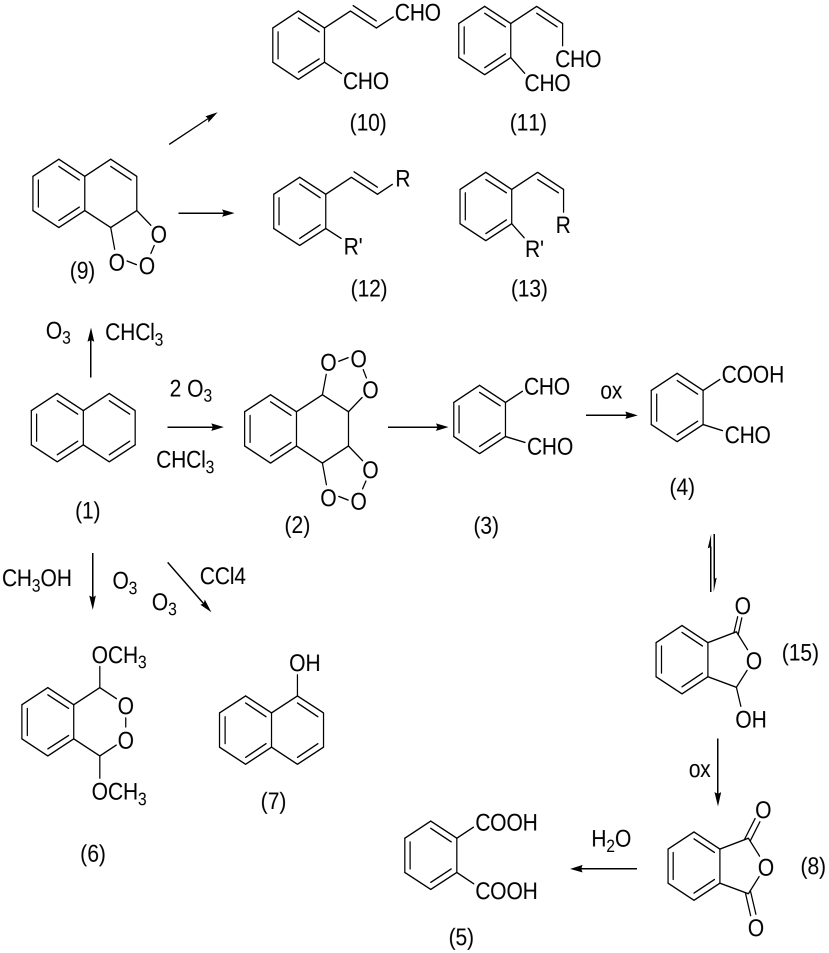
Limiting the concentration of ozone leads to very high conversion of the starting material, except in the reaction at -25 °C with a 1:1 stoichiometry. This confirms the validity of the kinetic equation (1) since the higher concentration of ozone at low temperature is balanced by the decrease of useful collisions in the bimolecular reaction.

Limiting the concentration of ozone, and hence of dioxygen, has the effect of increasing the amount of acidic material formed (compounds 4, 10, 11, 12 and 13) over neutral compounds (3), (8).

In conclusion, the oxidation of naphthalene (1) with excess ozone produces monocyclic aromatics that may give phthalic anhydride (8) in high yield, in a green procedure[15].

---

[15] Matlack, A. S., *Introduction to Green Chemistry*, (2001), Markel Dekker, New York, Basel.


CHO
CHO
(10)
CHO
CHO
(11)
R
R'
(12)
R
R'
(13)
O
O-O
(9)
O3 CHCl3
2 O3
CHCl3
O-O
O
O
O-O
(1)
(2)
CHO
CHO
(3)
ox
COOH
CHO
(4)
CH3OH
O3
O3
CCl4
O
O
OH
(15)
OCH3
O
O
OCH3
(6)
OH
(7)
ox
COOH
COOH
(5)
H2O
O
O
O
(8)

2.4. The ozonation of N-phenylmorpholine: products and reaction mechanism

2.4.1. Introduction

The fundamental problem in the functionalization of saturated hydrocarbons is that their components, carbon and hydrogen, do not have electron pairs, and the molecules do not have an orbital of sufficient energy which are easily accessible. Thus, very reactive reagents and/or extreme reaction conditions are usually required. The oxidation of alkanes is an example. Moreover, reaction products are usually more reactive than the starting materials, thereby, undesired side reactions may occur[1].

The reactivity of ozone with organic molecules has been the focus of organic synthesis research for decades[2]. Moreover, the selective oxidation of alkanes has been an important objective of synthetic chemistry. Generally these reactions use metal centered systems

---

[1] Weissermel, Arpe, H. J., *Industrial Organic Chemistry,* (VCH, Weinheimn, 1993);

[2] Bailey, P.S., Ozonation in Organic Chemistry, (New York, Academic Press, 1981) p. 255;

which mimic monooxygenases. Examples are cytochrome P-450 and methanemonoxygenase mimics[3]. The oxidation of unactivated carbon-hydrogen bonds has been achieved using systems where a metal-centered catalyst such as a tertiary alkylhydroperoxide iron (III)[4], manganese, vanadium, ruthenium is needed. Cobalt is used as the catalyst for the oxidation of cyclohexane to cyclohexanone and cyclohexanol with dioxygen[5]. The disposal of metal-containing wastes is an important problem in this case. The use of dioxirane as oxidizing agents[6], the functionalization of alkanes in superacidic media[7], the

---

[3] Arends, I.W.C.E., Mac Faul, P.A., Snelgrove, D.W., Wayer D.D.M, Ingold K.U. in Minisci, F. ed. *Free Radicals in Biology and Environment* (New York, Kluver Academic Publishers, 1997) p.79-90

[4] Gross, Z., Simkhovich, L., “Ozone as primary oxidant in iron(III) porphyrin catalyzed hydroxylation of hydrocarbons”, Journal of Molecular Catalysis -A - Chemical -, 117, 243-248, (1997);

[5] Kochi, J., Sheldon, R., *Metal Catalysed Oxidations of Organic Compounds* (New York, Academic Press,.1981);

[6] Reiser, O., “Oxidation of Weakly Activated C-H Bonds”, Angew. Chem. Int. Ed., 33,_69-72 (1994); Minisci, F., Zhao, L.H., Fontana, F., Bravo, A.“Free-radicals in the oxidation and

---

halogenation of alkanes by dimethyldioxirane: An oxygen rebound mechanism", Tetrahedron Lett, 1697-1700 (1995); Bravo, A., Fontana, F., Fronza, G., Mele, A., Minisci, F., "Induced homolysis of dimethyldioxirane by alkanes and alkyl radicals in oxidation processes. The dramatic role of molecular oxygen and radical inhibitors", J. Chem. Soc. Chem. Commun., 1573-1574 (1995); Vanni, R., Garden, S.J., Banks, J. T., Ingold, K.U., "Mechanism of hydroxylation of alkanes by dimethyldioxirane. A radical-clock study", Tetrahedron Letters, 7999-8002 (1995); Asensio, G., Mello, R., Gonzalez Nunez, M.E., Boix, C., Royo, C.J., "The oxidation of alkanes with dimethyldioxirane; A new mechanistic insight", Tetrahedron Letters, 2373-2376 (1997); Adam,W., Curci, R., D'Accolti, L., Dinoi, A., Fusco, C., Gasparrini, C., Kluge, R., Paredes, R., Schulz, M., Smerz, A.K., Veloza, L. A., Weinkotz, S., Winde, R., "Epoxidation and oxygen insertion into alkane CH bonds by dioxirane do not involve detectable radical pathways", Chemistry - A European Journal, 3, 105-109 (1997);

[7] Jacquesy, J. C., Jouannetaud, M. P., Martin, A., "Functionalisation of nonactivated bonds in superacidic media", Bulletin de la Societe Chimique de France, 134, 425-438 (1997).

insertion of oxygen by di(perfluoroalkyl)oxaziridines[8] and the oxidation by fluorine in aqueous acetonitrile are metal-free alternatives which have been proposed lately.

Ozone is a metal-free alternative to these methods. This reactant has been used by us for the oxidation of cycloalkanes to cycloalkanol and cycloalkanones [9], ethers to esters[10] , amines to amides[11]. These

---

[8] Brambilla, A., Rindone, B., Polesello, S., Galassi, S., Balestrini, R., “The fate of triazine pesticides in river Po water”, The Science of the Total Environment, 132, 339-348 (1993); .Bolzacchini, E., Brambilla, A., Orlandi, M., Polesello, S., Rindone, B., “Oxidative Pathways in the degradation of triazine herbicides: A mechanistic approach”, Wa. Sci. Tech., 30, 129-136 (1994); Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., “, Reactivity of organic micropollutants with ozone: a kinetic study”, Life Chemistry Reports, 13, 79-84, (1995);

[9] Rindone, B., Saliu, F., Suarez Bertoa, R., Functionalization of the Unactivated Carbon-Hydrogen Bond Via Ozonation, *Ozone: Science & Engineering*, 30(2), 165-171 (2008);

[10] Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., “Reactivity of two models of non ionic surfactants with ozone”, *Water Research*, 31, 1839-1846 (1997);

studies suggest that ozone is a suitable oxidant but the process requires improvement of both conversion and selectivity.

Several reaction mechanisms have been proposed to explain the formation of the reaction products. Ozone is believed to act as an electrophile towards π systems, heteroatoms and in some cases also towards carbon and a 1,3-dipolar insertion of ozone into an activated C-H bond yields alkyl hydrotrioxides ROOOH[12]. Alternatively a hydrogen abstraction followed by the formation of the radical pair R$^{\cdot}$ $^{\cdot}$OOOH which then recombine will again form ROOOH. A hydride abstraction by ozone and the formation of the ion pair R+ -OOOH that

---

[11] Brambilla, A., Rindone, B., Polesello, S., Galassi, S., Balestrini, R., “The fate of triazine pesticides in river Po water”, *The Science of the Total Environment*, 132, 339-348 (1993); .Bolzacchini, E., Brambilla, A., Orlandi, M., Polesello, S., Rindone, B., “Oxidative Pathways in the degradation of triazine herbicides: A mechanistic approach”, *Wa. Sci. Tech.*, 30, 129-136 (1994); Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., “, Reactivity of organic micropollutants with ozone: a kinetic study”, *Life Chemistry Reports*, 13, 79-84 (1995);

[12] Giamalva, D.H., Church, D.F., Pryor, W.A., “Kinetics of ozonation. 5 Reaction of ozone with carbon-hydrogen bonds”, *Journal of the American Chemical Society*, 108, 7678-7681 (1981);

can combine to form again ROOOH[13]. Hydrogen atom and hydride abstraction may be two extremes between which the reaction path may vary according to diverse factors as solvent and temperature.

The formation of hydrotrioxides in the reactions of acetals with ozone has been reviewed[14].

We present a combination of experimental and quantum chemical studies for elucidating the selectivity of the reaction of ozone secondary carbon-hydrogen bonds α to nitrogen or oxygen. N-phenylmorpholine **1** has been selected as a suitable model for this

---

[13] Giamalva, D.H., Church, D.F., Pryor, W.A., "Kinetics of ozonation. 5 Reaction of ozone with carbon-hydrogen bonds", J. Am. Chem. Soc., 108, 7678-7681 (1981);

[14] Houben Weyl, *Methoden der Organische Chemie* Vol E13, (Stuttgart, New York, George Thieme Verlag 1988) p. 1118; Plesnicar, B., Cerkovnik, J., Tekavec, T., Koller, J., Chem. Eur. J., 6, 809-819, (2000); Plesnicar, B., Cerkovnik, Tuttle, T., Kraka, E., Cremer, D., J. Amer. Chem. Soc., 124, 11260-11261, (2002); Wu, A., Cremer, D., Plesnicar, B., J. Amer. Chem. Soc., 125, 9395-9402, (2003); Tuttle, T., Cremer, D., Plesnicar, B., Cerkovnik, J. Amer. Chem. Soc., 126, 16093-16104, (2004);

study. Two equivalent CH_2 groups α to nitrogen and two equivalent CH_2 groups α to oxygen are present in this molecule.

2.4.2. Discussion

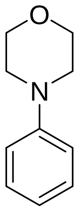
N-phenylmorpholine **1** in dichloromethane or acetonitrile was treated with excess ozone at different temperatures and with different reaction times. The experiments were performed in duplicate.

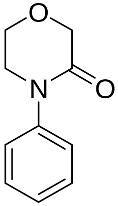
In dichloromethane at 25ºC, after 1.5 h, 80% of the starting material had been converted into products. Table 1 summarizes the results obtained. Two reaction products could be separated by silica gel chromatography and were identified as the lactame **2** and the diformylderivative **3** (Scheme 1) by comparison of their IR, MS, ^{1}H-NMR and ^{13}C-NMR spectra with those of authentic specimens[15] [16]. Recovery of material after the chromatography was 48%, thus showing that one half of the starting material had been converted into other products which could not be isolated and characterized.

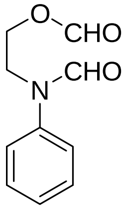
---

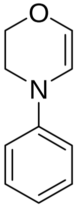
[15] Tulyaganov, S. R.; Khasanov, S. A.. Synthesis of some aromatic aminoalcohols and their oxazolidine derivatives, *Uzbekskii Khimicheskii Zhurnal* 10(4), 32-5 (1966);

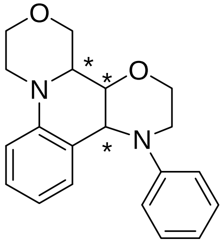
[16] Thomas, C., Berwe, M., Straub, A., *PCT Int. Appl.* (2005), 16 pp. CODEN: PIXXD2 WO 2005026135 A1 20050324;

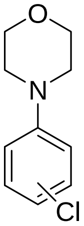

(1)


(2)


(3)


(4)

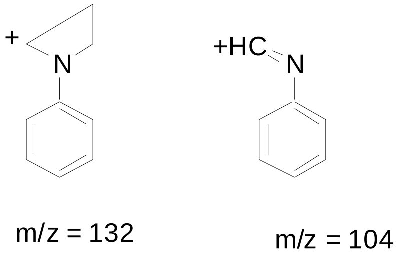

(5)


(6)

This was not surprising since compounds **2** and **3** were converted upon treatment with excess ozone in both solvents into a mixture of secondary reaction products which could not be separated.

The reaction was repeated at 0 °C in dichloromethane for 1 h. The conversion was 72% and compounds **2** and **3** were again separated by silica gel chromatography. Recovery of material after the chromatography was 72%. However, traces of two other reaction products could be observed. The first had in the mass spectrum the molecular ion at m/z = 161 and fragments at m/z = 132 (loss of ethylene + H), m/z = 104 (another loss of ethylene), m/z = 77 (phenyl cation). Based on the fragmentation shown in Scheme 2 the structure of dehydroderivative **4** was suggested for this compound. The second had the molecular ion at m/z =322. This suggested the dimeric structure **5**, constituted by 8 isomers because of the three stereogenic carbons.

Scheme 2



In a reaction at -20ºC in dichloromethane for 0.5 h the conversion was 100% and compounds **2** and **3** were isolated by silica gel chromatography. Recovery of material after the chromatography was very poor: 27%.

When N-phenylmorpholine **1** in acetonitrile was treated with excess ozone at 25, 0 and -20 ºC for 0.5 h a complete conversion was observed and again lactame **2** and diformylderivative **3** were isolated. Again, poor recovery was observed: 34%, 40% and 45% respectively.

In summary, the collected data show that:

1. The reaction is faster in acetonitrile than in dichloromethane.

2. The conversion of N-phenylmorpholine **1** in acetonitrile is complete at all of the temperatures investigated. In dichloromethane the conversion is complete only at -20 °C, while partial conversion is observed at 0 °C and 25 °C. Therefore, in dichloromethane the conversion is larger at lower rather than at higher temperatures.

3. Mass balance is generally poor, due to the further oxidation of the primary reaction products. In particular, compounds bearing a formyl group could give carboxylic acids. This reaction could be due to hydrogen peroxide, ozone or dioxygen itself. Also polymerization could lead to loss of material.

4. Compounds **4** and **5** are found only in reaction in which some unreacted N-phenylmorpholine **1** is still present.

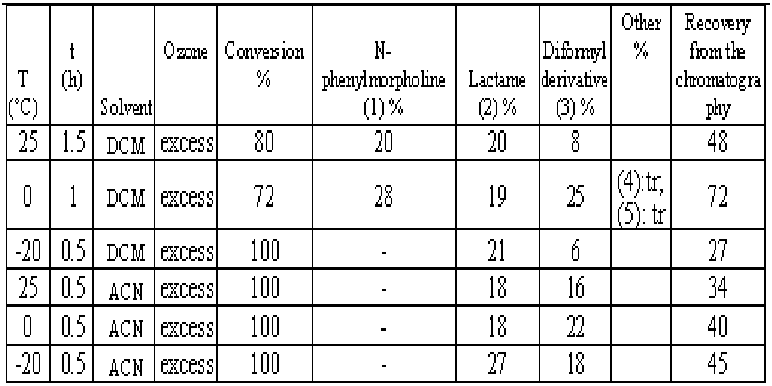
The higher reaction rate observed in acetonitrile compared to dichloromethane may be explained by a solvent polarity effect on the reaction mechanism (*vide infra*). An alternative explanation which also accounts for the larger conversion at lower temperatures observed in dichloromethane, can be proposed by considering the solubility of ozone in the two solvents and at different temperatures. The solubility of ozone in dichloromethane and acetonitrile at the studied temperatures is shown in Table 1 (the solubility has been determined by dissolving ozone in the solvent for 15 min at the appropriate temperature and measuring its concentration via iodometric titration). The solubility clearly increases, for both solvents, by lowering the temperature. The rate law for the ozonation of organic compounds in water has been determined[17] as:

$$v = k\,[\text{organic compound}][\text{ozone}]$$

Hence, an increase in the concentration of ozone, such as that resulting from the lower temperature experiments should results in an increase of the second order reaction rate and hence in the conversion of N-phenylmorpholine **1**. The higher solubility of ozone in acetonitrile than in dichloromethane is also compatible with the higher reaction rate observed in the former solvent.

---

[17] Hoigne, J., Bader, H., Ozonation of water: selectivity and rate of oxidation of solutes, *Ozone: Science & Engineering* 1(1), 73-85 (1979); Rate constants of reactions of ozone with organic and inorganic compounds in water. I. Nondissociating organic compounds, *Water Research* 17(2), 173-83 (1983);



T (°C)	t (h)	Solvent	Ozone	Conversion %	N-phenylmorpholine (1) %	Lactame (2) %	Diformyl derivative (3) %	Other %	Recovery from the chromatography
25	1.5	DCM	excess	80	20	20	8		48
0	1	DCM	excess	72	28	19	25	(4):tr, (5): tr	72
-20	0.5	DCM	excess	100	-	21	6		27
25	0.5	ACN	excess	100	-	18	16		34
0	0.5	ACN	excess	100	-	18	22		40
-20	0.5	ACN	excess	100	-	27	18		45

Table 1. Reaction yields after chromatographic separation of the reaction of N-phenylmorpholine with ozone at different temperatures (DCM = dichloromethane; ACN= acetonitrile)

In order to get a better understanding of the regiochemistry of the reaction, and the distribution of products, the reaction mechanism has been investigated computationally through the identification of the relevant stationary points (minima and saddle points) along the reaction coordinate of the pathways reported in Scheme 3. The calculations have been performed in *vacuum*, as well as by using an implicit solvent model for acetonitrile and dichloromethane. The first step in the proposed mechanism is the formation of the hydrotrioxide intermediate **7**. This process may occur through a hydride or hydrogen transfer from a methylenic carbon atom to the terminal oxygen atom of O_3. The hydride transfer leads to the formation of the N-phenylmorpholyn cation and the hydrotrioxide anion (HO_3^-), while the hydrogen transfer leads to the formation of the N-phenylmorpholyn and the hydrotrioxide ($HO_3\cdot$) radicals. The recombination of the terminal oxygen atom of HO_3^- or $HO_3\cdot$ with the methylenic carbon atom will then lead to **7**. The process may also occur through a concerted mechanism where hydrogen transfers and C-O bond formation occurs simultaneously. The attack by ozone on **1** can occur at the methylenic group in α position to nitrogen or oxygen, giving rise to the two regioisomers **7** and **8** represented in Scheme 4.

The key hydrotrioxide intermediates **7** and **8** may further evolve following the pathways:

1) Dissociation to a carbonyl compound and hydrogen peroxide (path a)

2) Dismutation to an alcohol and dioxygen (path b). Singlet dioxygen is reported to be formed in this step[18].

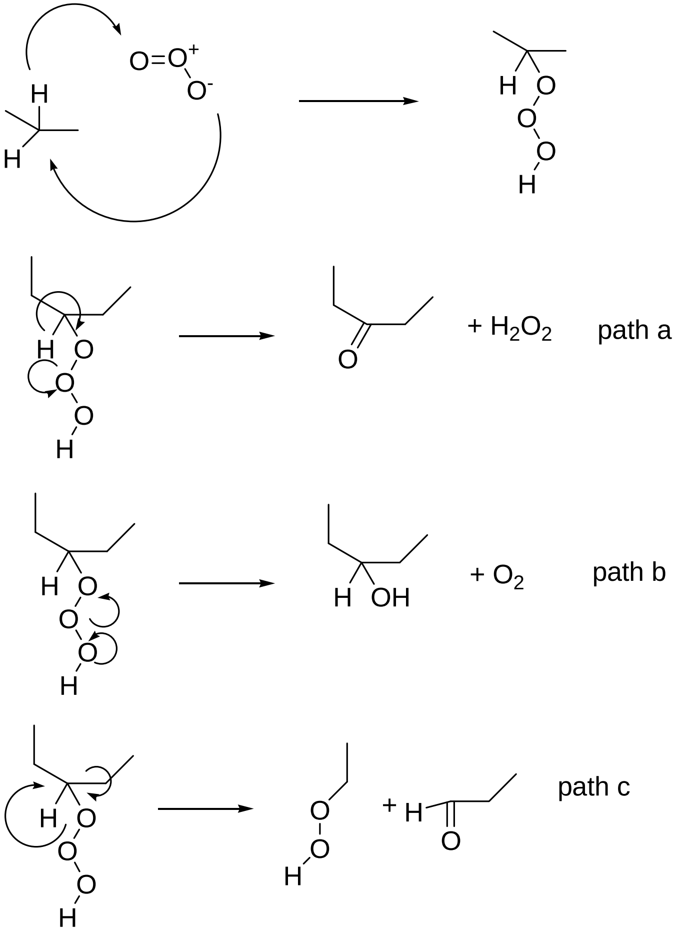
3) Rearrangement to an aldehyde and a hydroperoxide with further oxidation to carboxylic acids (path c).

Previously studies on alkanes and ethers reported that path a) is most important and forms carbonyl compounds which are eventually

---

[18] Munoz, F., Mvula, E., Braslavsky, S. E., von Sonntag, C., Singlet dioxygen formation in ozone reactions in aqueous solution, *Journal of the Chemical Society*, Perkin Transactions 2 (7), 1109-1116 (2001);

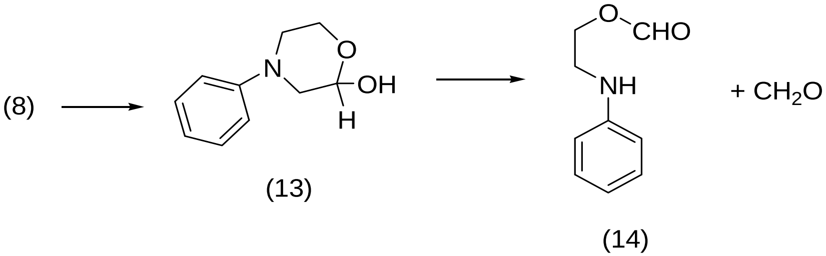
further oxidized to open-chain products, while Path b) is much less important and gives minor amounts of the corresponding alcohols. Path c) is probably involved in the formation of shorter carbon chain acids.

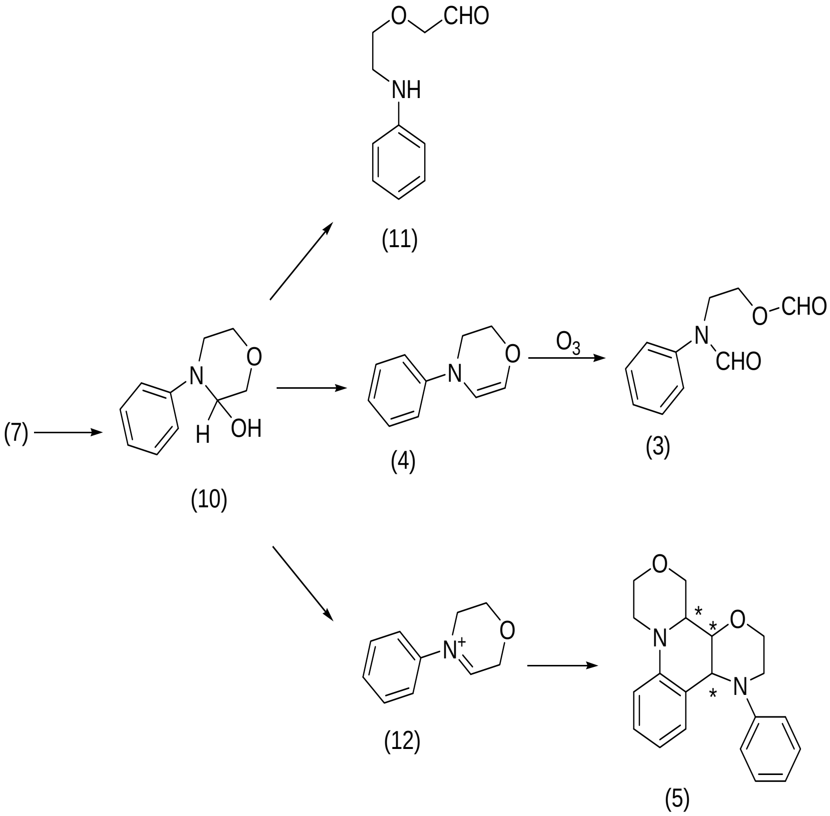


The fragmentation of the hydrotrioxide **7** via path a give the lactame **2**, which, in fact is the major product observed experimentally. The alternative formation of the isomeric hydrotrioxide **8** seems not to occur because the lactone **9** has never been found. Moreover, fragmentation of hydrotrioxide **7** via path b should give the emiaminal **10** (Scheme 5). Loss of water from **10** should give the dehydroderivative **4**, which was found in trace amounts because of its fast oxidation to the diformylderivative **3**. Alternatively, the dehydration to the immonium ion **11** is the origin of the dimeric material **6**, in accord with dimerization of N-phenylpyrrolidine upon ozonation[19]. Again, the emiacetal **13**, deriving from the isomeric hydrotrioxide **8** seems not to be formed, since the final formylderivative **14** was never found.

---

[19] Meth-Cohn, O., Kerr, G. H., Ozonation of tertiary aromatic amines, *J. Chem. Soc.* (c), 1369-74, (1971) (1971);


(8)
N
O
OH
H
(13)
O
CHO
NH
(14)
+ CH2O



The computational investigation of the reaction mechanism, summarized by the energy profile shown in Figure 1, explains the regioselectivity and the products distribution observed experimentally. In Table 3 are also reported energies and energy differences of all of the species considered.

A detailed study of the potential energy surface (PES) of the N-phenylmorpholine – O_3 supramolecular system lead to the characterization of three van der Waals complexes differing for the orientation of O_3 with respect to the substrate (**1a** – **1c**; see Figure 2). The most stable complex **1a** is about 7 kcal mol^{-1} lower in energy than the two separate reactants. In this complex the two terminal atoms of O_3 are roughly in the plane of the axial C-H bonds of the methylene groups in α to nitrogen (see Figure 2). The charge of O_3 in **1a** is equal to about -0.4 indicating a significant charge transfer from the substrate to O_3 in the van der Waals complex. Correspondingly, the O---H-C distances are as short as about 1.9 Å. It is worth noting that the complex with O_3 at the equivalent position with respect to the axial C-H bonds of the methylene groups in α to oxygen **1b** is more stable than separate reactants by only about 2 kcal mol^{-1}. In the third van der Waals complex **1c** O_3 is oriented along the principal axis of the N-phenylmorpholyne and is about 6 kcal mol^{-1} more stable than the separate reactants.

The reaction, starting from complexes **1a** and **1c**, can proceed along two different paths depending on the secondary carbon atom attacked by ozone, namely that in α to nitrogen or that in α to oxygen.

In both cases the formation of the hydrotrioxide intermediates **7** and **8** proceeds through a hydrogen abstraction mechanism followed by recombination of the ionic or radical pairs (see below). In spite of the many attempts made, we were not able to find a transition state for the concerted mechanism.

The transition state for the hydrogen abstraction in α to nitrogen **TS-N** is shown in Figure 2. In *vacuum*, the corresponding activation energy (E_a), calculated with respect to the separate reactants, is equal to 7.6 kcal mol^{-1} (12.9 kcal mol^{-1} when calculated with respect to the complex **1a**). The hydrogen abstraction in α to oxygen leads to the transition state **TS-O** (see Figure 2) which is 13.2 kcal mol^{-1} higher than the separate reactants (18.7 kcal mol^{-1} when calculated with respect to the complex **1a**); a value about 7 kcal mol^{-1} higher than that calculated for **TS-N**.

Notably, the activation energies for both **TS-N** and **TS-O** became significantly smaller when the reaction is carried out in dichloromethane or acetonitrile solutions. The reduction of the activation energies is also a function of the polarity of the solvent. In fact, for **TS-N**, E_a decreases from 7.6 kcal mol^{-1} in *vacuum* to 2.5 kcal mol^{-1} in dichloromethane, to a value as small as equal to 0.7 kcal mol^{-1} in acetonitrile. In the case of **TS-O** the reduction is parallel of that calculated for **TS-N**; E_a decreases from 13.2 kcal mol^{-1} in *vacuum* to 9.4 kcal mol^{-1} in dichloromethane, and to 8.0 kcal mol^{-1} in acetonitrile.

TS-N and **TS-O** can evolve through a homolytic bond dissociation to form a radical pair, or through a heterolytic bond dissociation to form an ionic pair. The homolytic H-abstraction in α to nitrogen and oxygen lead to the radical species **Rad-N** and **Rad-O** (see Figure 2), respectively, and $O_3H\cdot$. The **Rad-N** – $O_3H\cdot$ radical pair is slightly lower in energy than the separate reactants in *vacuum* (ΔE = -0.9 kcal mol^{-1}). The stability of this radical pair increases in the two solvents considered in this work (see Table 3 and Figure 1). It is worth noting than the **Rad-N** – $O_3H\cdot$ pair is significantly more stable in dichloromethane (ΔE = -6.3 kcal mol^{-1}) than in acetonitrile (ΔE = -2.1 kcal mol^{-1}).

In *vacuum* the **Rad-O** – $O_3H\cdot$ radical pair is less stable than separate reactants by about 6 kcal mol^{-1}. The formation of the **Rad-O** – $O_3H\cdot$ radical pair is therefore disfavored with respect to the formation of the **Rad-N** – $O_3H\cdot$ pair by about 7 kcal mol^{-1}. The effects of the solvents on the stability of the **Rad-O** – $O_3H\cdot$ pair is parallel to that discussed for the **Rad-N** – $O_3H\cdot$ pair; in dichloromethane the **Rad-O** – $O_3H\cdot$ pair is significantly more stable than in *vacuum* (ΔE = 0.0 kcal mol^{-1}) while in acetonitrile is only slightly more stable than in *vacuum* (ΔE = 4.5 kcal mol^{-1}).

The abstraction of the hydride ion from the methylenic group in α to nitrogen and oxygen leads to the formation of a ionic pair composed by the carbocations **Cat-N** and **Cat-O**, respectively (see Figure 2), and the hydrotrioxide anion O_3H^-. The formation of this ionic pair is clearly disfavored in *vacuum* by more than 100 kcal mol^{-1}. As expected, the presences of a polar solvent strongly stabilize the ionic pair. Indeed, the **Cat-N** – O_3H^- pair is more stable than the separate reactants by 5.4 and 15.1 kcal mol^{-1} in dichloromethane and acetonitrile, respectively (see Table 3 and Figure 1b). The effect of the solvents is similar for the **Cat-O** – O_3H^- pair, even though in the latter case the ionic pair remains less stable than separate reactants by 15.1 and 4.9 kcal mol^{-1} in dichloromethane and acetonitrile, respectively (see Table 3 and Figure 1b). These results also indicate that in the two solvents **Cat-N** is more stable than **Cat-O** by about 10 kcal mol^{-1}.

After the formation of the ionic or radical pairs, the terminal oxygen of the O_3H^- or $O_3H\cdot$ species can easily approach the unsaturated carbon atom forming a carbon-oxygen bond and leading to the hydrotrioxides intermediates **7**, or **8**. These intermediates have similar energies and are significantly more stable than separate reactants (in *vacuum* ΔE = 44.3 kcal mol^{-1} for **7** and -45.4 kcal mol^{-1} for **8**.

The formation of the hydrotrioxide intermediates (**7**, **8**) is the crucial step in order to explain the regioselectivity of the reaction. The results illustrated above clearly show that the methylene group in α to nitrogen is more reactive with ozone than that in α to oxygen, as the activation energy for the former process is significantly smaller than that for the latter. Also, the radical or ionic pair formed by the hydrogen abstraction in α to nitrogen is more stable than that formed by hydrogen abstraction in α to oxygen. In fact, in dichloromethane and acetonitrile, the radical or ionic pair given by the attack of ozone in α to nitrogen is always more stable than separate reactants, while the radical or ionic pair given by the attack of ozone in α to oxygen is less stable than separate reactants. The smaller activation energy and the higher stability of the ionic or radical pair as intermediates in the reaction make significantly more favorable the functionalization α to nitrogen and the formation of the hydrotrioxide **7**.

In acetonitrile the ionic pair is more stable than the radical pair by about 13 kcal mol^{-1} indicating that the hydrogen abstraction occurs through an ionic mechanism, as already observed for the ozonation of other substrates[9]. In dichloromethane the radical and ionic pair are almost isoenergetic, suggesting a competition between the ionic and radical mechanism.

A relevant result illustrated above is that the activation energy for the hydrogen abstraction process decreases by raising the polarity of the solvent. This would explain the higher rate of reaction observed experimentally in acetonitrile than in dichloromethane. This solvent polarity effect is synergic with the effect due to the higher solubility of ozone in acetonitrile discussed above. We suggest that both effects contribute to the different reaction rate observed in the two solvent.

Hydrotrioxides **7** or **8** could evolve to give the final products following three different pathways (Scheme 3). Calculations were also performed for these pathways in order to obtain the mechanisms which lead in the formation of the lactame **2**, and the emiaminal **10** as precursor of the diformylderivative **3**.

Dismutation of hydrotrioxides (**7-8**) via path (b) leads to the formation of an emiaminal **10** or an emiacetal **13** and O_2. These intermediates are energetically less stable than **7**, and **8** by about 6 and 5 kcal mol^{-1}, respectively. The activation energy of this reaction step is somewhat large; 46 and 45 kcal mol^{-1} for **TS-N-ALC** and **TS-O-ALC** with respect to the intermediates **7** and **8**. However, it should be noted that the emiaminal **10** could still react until a more stable product is formed, such as the dehydroderivate **4** which then gives the diformylderivative **3**.

The dissociation of hydrotrioxide **7** and **8** via path (a) leads to the formation of the lactame **2** and lactone **9**, respectively and hydrogen peroxide. The final products are significantly more stable than the separate reactants (about 100 kcal mol^{-1}) and the barrier that should be overcome is about 38 kcal mol-1 with respect to intermediates **7** and **8**. Even if very large, the energy of the transition state is negative if compared to the separate reactants. The excess energy gained from the system to form intermediates **7** and **8** can then be used to overcome the energy barrier.

In summary, the formation of the emiaminal **10** from hydrotrioxide **7** is an endothermic process, while the formation of the lactame **2** is a strongly exothermic process with an activation energy smaller than that calculated for the formation of **10**. However, as shown in Figure 1 the excess of energy provided by the formation of **7** is enough to overcome the energy barriers for the formation of both the lactame **2** and the emiaminal **10**, this results can account for a large formation of the emiaminal **10** even though it is significantly less stable than the lactame **2** and with an higher energy barrier.

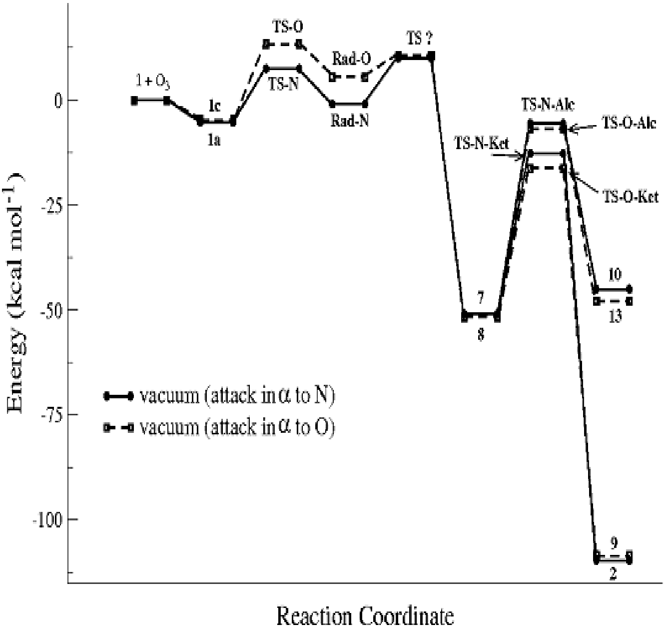


Figure 1. Energy diagram for the reaction of N-phenylmorpholine 1 with ozone calculated in *vacuum*.

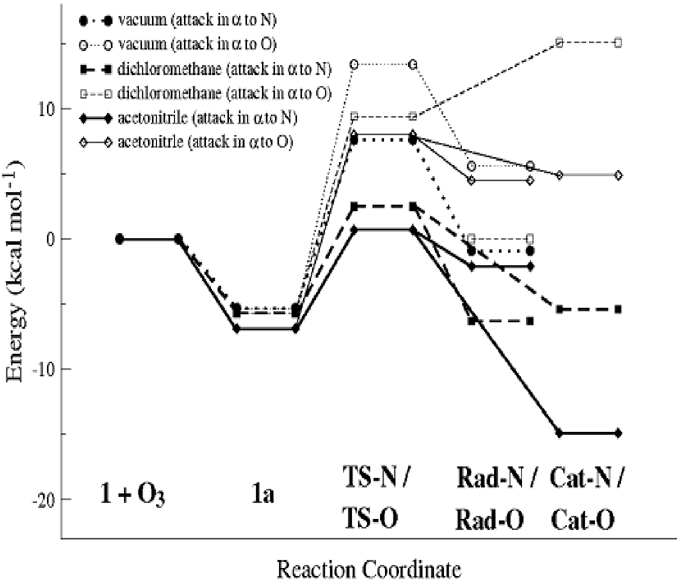


Figure 2. Energy diagram for the first step of the reaction of N-phenylmorpholine 1 with ozone calculated in *Vacuum* (—), dichloromethane (---), and acetonitrile (•••).

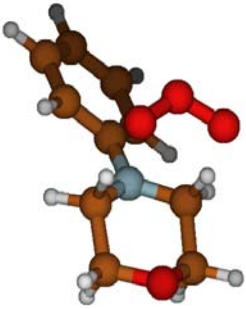
	Vacuum	CH_2Cl_2	CH_3CN
1 + O_3	-744.529356	-744.524501	-744.515195
1a	-744.537798	-744.533638	-744.526117
1b	-744.533298	-744.526254	-744.517835
1c	-744.5366842	-744.533636	-744.525067
TS-N	-744.517181	-744.520489	-744.514123
TS-O	-744.507943	-744.509504	-744.502466
Rad-N + O_3H	-744.530722	-744.534595	-744.518473
Rad-O + O_3H	-744.520355	-744.524452	-744.508044
Cat-N + O_3H^-	-744.373796	-744.533145	-744.538946
Cat-O + O_3H^-	-744.333227	-744.500463	-744.507351
7	-744.610575	–	-744.601174
8	-744.611791	–	-744.601819
TS-N-Alc	-744.538172	–	–
TS-O-Alc	-744.540183	–	–
10	-594.281794	–	–
13	-594.286521	–	–
O_2	-150.319228	–	–
TS-N-Ket	-744.549621	–	–
TS-O-Ket	-744.555237	–	–
2	-593.092427	–	–
9	-593.090627	–	–

Table 3. Energies (in Hartree)

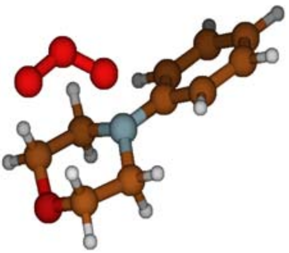
	Vacuum	CH_2Cl_2	CH_3CN
1 + O_3 → 1a	-5.3	-5.7	-6.9
1 + O_3 → 1b	-2.5	-1.1	1.7
1 + O_3 → 1c	-4.6	-5.7	-6.2
1 + O_3 → TS-N	7.6	2.5	0.7
1 + O_3 → TS-O	13.4	9.4	8.0
1 + O_3 → Rad-N	-0.9	-6.3	-2.1
1 + O_3 → Rad-O	5.6	0.0	4.5
1 + O_3 → Cat-N	97.6	-5.4	-14.9
1 + O_3 → Cat-O	123.1	15.1	4.9
1 + O_3 → 7	-51.0	–	–
1 + O_3 → 8	-51.7	–	–
1 + O_3 → TS-N-Alc	-5.5	–	–
1 + O_3 → TS-O-Alc	-6.8	–	–
1 + O_3 → 10	-45.0	–	–
1 + O_3 → 13	-47.9	–	–
1 + O_3 → TS-N-Ket	-12.7	–	–
1 + O_3 → TS-O-Ket	-16.2	–	–
1 + O_3 → 2	-109.7	–	–
1 + O_3 → 9	-108.5	–	–

Table 4. Energy differences (in kcal mol^{-1})

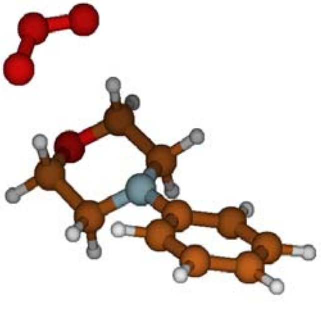
Molecular structures of all of the compounds investigated, calculated using the B3LYP/def-TZVP scheme



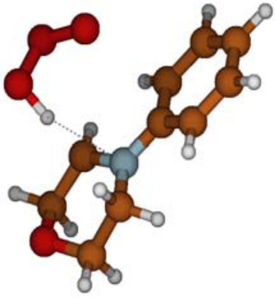
1a



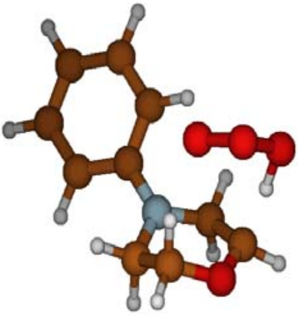
1c



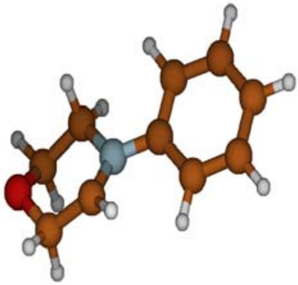
1b



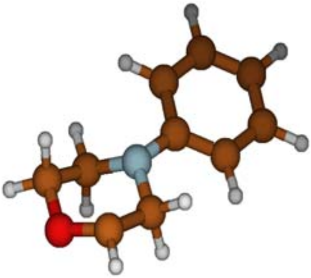
TS-N



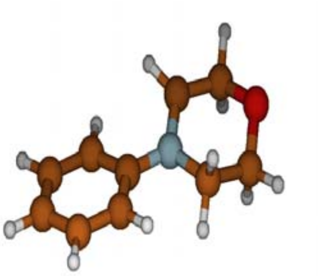
TS-O



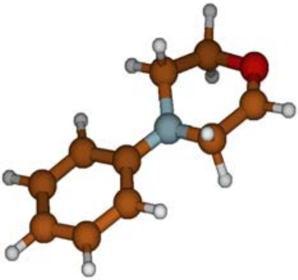
Rad-N



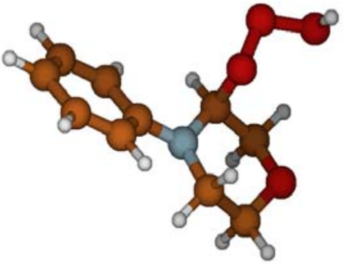
Rad-O



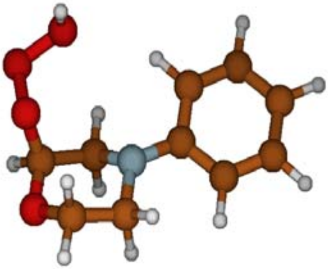
Cat-N



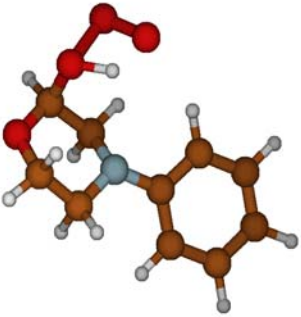
Cat-O



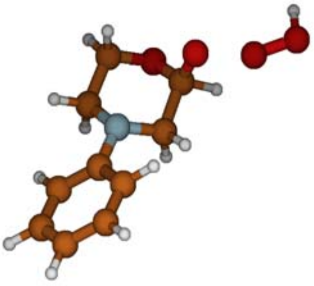
7



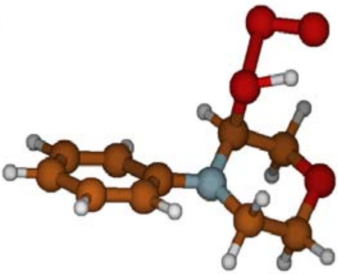
8



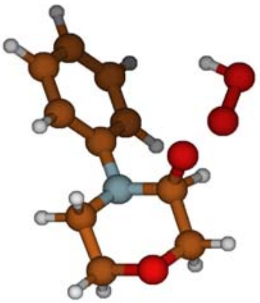
TS-N-Alc



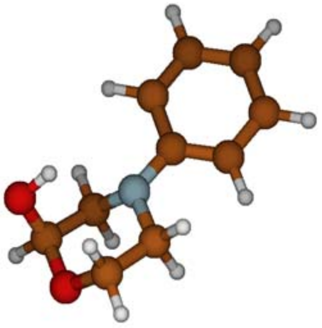
TS-N-Ket



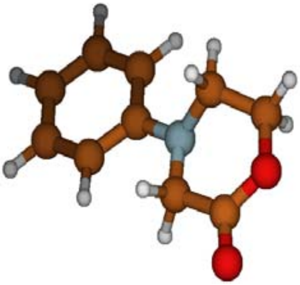
TS-O-Alc



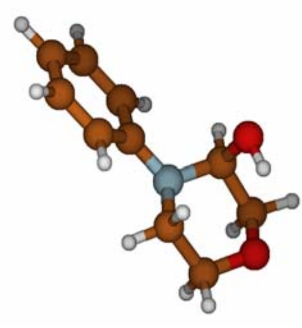
TS-O-Ket



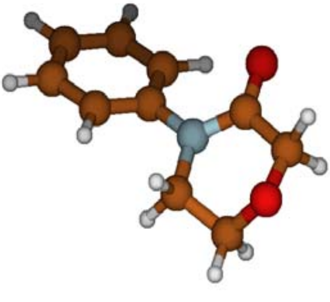
13



9



10



2

2.5. Metal free oxidations: the ozonation of cyclohexane. A mechanistic approach

2.5.1. Introduction

From ethylene, ethylene oxide is produced with the catalysis of Ag, acetaldehyde with the catalysis of Cu and Pd, aldehydes with carbon monoxide and the catalysis of Co. From propylene, acrolein is produced with the catalysis of Cu and Si. Aromatics are produced from reforming with the catalysis of Pt and Re. From benzene or naphthalene, maleic anhydride or phthalic anhydride are produced with the catalysis of V[1]. Recycle or disposal of the spent metal catalyst is a major problem in these cases[2].

The selective oxidation of alkanes is particularly difficult[3]. Co is used as the catalyst for the oxidation of cyclohexane to cyclohexanone

---

[1] Weissermel, Arpe, H. J., *Industrial Organic Chemistry,* (VCH, Weinheimn, 1993);

[2] Matlack, A.S., *Introduction to Green Chemistry*, (Markel Dekker, New York, Basel, 2001);

[3] Kochi, J., Sheldon, R., *Metal Catalysed Oxidations of Organic Compounds* (New York, Academic Press,.1981);

and cyclohexanol with dioxygen. Metal centered systems which mimic monooxygenases such as cytochrome P-450 and methanemonoxygenase mimics are also used[4].

Metal free alternatives use dioxiranes as oxidising agents[5], the oxidation of alkanes in superacidic media[6], ozone[7].

---

[4] Arends, I.W.C.E., Mac Faul, P.A., Snelgrove, D.W., Wayer D.D.M, Ingold K.U. in Minisci, F. ed. *Free Radicals in Biology and Environment* (New York, Kluver Academic Publishers, 1997) p.79-90;

[5] Reiser, O., "Oxidation of Weakly Activated C-H Bonds", Angew. Chem. Int. Ed., 33,_69-72 (1994); Minisci, F., Zhao, L.H., Fontana, F., Bravo, A."Free-radicals in the oxidation and halogenation of alkanes by dimethyldioxirane: An oxygen rebound mechanism", Tetrahedron Lett, 1697-1700 (1995); Bravo, A., Fontana, F., Fronza, G., Mele, A., Minisci, F., "Induced homolysis of dimethyldioxirane by alkanes and alkyl radicals in oxidation processes. The dramatic role of molecular oxygen and radical inhibitors", J. Chem. Soc. Chem. Commun., 1573-1574 (1995); Vanni, R., Garden, S.J., Banks, J. T., Ingold, K.U., "Mechanism of hydroxylation of alkanes by dimethyldioxirane. A radical-clock study", Tetrahedron Letters, 7999-8002 (1995); Asensio, G., Mello, R., Gonzalez Nunez, M.E., Boix, C., Royo, C.J., "The oxidation of alkanes with dimethyldioxirane; A new mechanistic insight",

---

Ozone has been used in the iron porphyrin-catalyzed oxygenation of alkanes[8]. Moreover, the ozonation of cyclodecane gives cyclodecanone in organic solvents[9], of ethers in acidic buffer forms

---

Tetrahedron Letters, 2373-2376 (1997); Adam,W., Curci, R., D'Accolti, L., Dinoi, A., Fusco, C., Gasparrini, C., Kluge, R., Paredes, R., Schulz, M., Smerz, A.K., Veloza, L. A., Weinkotz, S., Winde, R., "Epoxidation and oxygen insertion into alkane CH bonds by dioxirane do not involve detectable radical pathways", Chemistry - A European Journal, 3, 105-109 (1997);

[6] Jacquesy, J. C., Jouannetaud, M. P., Martin, A., "Functionalisation of nonactivated bonds in superacidic media", Bulletin de la Societe Chimique de France, 134, 425-438 (1997);

[7] Bailey, P.S., *Ozonation in Organic Chemistry*, (New York, Academic Press, 1981,) p. 255;

[8] Gross, Z., Simkhovich, L., "Ozone as primary oxidant in iron(III) porphyrin catalyzed hydroxylation of hydrocarbons", Journal of Molecular Catalysis -A - Chemical -, 117, 243-248, (1997);

[9] Rindone, B., Saliu, F., Suarez Bertoa, R., Functionalization of the unactivated carbon-hydrogen bond via ozonation, Ozone Science & Engineering, 30, 165-171, (2008);

esters[10], and the ozonation of amines forms amides and N-dealkylation products[11].

The formation of hydrotrioxides in the reactions of acetals with ozone has been reviewed[12].

---

[10] Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., "Reactivity of two models of non ionic surfactants with ozone", Water Research, 31, 1839-1846 (1997);

[11] Brambilla, A., Rindone, B., Polesello, S., Galassi, S., Balestrini, R., "The fate of triazine pesticides in river Po water", The Science of the Total Environment, 132, 339-348 (1993); Bolzacchini, E., Brambilla, A., Orlandi, M., Polesello, S., Rindone, B., "Oxidative Pathways in the degradation of triazine herbicides: A mechanistic approach", Wa. Sci. Tech., 30, 129-136 (1994); Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., ", Reactivity of organic micropollutants with ozone: a kinetic study", Life Chemistry Reports, 13, 79-84, (1995);

[12] Houben Weyl, *Methoden der Organische Chemie* Vol E13, (Stuttgart, New York, George Thieme Verlag 1988) p. 1118; Plesnicar, B., Cerkovnik, J., Tekavec, T., Koller, J., Chem. Eur. J., 6, 809-819, (2000); Plesnicar, B., Cerkovnik, Tuttle, T., Kraka, E., Cremer, D., J. Amer. Chem. Soc., 124, 11260-11261, (2002); Wu, A., Cremer, D., Plesnicar, B., J. Amer. Chem. Soc., 125, 9395-

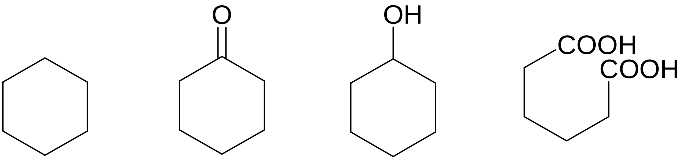
Here we report the functionalization of the unactivated carbon-hydrogen bond of cyclohexane, cis- and trans-decalin with ozone to give oxygenated products. The aim is to get a better understanding of the parameters to be set up in order to improve conversion and selectivity in ozonation of alkanes.

2.5.2. *Discussion*

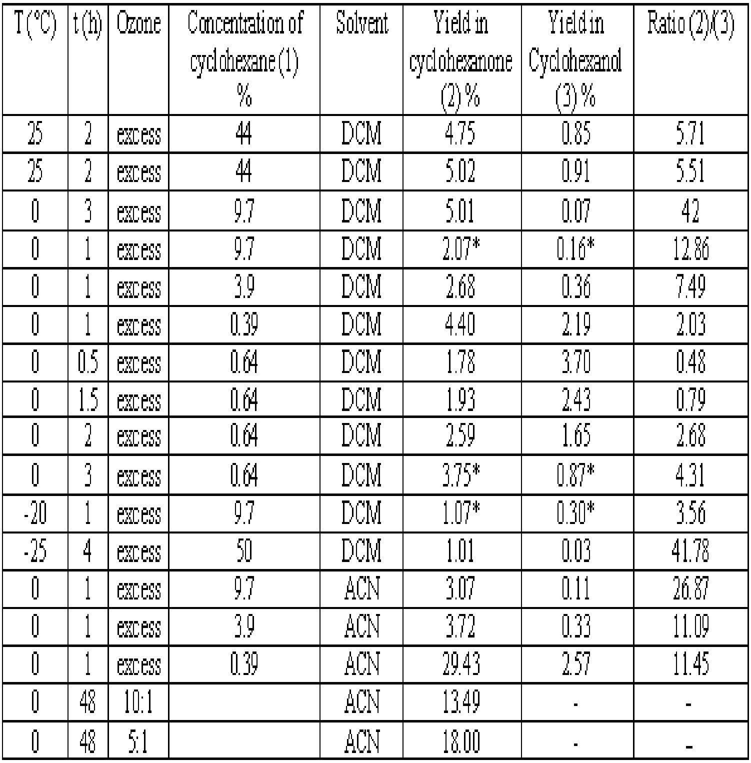
Cyclohexane **1** was oxidized by bubbling ozone at 25 °C, 0 °C, -20 °C or -25 °C in 10 mL of a solution of cyclohexane 1 in dichloromethane (DCM) or acetonitrile (AN) for a period ranging from 0.5 to 4 h. The amount of cyclohexanone **2** and cyclohexanol 3 (Scheme 1) formed was evaluated by comparison of the GLC trace of the reaction mixture added of a known amount of n-decane with that of a mixture of known amounts of n-decane and cyclohexanone **2** or cyclohexanol **3** (double standard method). Some of these results were validated by ^{1}H NMR (Table 1).

9402, (2003); Tuttle, T., Cremer, D., Plesnicar, B., Cerkovnik, J. Amer. Chem. Soc., 126, 16093-16104, (2004);

Scheme 1



(1) (2) (3) (4)



T (°C)	t (h)	Ozone	Concentration of cyclohexane (1) %	Solvent	Yield in cyclohexanone (2) %	Yield in Cyclohexanol (3) %	Ratio (2)/(3)
25	2	excess	44	DCM	4.75	0.85	5.71
25	2	excess	44	DCM	5.02	0.91	5.51
0	3	excess	9.7	DCM	5.01	0.07	42
0	1	excess	9.7	DCM	2.07*	0.16*	12.86
0	1	excess	3.9	DCM	2.68	0.36	7.49
0	1	excess	0.39	DCM	4.40	2.19	2.03
0	0.5	excess	0.64	DCM	1.78	3.70	0.48
0	1.5	excess	0.64	DCM	1.93	2.43	0.79
0	2	excess	0.64	DCM	2.59	1.65	2.68
0	3	excess	0.64	DCM	3.75*	0.87*	4.31
-20	1	excess	9.7	DCM	1.07*	0.30*	3.56
-25	4	excess	50	DCM	1.01	0.03	41.78
0	1	excess	9.7	ACN	3.07	0.11	26.87
0	1	excess	3.9	ACN	3.72	0.33	11.09
0	1	excess	0.39	ACN	29.43	2.57	11.45
0	48	10:1		ACN	13.49	-	-
0	48	5:1		ACN	18.00	-	-

Table 1. Reactivity of cyclohexane (1) with ozone (DCM = dichloromethane; ACN = acetonitrile). *result validated by ^{1}H NMR.

The selectivity in cyclohexanone **2** and cyclohexanol **3** as a function of time was studied at 0 °C starting from cyclohexane 0.64% v/v in dichloromethane. The longer is the reaction time, the higher is the yield in cyclohexanone **2**. On the contrary, the amount of cyclohexanol **3** decreases with time (Figure 1). This behaviour should be due to the major reactivity of cyclohexanol **3** with the oxidants in solution, e.g. ozone, hydrogen peroxide, dioxygen, with respect to cyclohexanone **2**. One of the products of further oxidation is adicpic acid **4**, which, indeed, has been observed as reaction product.

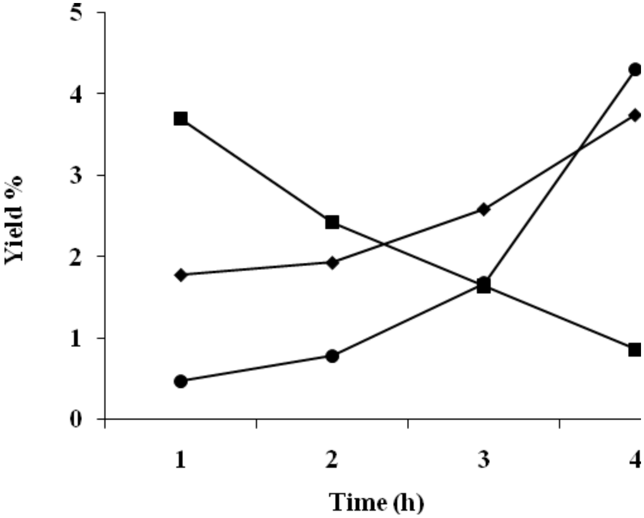


Figure 1: Product yields vs time in the ozonation at 0 °C of cyclohexane 1, 0.64 % in dichloromethane. ♦ Cyclohexanone 2; ■

Cyclohexanol 3; ● 2/3 ratio.

The influence of the concentration of cyclohexane on the distribution of reaction products has been investigated for both solvents, at 0 °C and a time of 1 h. Figures 2 and 3 illustrate this influence in dichloromethane and acetonitrile, respectively. The highest yield in cycloxehanone **2** occurs when the reaction is carried out in acetonitrile with an initial concentration of 0.39% v/v of cyclohexane **1**.

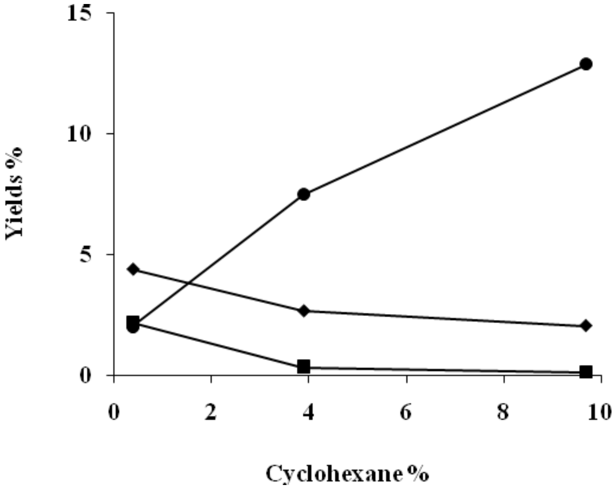


Figure 2. The influence of the concentration of cyclohexane 1 in dichloromethane on the distribution of reaction products in a reaction at

0 °C for 1 h. ♦ Cyclohexanone 2; ■ Cyclohexanol 3; ● 2/3 ratio.

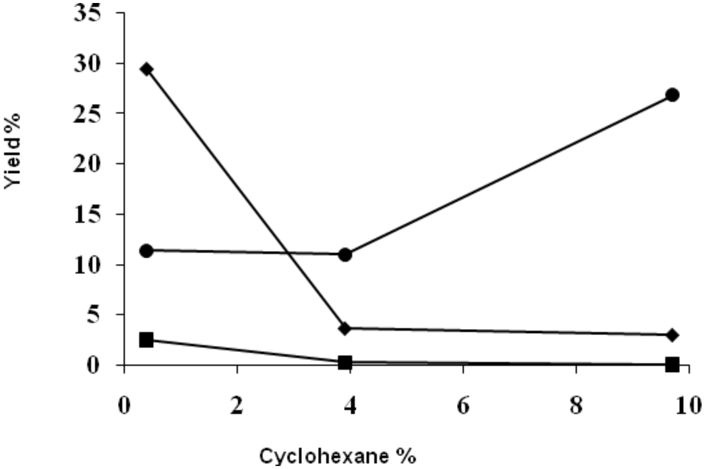


Figure 3. The influence of the concentration of cyclohexane 1 in acetonitrile on the distribution of reaction products in a reaction at 0 °C for 1 h. ♦ Cyclohexanone 2; ■ Cyclohexanol 3; ● 2/3 ratio.

In order to minimize the further oxidation of primary reaction products, the reaction was carried out in acetonitrile using a controlled amount of ozone. A good yield in cyclohexanone **2** was thus obtained at 0 °C after 48 h reaction. In these conditions cyclohexanol **3** was not observed among the reaction products.

In summary the results shown above suggest that:

1. Cyclohexanone **2** and cyclohexanol **3** are formed in two independent pathways, but are further oxidised to ring-opening products.
2. Cyclohexanol **3** is more reactive than cyclohexanone **2** toward further oxidation.
3. Ozonation of cyclohexane **1** gives higher yields of primary products when carried out in acetonitrile than in dichloromethane.
4. The concentration of cyclohexane **1** must be kept as low as possible, in order to maximize the yield in cyclohexanone **2**.
5. Limitation in the amount of ozone in the reaction results in higher yields in cyclohexanone **2**; cyclohexanol **3** was not found in these conditions.

2.5.3. *The proposed reaction mechanism*

A plausible reaction mechanism for the ozonation of cyclohexane is reported in Scheme 2. Hydrogen or hydride transfer from a methylenic carbon[13] leads to the formation of the hydrotrioxide

---

[13] Houben Weyl, *Methoden der Organische Chemie* Vol E13, (Stuttgart, New York, George Thieme Verlag, 1988) p. 1118; Avzyanova, E. V., Timerghazin, Q. K., Khalizov, A. F., Khursan, S. L., Spirikhin, L. V., Shereshovets, V. V., Formation of hydrotrioxides during ozonation of hydrocarbons on silica gel. Decomposition of hydrotrioxides J. Phys. Org. Chem. 13, 87–96, (2000); Plesnicar, B., Cerkovnik, J., Tekavec, T., Koller, J., ^{17}O NMR Spectrospic Characterization and the Mechanism of Formation of Alkyl Hydrotrioxides (ROOOH) and Hydrogen Trioxide (HOOOH) in the Low-Temperatures Ozonation of Isopropyl Alcohol and Isopropyl Methyl Ether: Water-Assisted Decomposition. Chem. Eur. J., 6, 809-819, (2000); Plesnicar, B., Cerkovnik, Tuttle, T., Kraka, E., Cremer, D., Evidence for the HOOO- anion in the ozonation of 1,3-dioxolanes: Hemiortho esters as the primary products. J. Amer. Chem. Soc., 124, 11260-11261, (2002); Wu, A., Cremer, D., Plesnicar, B., The Role of the $HOOO^-$ Anion in the Ozonation of Alcohols: Large Differences in the Gas-Phase and the Solution-Phase Mechanism. J. Amer. Chem. Soc.,

intermediate **5**. This mechanistic scheme has been suggested to account for the oxygenation of cycloalkanes to cycloalkanones[14], ether to esters[15] and for the oxygenation of amines to amides[16].

125, 9395-9402, (2003); Tuttle, T., Cremer, D., Plesnicar, B., Cerkovnik, Hemiortho Esters and Hydrotrioxides as the Pimary Products in the Low-Temperature Ozonation of Cyclic Acetals: An Experimental and Theoretical Investigation. J. Amer. Chem. Soc., 126, 16093-16104 (2004).

[14] Rindone, B., Saliu, F., Suarez Bertoa, R., Functionalization of the unactivated carbon-hydrogen bond via ozonation, Ozone Science & Engineering, 30, 165-171, (2008);

[15] Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., Reactivity of two models of non ionic surfactants with ozone, Water Research, 31, 1839-1846 (1997);

[16] Brambilla, A., Rindone, B., Polesello, S., Galassi, S., Balestrini, R., The fate of triazine pesticides in river Po water, The Science of the Total Environment, 132, 339-348 (1993); Bolzacchini, E., Brambilla, A., Orlandi, M., Polesello, S., Rindone, B., Oxidative Pathways in the degradation of triazine herbicides: A mechanistic approach, Wa. Sci. Tech., 30, 129-136 (1994); Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone,

The hydrotrioxide intermediate **5** may further evolve following three pathways (Scheme 2):

4) Dissociation to a carbonyl compound and hydrogen peroxide (path a)

5) Dismutation to an alcohol and dioxygen (path b).

6) Rearrangement to an aldehyde and a hydroperoxide with further oxidation to carboxylic acids (path c).

In order to get a better understanding of the mechanistic details and products distribution, the reaction mechanism was studied computationally, by DFT methods, through the identification if the relevant stationary points (minima and saddle points) along the reaction coordinate. Calculations were performed in *vacuum*, as well as in dichloromethane and acetonitrile, as reported in the computational methods section. The energy profile calculated for the ozonation reaction is illustrated in Figure 4, while the optimized structures of the investigated compounds are shown in Figures 5 and 6

B., Reactivity of organic micropollutants with ozone: a kinetic study, Life Chemistry Reports, 13, 79-84, (1995);

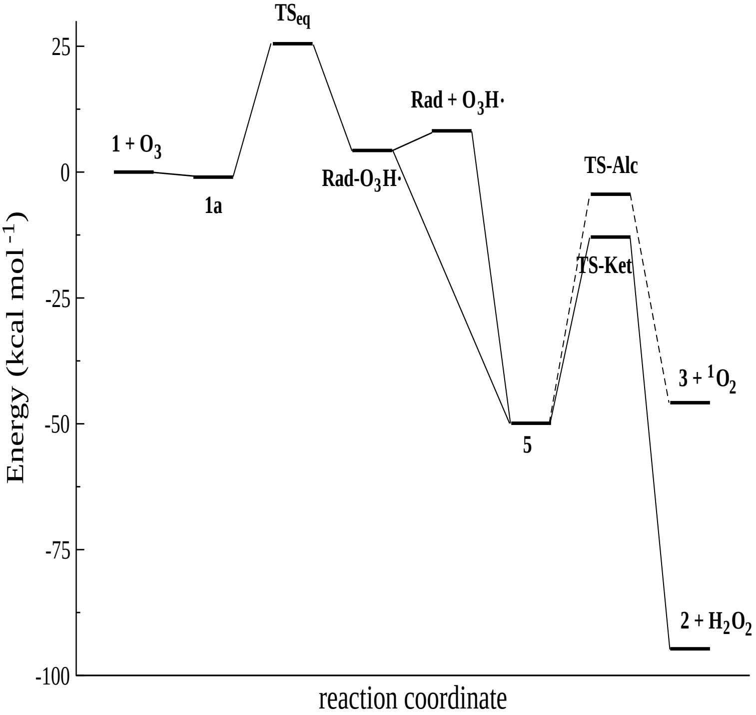


Figure 4. Energy diagram for the reaction of cyclohexane 1 with ozone calculated in *vacuum*.

Cyclohexane (**1**) in *vacuum* forms with ozone the van der Waals complex **1a** (see Figure 5) with an interaction energy of about 1 kcal mol^{-1}. The interaction energy is even positive (1 kcal mol^{-1}) in dichloromethane, indicating that the van der Waals complex is not stable in this solvent, and it is about -3 kcal mol^{-1} in acetonitrile. Two transition states, **TS$_{eq}$** and **TS$_{ax}$** (Figure 6), have been located for the abstraction of a methylenic hydrogen atom and the formation of the hydrotrioxide intermediate (**5**). As shown in Figure 6, the two TSs correspond to the abstraction of the equatorial ($\mathbf{TS_{eq}}$), and axial hydrogen ($\mathbf{TS_{ax}}$) atoms, and, as shown in Table 2 the calculated activation energies are very similar (within 2 kcal mol^{-1}). The activation energy calculated in *vacuum* is equal to about 26 kcal mol^{-1} (26.2 and 25.5 for $\mathbf{TS_{ax}}$ and $\mathbf{TS_{eq}}$, respectively). Notably, the activation energy decreases by about 7 kcal mol^{-1} (for $\mathbf{TS_{ax}}$) in dichloromethane, and by further 2 kcal mol^{-1} in acetonitrile, thus indicating an effect of the solvent on the rate of this process.

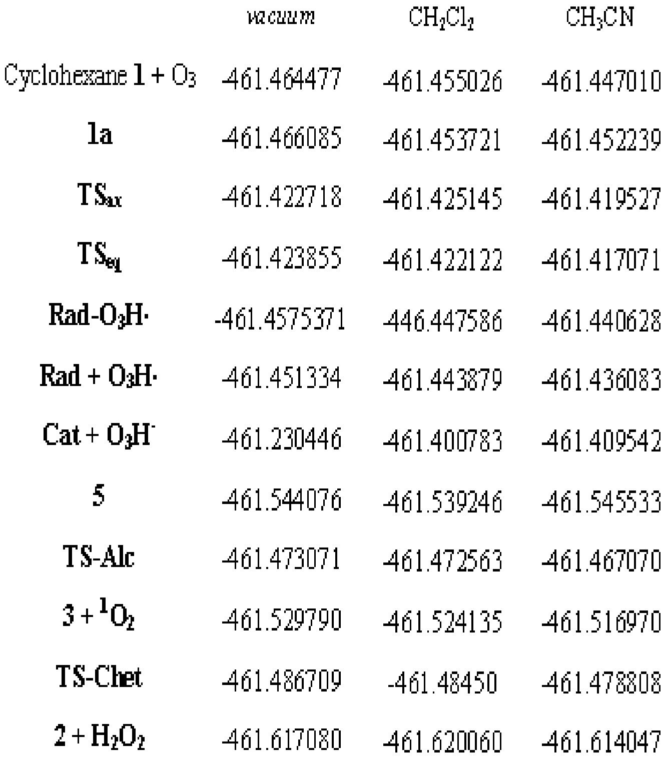
In *vacuum*, at the TS, the hydrogen atom is at a distance of about 1.1 and 1.6 Å from the oxygen and carbon atoms, respectively. The other terminal oxygen of ozone is at 2.9-3.0 Å from the carbon atom involved in the abstraction of hydrogen, a distance for which is difficult to discriminate between a hydrogen abstraction mechanism, with the formation of a radical or ionic pair, or a concerted mechanism, in which the formation of C-O bond occurs simultaneously to the transfer of the hydrogen atom[17]. When the calculation is performed in dichloromethane or acetonitrile, the C-O

---

[17] Giamalva, D.H., Church, D.F., Pryor, W.A., Kinetics of ozonation. 5 Reaction of ozone with carbon-hydrogen bonds, J. Am. Chem. Soc., 108, 7678-7681 (1981);

distance at the TS increases up to about 3.5-3.6 Å, values more consistent with a hydrogen abstraction mechanism (see Figure 6). The occurrence of the hydrogen abstraction mechanism is also supported by the location of a stable interacting radical pair (**Rad-O_3H·**) by a geometry optimization on a minimum of the PES, starting from the TS. This interacting radical pair is about 4 kcal mol^{-1} less stable than the separate reactants and is only little affected by the presence of the solvent (see Table 2). It should be noted that such a calculation has been performed using the unrestricted broken symmetry approximation (BS), namely by localizing the two unpaired electrons on different sites in a singlet arrangement. As it is known, the BS wavefunction is not a pure spin state – it is a mix of a singlet and triplet state – and the corresponding energy should be considered as an upper limit to the energy of a pure spin state. The energy for the dissociation of the interacting radical pair to give separate radicals (**Rad + O_3H·**) is equal to about 2-4 kcal mol^{-1}. Thus, the separate radical pair is about 6-8 kcal mol^{-1} less stable than separate reactants.

Table 2. Energies (in Hartree) and relevant energy differences (in kcal mol^{-1}) of the compounds investigated in this work computed using the B3LYP/cc-pVTZ computational scheme



	vacuum	CH_2Cl_2	CH_3CN
Cyclohexane **1** + O_3	-461.464477	-461.455026	-461.447010
1a	-461.466085	-461.453721	-461.452239
TS_{ax}	-461.422718	-461.425145	-461.419527
TS_{eq}	-461.423855	-461.422122	-461.417071
Rad-$O_3H\cdot$	-461.4575371	-446.447586	-461.440628
Rad + $O_3H\cdot$	-461.451334	-461.443879	-461.436083
Cat + O_3H^-	-461.230446	-461.400783	-461.409542
5	-461.544076	-461.539246	-461.545533
TS-Alc	-461.473071	-461.472563	-461.467070
3 + $^1O_2$	-461.529790	-461.524135	-461.516970
TS-Chet	-461.486709	-461.48450	-461.478808
2 + H_2O_2	-461.617080	-461.620060	-461.614047

	vacuum	CH_2Cl_2	CH_3CN
$1 + O_3 \rightarrow$ 1a	-1.0	0.8	-3.2
$1 + O_3 \rightarrow TS_{ax}$	26.2	18.8	17.2
$1 + O_3 \rightarrow TS_{eq}$	25.5	20.6	18.8
$1 + O_3 \rightarrow$ Cat + O_3H^-	147.9	33.2	26.8
$1 + O_3 \rightarrow$ Rad-$O_3H\cdot$	4.3	4.7	4.0
$1 + O_3 \rightarrow$ Rad + $O_3H\cdot$	8.2	7.0	6.9
$1 + O_3 \rightarrow 5$	-49.9	-53.7	-58.5
$1 + O_3 \rightarrow$ TS-Alc	-4.4	-11.8	-9.3
$5 \rightarrow$ TS-Alc	44.6	41.8	49.2
$1 + O_3 \rightarrow 3 + {}^1O_2$	-40.0	-44.2	-40.6
$5 \rightarrow 3 + {}^1O_2$	9.0	9.5	17.9
$1 + O_3 \rightarrow$ TS-Chet	-12.9	-19.3	-16.7
$5 \rightarrow$ TS-Chet	36.0	34.4	41.9
$1 + O_3 \rightarrow 2 + H_2O_2$	-94.7	-104.4	-101.5
$5 \rightarrow 2 + H_2O_2$	-45.8	-50.7	-43.0

The formation of an ionic pair (**Cat-O_3H-**) from the abstraction of an hydride ion has also been considered. In this case, however, the energy of the ionic pair is exceedingly high, not only, as expected, in *vacuum*, but also in dichloromethane and acetonitrile where it is less stable than separate reactants by 33, and 27 kcal mol^{-1}, respectively (see Table 2). Therefore, from the results discussed above, we can conclude that the reaction should proceed with the formation of a radical pair followed by the C-O bond formation which yields **5**.

The hydrotrioxide **5** was found to be significantly more stable than reactants in *vacuum*, as well as in the two media (-50 kcal mol^{-1} in *vacuum*, -54 kcal mol^{-1} in dichloromethane and -59 kcal mol^{-1} in acetonitrile).

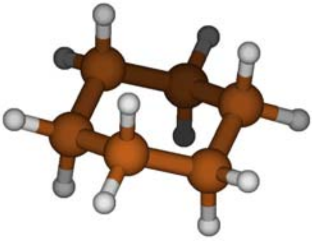
The decomposition of hydrotrioxide **5** via (path a) leads to the formation of cyclohexanone **2** and hydrogen peroxide which are the most stable products formed in this reaction, (ΔE = -95, -104, -101 kcal mol^{-1} in *vacuum*, dichloromethane, and acetonitrile, respectively; see Table 2). However the calculated activation energy of this process is as large as about 35 kcal mol^{-1} (**TS-Ket**, see Table 2 and Figure 4)

Dismutation via pathway (b) leads to the formation of a cyclohexanol **3** and $^1O_2$ [21]. O_2 as product of this reaction is in the singlet state in order to preserve spin angular moment. This products, in *vacuum* as well as in solution, are energetically less stable than the hydrotrioxide intermediate **5** by about 10 kcal mol^{-1}, thus, more than

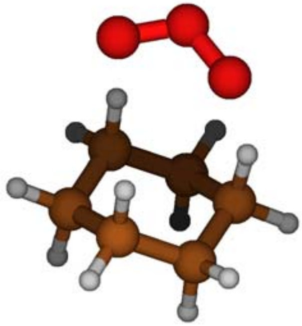
55 kcal mol^{-1} less stable than the products of path a. The activation energy of the **5** → **3** + O_2 process is also higher than that calculated for path a by about 9 kcal mol^{-1} (**TS-Alc**, see Table 2 and Figure 4). Although the large activation energies calculated for the formation of both cyclohexanone **2** and cyclohexanol **3**, the energy excess provided by the formation of the hydrotrioxide intermediate **5** should be sufficient to surmount the barriers. In fact, both **TS-Ket** and **TS-Alc** are lower in energy with respect to the separate reactants (see Figure 4). On the other hand, the smaller activation energy calculated for path a, as well as the significantly larger stability of the products explain the higher yield in cyclohexanone **2** compared to the cyclohexanol **3**.

In conclusion, the ozonation of cyclohexane is a mild and selective metal-free method for the preparation of cyclohexanone and cyclohexanol. This procedure is in the line of sustainability in chemical reactions which is one of the major goals in "green chemistry".

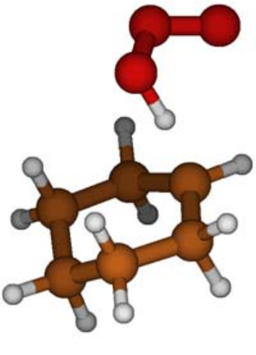
Figure 5. Molecular structures of the investigated compounds calculated using the B3LYP/cc-pVTZ scheme.



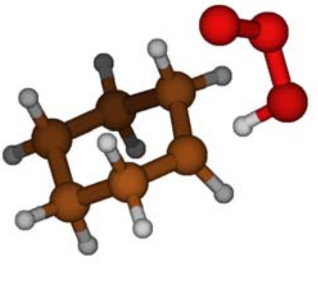
1



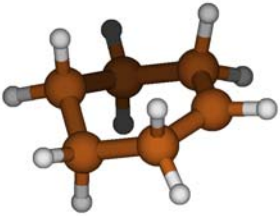
1a



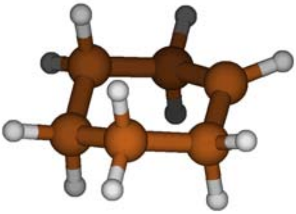
TS$_{ax}$



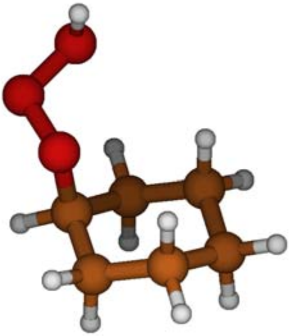
TS$_{eq}$



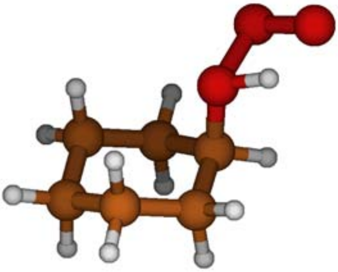
Rad



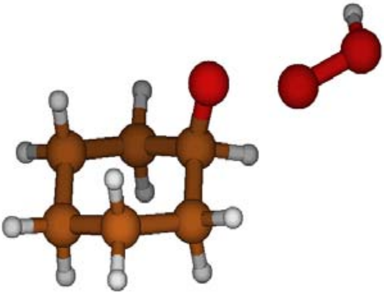
Cat



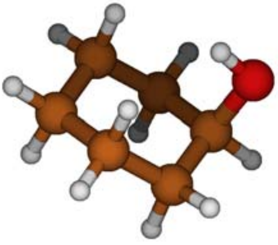
5



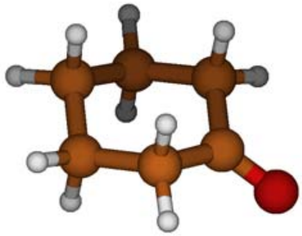
TS-Ket



TS-Alc

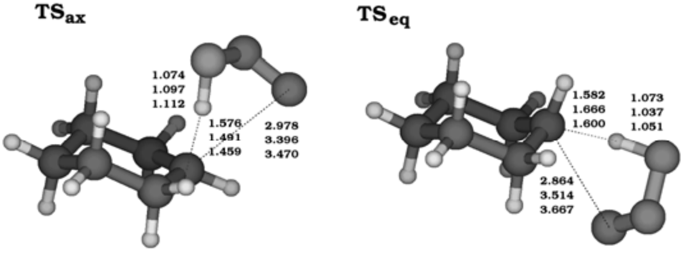


3



2

Figure 6. Geometries of the transition states TS_{eq} and TS_{ax} calculated using the B3LYP/ cc-pVTZ scheme. Distances (in Å) from top to bottom, refer to the optimized structures in *vacuum*, dichloromethane, and acetonitrile, respectively.



2.6. Metal free oxidations: the ozonation of cis- and trans-decalin. a mechanistic approach

2.6.1. Introduction

From ethylene, ethylene oxide is produced with the catalysis of Ag, acetaldehyde with the catalysis of Cu and Pd, aldehydes with carbon monoxide and the catalysis of Co. From propylene, acrolein is produced with the catalysis of Cu and Si. Aromatics are produced from reforming with the catalysis of Pt and Re. From benzene or naphthalene, maleic anhydride or phthalic anhydride are produced with the catalysis of V[1]. Recycle or disposal of the spent metal catalyst is a major problem in these cases[2].

The selective oxidation of alkanes is particularly difficult[3]. Co is used as the catalyst for the oxidation of cyclohexane to cyclohexanone

---

[1] Weissermel, Arpe, H. J., *Industrial Organic Chemistry,* (VCH, Weinheimn, 1993).

[2] Matlack, A.S., *Introduction to Green Chemistry*, (Markel Dekker, New York, Basel, 2001)

[3] Kochi, J., Sheldon, R., *Metal Catalysed Oxidations of Organic Compounds* (New York, Academic Press,.1981);

and cyclohexanol with dioxygen[4] Metal centered systems which mimic monooxygenases such as cytochrome P-450 and methanemonoxygenase mimics are also used[5].

Metal free alternatives use dioxiranes as oxidising agents[6], the oxidation of alkanes in superacidic media[7], ozone[8].

---

[4] Cicloesano

[5] Arends, I.W.C.E., Mac Faul, P.A., Snelgrove, D.W., Wayer D.D.M, Ingold K.U. in Minisci, F. ed. *Free Radicals in Biology and Environment* (New York, Kluver Academic Publishers, 1997) p.79-90;

[6] Reiser, O., “Oxidation of Weakly Activated C-H Bonds”, Angew. Chem. Int. Ed., 33,_69-72 (1994); Minisci, F., Zhao, L.H., Fontana, F., Bravo, A.“Free-radicals in the oxidation and halogenation of alkanes by dimethyldioxirane: An oxygen rebound mechanism”, Tetrahedron Lett, 1697-1700 (1995); Bravo, A., Fontana, F., Fronza, G., Mele, A., Minisci, F., “Induced homolysis of dimethyldioxirane by alkanes and alkyl radicals in oxidation processes. The dramatic role of molecular oxygen and radical inhibitors”, J. Chem. Soc. Chem. Commun., 1573-1574 (1995); Vanni, R., Garden, S.J., Banks, J. T., Ingold, K.U., “Mechanism of hydroxylation of alkanes by dimethyldioxirane. A radical-clock study”, Tetrahedron Letters, 7999-8002 (1995); Asensio, G., Mello, R., Gonzalez Nunez, M.E., Boix, C., Royo, C.J., “The oxidation of

---

Ozone has been used in the iron porphyrin-catalyzed oxygenation of alkanes[9]. Moreover, the ozonation of cyclodecane to cyclodecanone

---

alkanes with dimethyldioxirane; A new mechanistic insight", Tetrahedron Letters, 2373-2376 (1997); Adam,W., Curci, R., D'Accolti, L., Dinoi, A., Fusco, C., Gasparrini, C., Kluge, R., Paredes, R., Schulz, M., Smerz, A.K., Veloza, L. A., Weinkotz, S., Winde, R., "Epoxidation and oxygen insertion into alkane CH bonds by dioxirane do not involve detectable radical pathways", Chemistry - A European Journal, 3, 105-109 (1997);

[7] Jacquesy, J. C., Jouannetaud, M. P., Martin, A., "Functionalisation of nonactivated bonds in superacidic media", Bulletin de la Societe Chimique de France, 134, 425-438 (1997);

[8] Bailey, P.S., *Ozonation in Organic Chemistry*, (New York, Academic Press, 1981,) p. 255;

[9] Gross, Z., Simkhovich, L., "Ozone as primary oxidant in iron(III) porphyrin catalyzed hydroxylation of hydrocarbons", Journal of Molecular Catalysis -A - Chemical -, 117, 243-248, (1997);

in organic solvents[10], of ethers in acidic buffer forms esters[11], and the ozonation of amines forms amides and N-dealkylation products[12].

The formation of hydrotrioxides in the reactions of acetals with ozone has been reviewed[13].

---

[10] Rindone, B., Saliu, F., Suarez Bertoa, R., Functionalization of the unactivated carbon-hydrogen bond via ozonation, Ozone Science & Engineering, 30, 165-171, (2008);

[11] Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., "Reactivity of two models of non ionic surfactants with ozone", Water Research, 31, 1839-1846 (1997);

[12] Brambilla, A., Rindone, B., Polesello, S., Galassi, S., Balestrini, R., "The fate of triazine pesticides in river Po water", The Science of the Total Environment, 132, 339-348 (1993); Bolzacchini, E., Brambilla, A., Orlandi, M., Polesello, S., Rindone, B., "Oxidative Pathways in the degradation of triazine herbicides: A mechanistic approach", Wa. Sci. Tech., 30, 129-136 (1994); Brambilla, A., Bolzacchini, E., Orlandi, M., Polesello, S., Rindone, B., ", Reactivity of organic micropollutants with ozone: a kinetic study", Life Chemistry Reports, 13, 79-84, (1995);

[13] Houben Weyl, *Methoden der Organische Chemie* Vol E13, (Stuttgart, New York, George Thieme Verlag 1988) p. 1118; Plesnicar, B., Cerkovnik, J., Tekavec, T., Koller, J., Chem. Eur. J.,

Here we report the functionalization of the unactivated carbon-hydrogen bond of cis- and trans-decalin with ozone to give oxygenated products.

2.6.2. Results and discussion

2.6.2.1. Oxidation of trans-decalin (1)

Two different reaction media were used for the ozonation of trans-decalin (1):

a) Dichloromethane solution.

b) Acetonitrile solution

The reactions were performed in triplicate. The reaction time was 1 h for a reaction temperature of -20 °C, 0 °C, 25 °C. The amount of unconverted material and reaction products was determined by GLC-MS using n-decane as the internal standard. Table 1 shows the results obtained. A conversion lower than 100% was observed in most cases.

Some reaction products retained the carbon atom skeleton of the starting materials. Trans-decalin-9-ol (2) and the two isomeric trans-

---

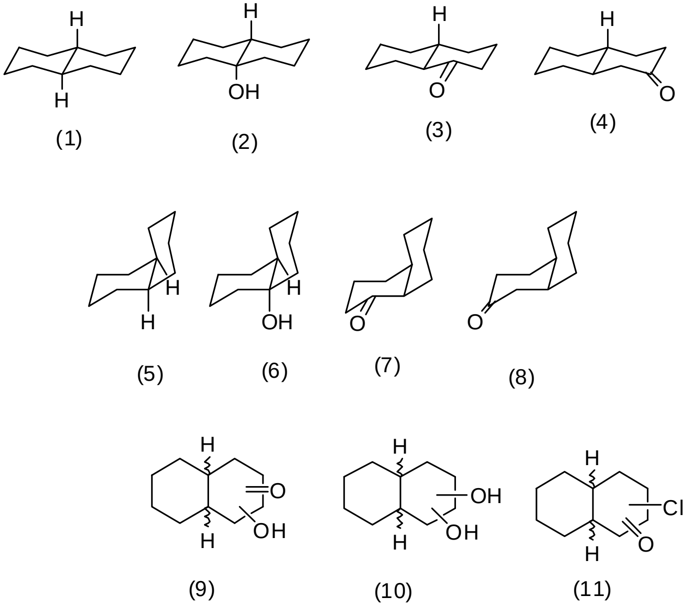
6, 809-819, (2000); Plesnicar, B., Cerkovnik, Tuttle, T., Kraka, E., Cremer, D., J. Amer. Chem. Soc., 124, 11260-11261, (2002); Wu, A., Cremer, D., Plesnicar, B., J. Amer. Chem. Soc., 125, 9395-9402, (2003); Tuttle, T., Cremer, D., Plesnicar, B., Cerkovnik, J. Amer. Chem. Soc., 126, 16093-16104, (2004);

decalin-2-one (3) and trans-decalin-3-one (4) were formed in similar amounts. A small amount of cis-decalin-9-ol (6) was present. Two isomers of a ketoalcohol (9) and a chlorinated decalone (11) in reactions performed in dichloromethane were noticed.

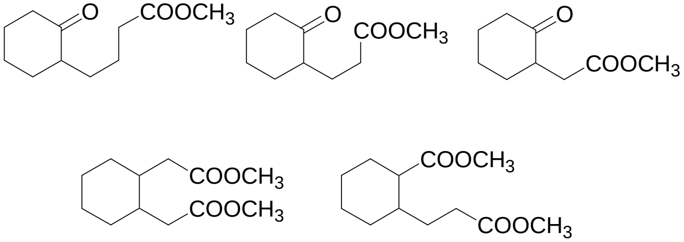
In trans-decalin-9-ol (2), oxygenation of the tertiary carbon has occurred with almost complete retention of configuration. Its yield was higher in dichloromethane than in acetonitrile.

Both in dichloromethane and at a major extent in acetonitrile most of the converted material was transformed into complex mixture of monocyclic carboxylic acids. Methylation with diazomethane and GLC-MS analysis allowed showing the presence of the methylesters shown in Scheme 2.

Scheme 1



Scheme 2



T (°C)	t (h)	Solvent	trans-decalin (1) %	trans-decalin-9-ol (2) %	cis-decalin-9-ol (6) %	trans-decalons (3) and (4) %	Carboxylic acids %	Ketoalcohols (9) (two isomers) %	1-cloro-decalin-2-one (11) %	Conversion %
25	1	DCH	8.85 ± 0.58	8.82 ± 0.80	0.11 ± 0.17	2.97 + 1.10	33		3.24	91.15 ± 0.58
0	1	DCH	15.86 ± 1.81	8.64 ± 0.31	-	5.98 + 2.72	n.d		2.91	84.14 ± 1.81
-20	1	DCH	48.90 ± 3.59	7.74 ± 0.42	-	4.64 + 2.66	n.d		2.54	51.10 ± 3.59
25	1	ACN	-	1.90 ± 1.08	-	2.04 + 3.10	54	1.96 +0.80		100
0	1	ACN	6.97 ± 1.89	4.82 ± 0.90	-	2.93 + 5.58	40	1.67 + 1.28		93.03 ± 1.89
-20	1	ACN	37.92 ± 0.45	4.13 ± 0.29	-	2.52 + 4.76	n.d			62.08 ± 0.45

Table 1. Reactivity of trans-decalin (1) with ozone

2.6.2.2. Oxidation of cis-decalin (5)

The same experimental approach was used for the oxidation of cis-decalin (5). Table 2 shows the results obtained. Cis-decalin (5) was completely converted in most cases.

Some reaction products retained the carbon atom skeleton of the starting materials. The most abundant of them was cis-decalin-9-ol (6), where oxygenation of the tertiary carbon with retention of configuration has occurred. Its yield was higher in dichloromethane than in acetonitrile and increased when lowering the reaction temperature. Also very small amounts of the isomeric trans-decalin-9-ol (10) were noticed. Minor amounts of the two isomeric cis-decalin-

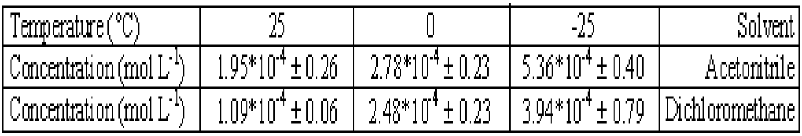
2-one (7) and cis-decalin-3-one (8), deriving from the oxygenation of the secondary carbons, were observed. Two isomers of a ketoalcohol (13) and the isomers of the diol (14) derived from further oxidation of the primary reaction products.

Again, most of the converted material was transformed into complex mixture of monocyclic carboxylic acids. Methylation with diazomethane and GLC-MS analysis allowed showing the presence of the methylesters shown in Scheme 2.

T t (°C) (h)	Solvent	cis-decalin (1) %	cis-decalin-9-ol (2) %	trans-decalin-9-ol (6) %	cis-decalons (3) and (4) %	Carboxylic acids %	Ketoalcohols (9) (2 isomers) %	Diol (10) %	Conversion %
25 1	DCH	-	9.25 ± 0.70	1.14 ± 0.26	-	32	1.11	1.70	100
0 1	DCH	-	10.30 ± 2.79	0.89 ± 0.17	-	27	0.94	1.08	100
-20 1	DCH	7.30 ± 2.09	20.18 ± 11.94	1.41 ± 0.38	1.40+ 1.03	n.d	1.90	1.72	92.70 ± 2.09
25 1	ACN	-	1.23 ± 1.19	0.78 ± 0.67	-	n.d	7.69		100
0 1	ACN	-	8.56 ± 3.67	1.99 ± 0.34	1.51+ 1.81	71	10.45 + 7.95		100
-20 1	ACN	1.02 ± 0.92	11.15 ± 1.28	1.79 ± 0.17	1.91+ 2.45	n.d	3.24		98.98 ± 0.92

Table 2. Reactivity of cis-decalin (1) with ozone (DCH = dichloromethane; ACN = acetonitrile)

In order to understand the effect of the solvent on these ozonation reactions, the solubility of ozone in dichloromethane or acetonitrile at the temperatures of this study is shown in table 3. This was accomplished by bubbling ozone in the solvent for 15 min and measuring its concentration via iodometric titration[14]. Measurements were performed in triplicate.



Temperature (°C)	25	0	-25	Solvent
Concentration (mol L^{-1})	$1.95*10^{-4} \pm 0.26$	$2.78*10^{-4} \pm 0.23$	$5.36*10^{-4} \pm 0.40$	Acetonitrile
Concentration (mol L^{-1})	$1.09*10^{-4} \pm 0.06$	$2.48*10^{-4} \pm 0.23$	$3.94*10^{-4} \pm 0.79$	Dichloromethane

Table 3. Solubility of ozone in dichloromethane or acetonitrile at different temperatures

These data suggest that:

Cis-decalin (5) is more reactive than trans-decalin (1) irrespective of the reaction conditions used. In fact, cis-decalin (5) is completely converted at 25 °C and 0 °C and is converted more than 90 % at -20 °C, whereas trans-decalin (1) is completely converted only at 25 °C in acetonitrile, and 91% converted in dichloromethane at the same temperature.

---

[14] Gordon, S. A,. Chughtai, A. R., Smith, D. M., Revisiting iodometric estimation as a reference method for ozone in laboratory gas streams, American Laboratory (2000), 32(9), 12-13;

Conversion of trans-decalin (1) is lower at lower temperature in both solvents (Figure 1).

Trans-decalin (1) is slightly more reactive in acetonitrile than in dichloromethane.

Hydroxylation at the tertiary position is a major pathway with cis-decalin (5) and, at a minor extent, with trans-decalin (1). The corresponding 9-hydroxyderivatives mostly retain the configuration of the starting material.

The selectivity (yield/conversion) in decalin-9-ols increases lowering the temperature (figures 2-3).

The selectivity (yield/conversion) in decalin-9-ols is lower in acetonitrile than in dichloromethane.

The secondary positions are transformed into the isomeric 2- and 3-decalones.

More 2- and 3-decalons with respect to 9-hydoxydecalins are found with cis-decalin (5) than with trans-decalin (1).

These primary reaction products are further oxidised as shown by the finding of two isomers of a ketoalcohol (9) and a diol (10). Fragmentation of the carbon chain by further oxidation of these intermediates gives the mixture of carboxylic acids which constitutes the major part of the recovered material.

High selectivity in ketoalcohols (9) is observed in the oxidation of cis-decalin (5) in acetonitrile at all the temperatures.

Chlorination occurs with trans-decalin (1) in dichloromethane.

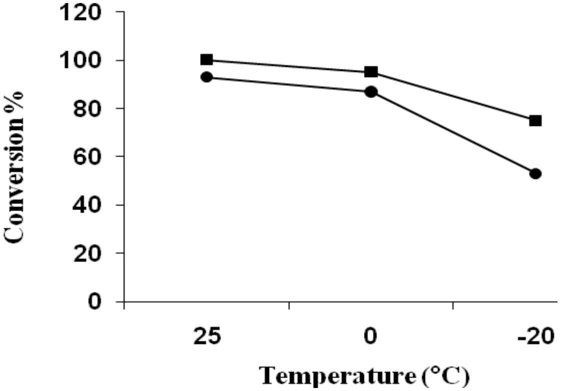


Figure 1: Conversion of trans-decalin (1) with temperature in both solvents.

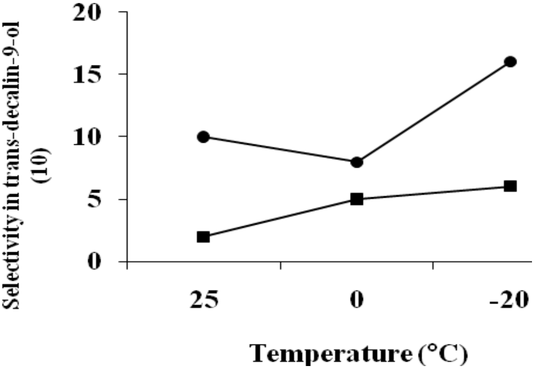


Figure 2: Selectivity in trans-decalin-9-ol (2) in the ozonation of trans-decalin (1) as a function of temperature

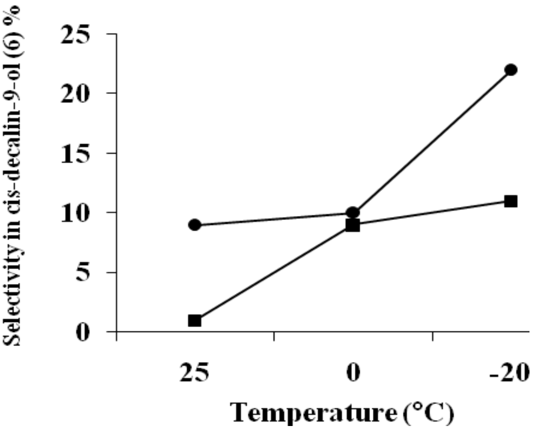


Figure 3: Selectivity in cis-decalin-9-ol (6) in the ozonation of cis-decalin (5) as a function of temperature.

The major reactivity of trans- (1) and cis-decalin (5) with ozone in acetonitrile than in dichloromethane is probably the result of the higher solubility of ozone in acetonitrile than in dichloromethane. The rate law for the ozonation of organic compounds in water has been determined[15] as:

---

[15] Hoigne, J., Bader, H., Ozonation of water: selectivity and rate of oxidation of solutes, Ozone: Science & Engineering (1979), 1(1), 73-85; Rate constants of reactions of ozone with organic and inorganic compounds in water. I. Nondissociating organic compounds, Water Research (1983), 17(2), 173-83;

$$v = k\,[\text{organic compound}][\text{ozone}] \qquad (1)$$

If this relationship holds also in organic solvents, an increase in the concentration of ozone results in an increase in the second order reaction rate and hence in the conversion of the organic substrates in our experiments.

The conversion of decalins is lower at lower temperatures in both solvents. The opposite behaviour had been noted[16] with naphthalene and had been attributed to the higher solubility of ozone in the solvents when lowering the temperature which results in an increase in the second order reaction rate and hence in the conversion of the substrates. This suggestion derives from the idea that the rate of the transfer of ozone from the gaseous to the condensed phase is faster than the rate of the addition reaction giving naphthalene monoozonide. Hence, the steady state concentration of ozone is its maximum solubility at the temperature of the experiment and this gives a higher

---

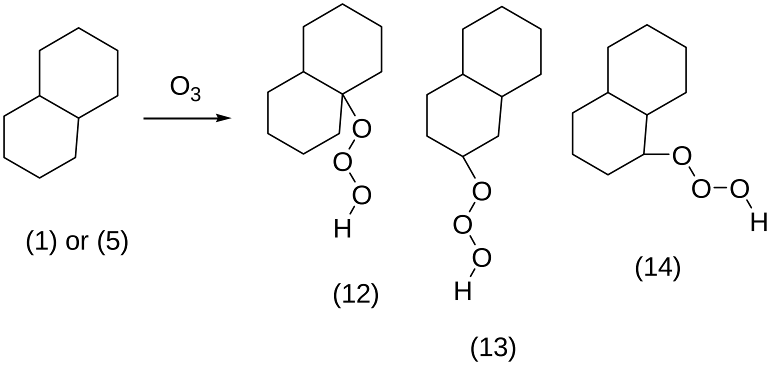
Wang, P. C., Matta, H. B., Kuo, C. H., Kinetics of ozonation of naphthalene and anthracene, Journal of the Chinese Institute of Chemical Engineers (1991), 22(6), 365-71;

[16] Rindone, B., Saliu, F., Suarez-Bertoa R., submitted to Ozone Scienze and Engineering;

reaction rate. Hence, the increase of the concentration of ozone at low temperature is a stronger effect then the decrease of rate constants when lowering the temperature due to a lower fraction of energetically useful collisions. With decalins, lowering the temperature results in a slower reaction occurring at the saturation concentration ozone. This suggests that the reaction occurs via a very energy-demanding hydrogen transfer, where the increase of the concentration of ozone a lower temperature does not counterbalance the decrease of useful collisions.

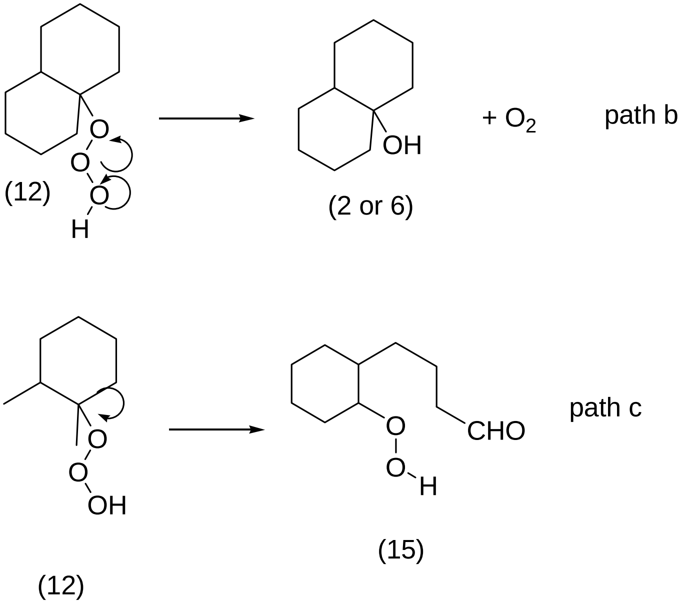
In order to get a better understanding of the regiochemistry of the reaction, and the distribution of products, the reaction mechanism has been investigated computationally through the identification of the relevant stationary points (minima and saddle points) along the reaction coordinate of the pathways reported in Scheme 3. The calculations have been performed in *vacuum*. The first step in the proposed mechanism is the formation of the three isomeric hydrotrioxides (**12-14**) for each compound, namely trans-decalin (**1**) and cis-decalin (**5**). The process may occur through a hydride or hydrogen transfer from the tertiary carbon or from the two methylenic carbons [22] to the terminal oxygen atom of O_3. The hydride transfer leads to the formation of the decalin cation and the hydrotrioxide anion (HO_3^-), while the hydrogen transfer leads to the formation of the decalinyl and the hydrotrioxide ($HO_3\cdot$) radicals. The recombination of the terminal oxygen atom of HO_3^- or $HO_3\cdot$ with the tertiary carbon or the methylenic carbons will then lead to (**12-14**), respectively. The process may also occur through a concerted mechanism where hydrogen transfers and C-O bond formation occurs simultaneously.

Scheme 3



The tertiary hydrotrioxide (12) decomposes to the tertiary alcohol (2) or (6) (path b) or cleaves to the aldehydohydroperoxide (15) (path c) (Scheme 4).

Scheme 4



The secondary hydrotrioxides (13-14) (Schemes 5 and 6) may: Dissociate to a carbonyl compound and hydrogen peroxide (path a)

7) Dismutate to an alcohol and dioxygen (path b). Singlet

---

dioxygen is reported to be formed in this step[17].

Rearrange an aldehyde and a hydroperoxide with further oxidation to carboxylic acids (path c).

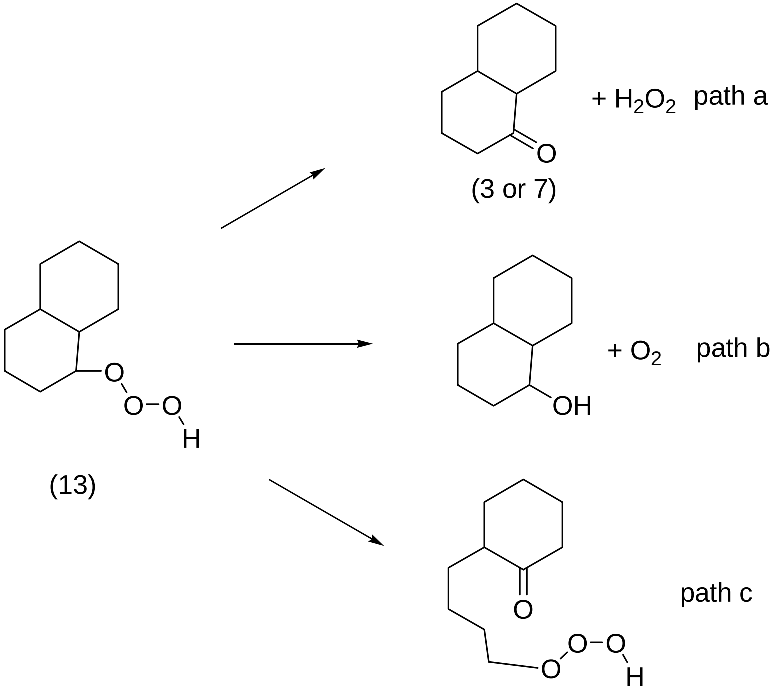
With alkanes and ethers path a) is the most important and forms carbonyl compounds which are eventually further oxidized to open-chain products.

Path b) is much less important and gives minor amounts of the corresponding alcohols. Path c) is probably involved in the formation of shorter carbon chain acids.

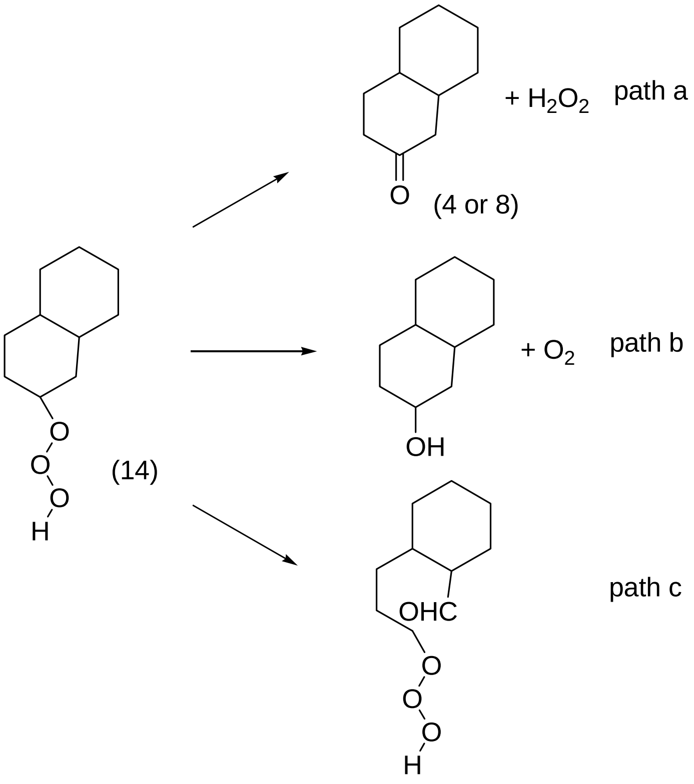
---

[17] Munoz, F., Mvula, E., Braslavsky, S. E., von Sonntag, C., Singlet dioxygen formation in ozone reactions in aqueous solution, *Journal of the Chemical Society*, Perkin Transactions 2 (7), 1109-1116 (2001);

Scheme 5



Scheme 6



2.6.1. *The proposed reaction mechanism*

The reaction mechanism was studied computationally through the identification if the relevant stationary points (minima and saddle points) along the reaction coordinate. The computational investigation of the reaction mechanism, summarized by the energy profile shown in Figure 5, explains the regioselectivity and the products distribution observed experimentally. In Table 3 are also reported energies and energy differences of all of the species considered.

Table 3. Energies (in Hartree) and relevant energy differences (in kcal mol^{-1}) of the compounds investigated in this work computed using the B3LYP/cc-pVDZ computational scheme

	Vacuum
1 + O_3	-617,3709673
5 + O_3	-617,3655038
1a-t	-617,3758542
1b-t	-617,3760114
1c-t	-617,3760114
5a-c	-617,3701035
5b-c	-617,3700919
5c-c	-617,3700919
TS-9-t	-617,3421033
TS-2-t	-617,3358436
TS-3-t	-617,3320284
TS-9-c	-617,3401414
TS-2-c	-617,3330505
TS-3-c	-617,3301521
Rad-9-t + O_3H	-617,3605908
Rad-2-t + O_3H	-617,3560534
Rad-3-t + O_3H	-617,3563183

	Vacuum
Rad-9-c + O_3H	-617,3562541
Rad-2-c + O_3H	-617,3525725
Rad-3-c + O_3H	-617,3517224
12-t	-617,4492372
14-t	-617,4503900
13-t	-617.4492131
12-c	-617,4490044
14-c	-617,4440561
13-c	-617,4439005
TS-Alc-t	-617,3845064
TS-Alc-c	-617,3808547
2	-617,4393650
6	-617,4355569

	Vacuum
1 + O3 → 1a-t	-3,1
1 + O3 → 1b-t	-3,2
1 + O3 → 1c-t	-3,2
5 + O3 → 5a-c	-2,9
5 + O3 → 5b-c	-2,9
5 + O3 → 5c-c	-2,9
1 + O3 → TS-9-t	18,1

	Vacuum
1 + O3 → TS-2-t	22,0
1 + O3 → TS-3-t	24,0
5 + O3 → TS-9-c	15,9
5 + O3 → TS-2-c	20,4
5 + O3 → TS-3-c	22,2
1 + O3 → Rad-9-t	6,5
1 + O3 → Rad-2-t	9,4
1 + O3 → Rad-3-t	9,2
5 + O3 → Rad-9-c	5,8
5 + O3 → Rad-2-c	8,1
5 + O3 → Rad-3-c	8,6
1 + O3 → 12-t	-49,1
1 + O3 → 14-t	-49,8
1 + O3 → 13-t	-52,4
5 + O3 → 12-c	-9,6
5 + O3 → 14-c	-49,3
5 + O3 → 13-c	-49,2
1 + O3 → TS- Alc-t	-11,9
5 + O3 → TS- Alc-c	-6,2
1 + O3 → 2	-42,9
5 + O3 → 6	-44,0

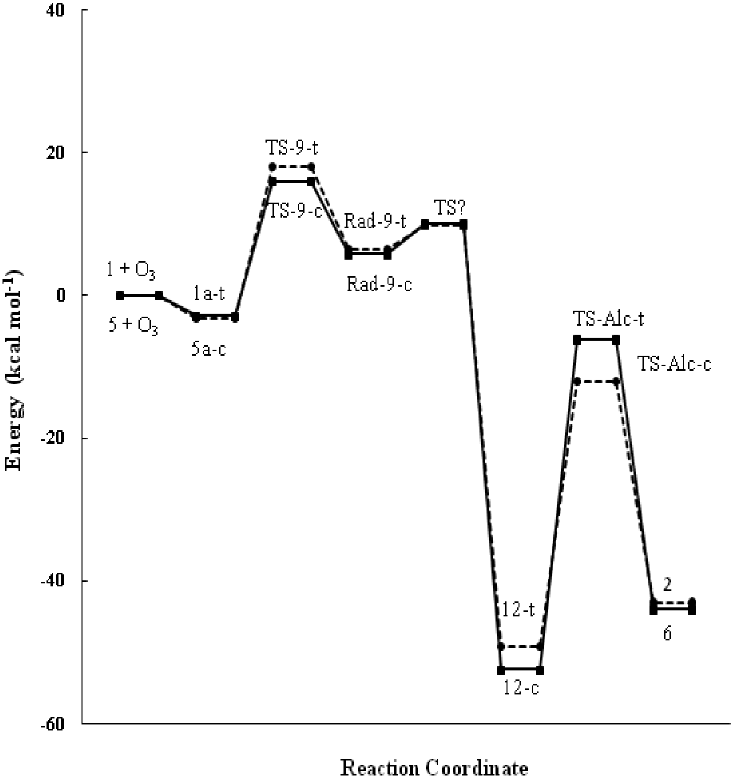
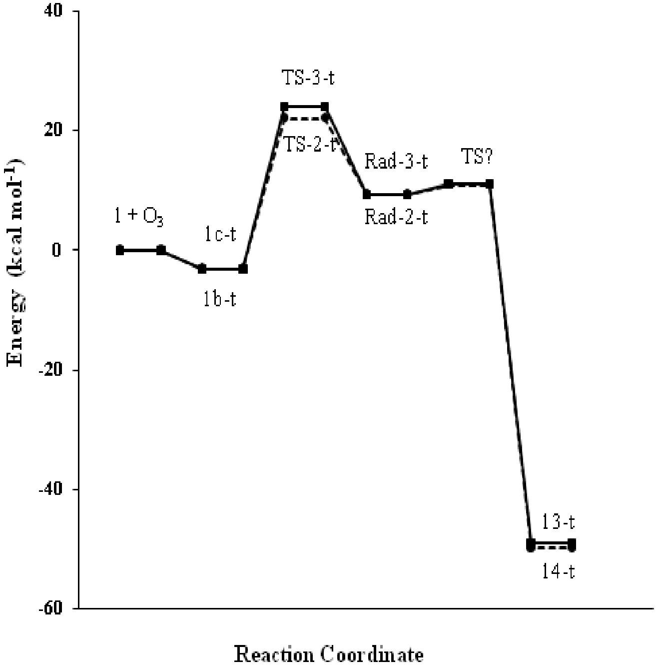
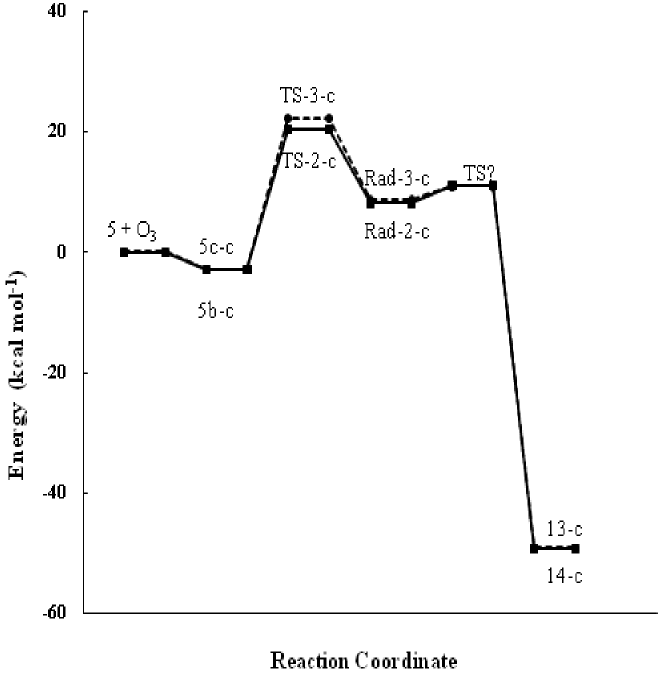


Figure 4. a) Energy diagram for the reaction of the tertiary carbon of the Trans-decaline 1 (---) and Cis-decaline 5 (—) with ozone calculated in *vacuum*



b) Energy diagram for the reaction of the secondary carbon s 3 (—) and 2 (---) of the Trans-decaline 1 with ozone calculated in *vacuum*.



c) Energy diagram for the reaction of the secondary carbon s 3(---) and 2(—) Cis-decaline 5 with ozone calculated in *vacuum*.

The formation of the hydrotrioxides (**12-14**) was studied considering both hydrogen abstraction and concerted mechanism.

A detailed study of the potential energy surface (PES) of the Cis-decanile – O_3 supramolecular system and Trans-decanile – O_3 supramolecular system lead to the characterization of three van der Waals complexes differing for the orientation of O_3 with respect to each substrate, and depending on which carbon is attack by the O_3 (**1a-t** - **1c-t** and **5a-c** - **5c-c**; see Figure 5). All the four complexes are more stable than the two separate reactants (trans-decalin (**1**) cis-decalin (**5**), and ozone).Hence, all van der Waals complexes **1a-t** - **1c-t** and **5a-c** - **5c-c** are more stable than the two separate reactants by about 3 kcal mol^{-1}(see Table 4).

The reaction, starting from complexes **1a-t** - **1c-t** and **5a-c** - **5c-c**, can proceed along six different paths depending on which carbon is attacked by ozone, namely that the trans and cis tertiary carbons and the two secondary carbons of each molecule. In all the cases the formation of the hydrotrioxide intermediates **12-14** proceeds through a hydrogen abstraction mechanism followed by recombination of the ionic or radical pairs. Although several attempts were made, we were unable to find a transition state for the concerted mechanism.

The transition state for the hydrogen abstraction over the tertiary carbon of the trans-decalin and cis-decaline (**TS-9-t** and **TS-9-c**, respectively) are shown in Figure 5. The corresponding activation energies (E_a), calculated with respect to the separate reactants, are equal to 18.1 kcal mol^{-1} and 15.9 kcal mol^{-1} (21.2 kcal mol^{-1} and 18.8 kcal mol^{-1} when calculated with respect to the complex **1a-t** and **5a-c**). The hydrogen abstraction over the secondary carbon 5 leads to the transition states **TS-2-t** and **TS-2-c** (see Figure 5) which are 22.0 kcal mol^{-1} higher than the separate reactants for both transitions states (23.0 kcal mol^{-1} when calculated with respect to the complex **1b-t, 5b-c**); and 3.9 and 6.1 kcal mol^{-1} higher than those obtained for **TS-9-t** and **TS-9-c,** respectively. Furthermore, The hydrogen abstraction over the secondary carbon 3 leads to the transition states **TS-3-t** and **TS-3-c** (see Figure 5) which are respectively 24.0 and 22.2 kcal mol^{-1} higher than the separate reactants (26.9 kcal mol^{-1} and 25.1 kcal mol^{-1} when calculated with respect to the complex **1c-t** and **5c-c**); and 5.9 and 6.3 kcal mol^{-1} higher than that obtained for **TS-9-t** and **TS-9-c**, respectively. Nevertheless, the hydrogen abstraction over the secondary carbon 2 leads to the transition states **TS-2-t** and **TS-2-c** (see Figure 5) which are respectively 18.1 and 20.4 kcal mol^{-1} higher than the separate reactants (21.2 kcal mol^{-1} and 23.3 kcal mol^{-1} when calculated with respect to the complex **1c-t** and **5c-c**); and 3.4 and 4.5 kcal mol^{-1} higher than that obtained for **TS-9-t** and **TS-9-c**, respectively.

Transition stated can evolve through a homolytic bond dissociation to form a radical pair when calculations are performed in *vacuum*. The homolytic H-abstraction in the carbons 9, 2 and 3 of each compound lead to the radical species **Rad-9-t**, **Rad-2-t**, **Rad-3-t** and **Rad-9-c**,

Rad-2-c, **Rad-3-c** and **Rad-3-c** (see Figure 2), respectively, and $O_3H\cdot$. All six **Rad** – $O_3H\cdot$ radical pairs are considerably higher in energy than the separate reactants in *vacuum* (see Table 4).

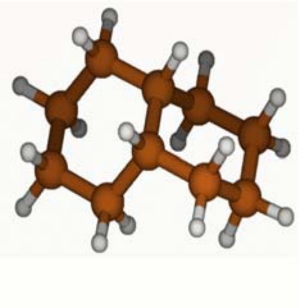
After the formation of radical pairs, the terminal oxygen of the $O_3H\cdot$ specie may easily attack the unsaturated carbon atom forming a carbon-oxygen bond and leading to the hydrotrioxides intermediates **12-14**. These intermediates have similar energies and are significantly more stable than separate reactants (see Table 4).

The formation of the hydrotrioxide intermediates (**12** cis and trans) is the key to understand the greater reactivity of cis-decalin (**5**) over trans-decalin (**1**). In fact, a difference of 2.2 kcal·mol^{-1} between **TS-9-t** and **TS-9-c** make more favorable the functionalization of cis-decalin (**5**) than the functionalization of trans-decalin (**1**). However, this difference is not enough to discriminate one reaction over the other.

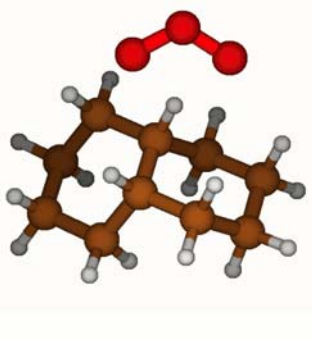
On the other hand, it was found that the activation barrier for the transitions state of the secondary carbons (**TS-2 TS-3**) is greater by 3.4, 5.4 kcal mol^{-1} and 4.5, 6.3 kcal mol^{-1} when compared with that of the tertiary carbon (**TS-9**) of each molecule (trans and cis-decaline, respectively). This difference indicates the faster reaction of ozone with the tertiary carbon compared to secondary carbons, making selective the reaction towards the former in both compounds. The result would also suggest a grater reactivity of the secondary carbon 2 compared to 3. However, none of the experimental data presented could confirm this result.

Hydrotrioxides **12-t** and **12-c** could evolve to give the final products **2** and **6** following just one pathway, path b) (Scheme 4). Calculations were also performed for these pathways in order to obtain the mechanisms which lead in the formation of the trans-9-hydroxydecalin **1** and cis-9-hydroxydecalin **5**. Final products **2** and **6** are significantly more stable than the separate reactants (-42.9 kcal mol^{-1} and -44.0 kcal mol^{-1}) and the barrier that should be overcome is about 37.4 kcal mol^{-1} and 43.6 kcal mol^{-1} (**TS-Alc-t**, **TS-Alc-c**; see Figure 5) with respect to corresponding intermediates **12-t** and **12-c**.

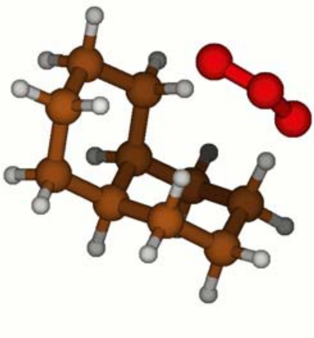
Figure 5. Molecular structures of the investigated compounds calculated using the B3LYP/cc-pVDZ scheme.



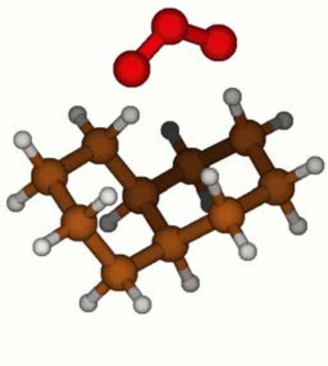
5



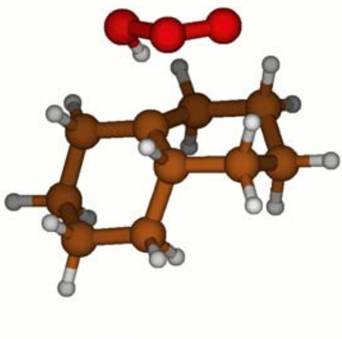
5a-c



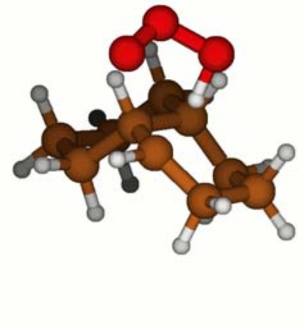
5b-c



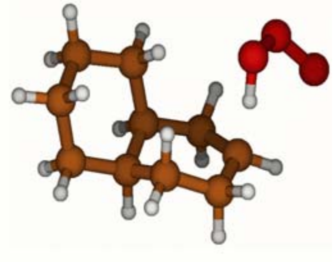
5c-c



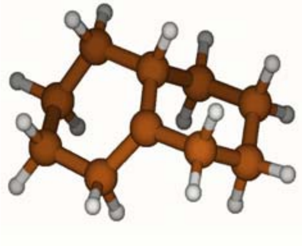
TS-9-c



TS-2-c

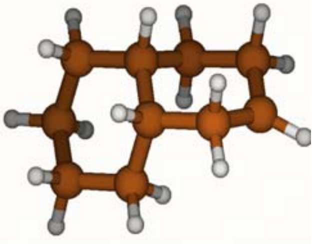


TS-3-c

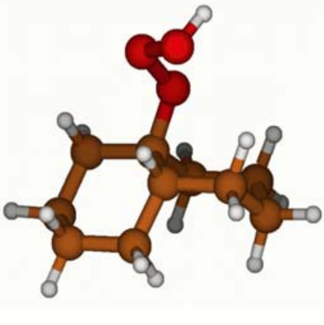


Rad-9-c

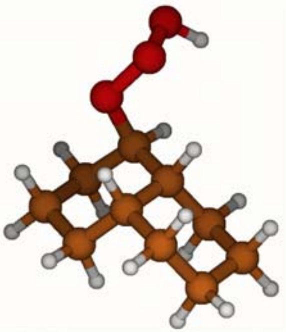
Rad-2-c



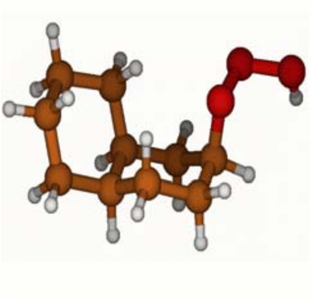
Rad-3-c



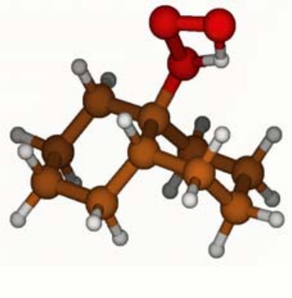
12-c



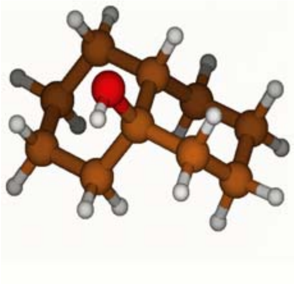
14-c



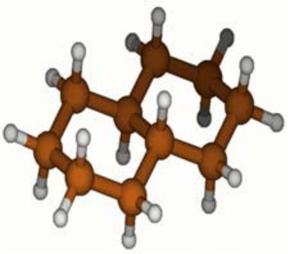
13-c



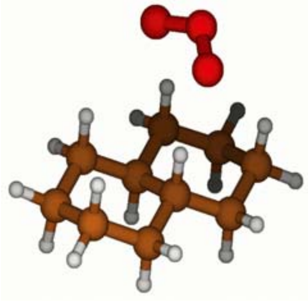
TS-Alc-c



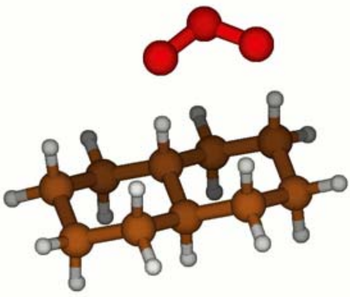
6



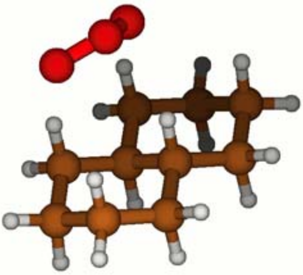
1



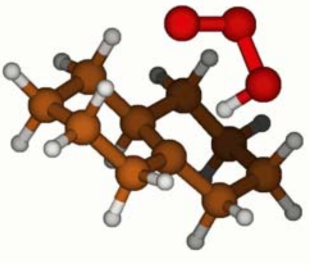
1a-t



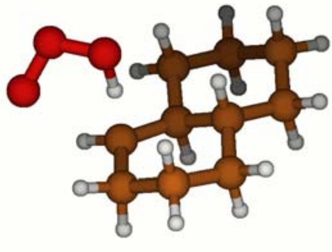
1b-t



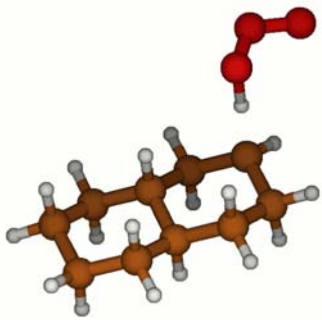
1c-t



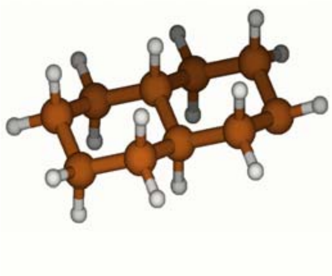
TS-9-t



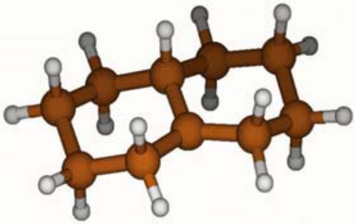
TS-2-t



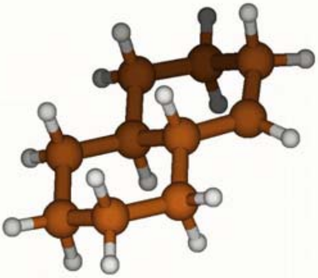
TS-3-t



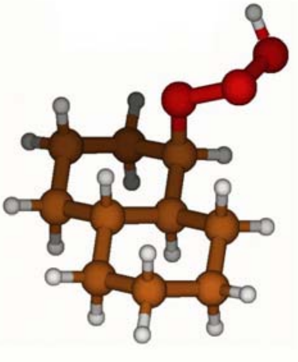
Rad-3-t



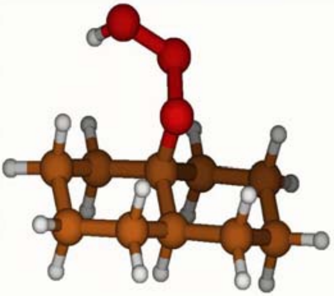
Rad9-t



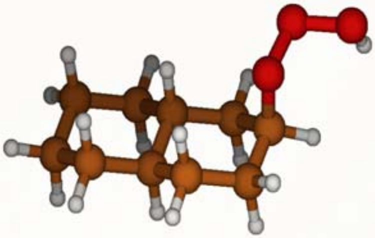
Rad-2-t



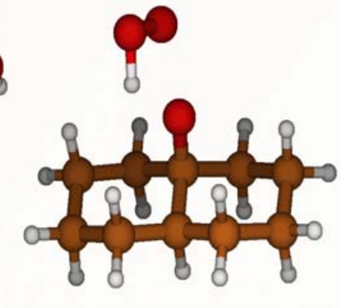
12-t



14-t



13-t



TS-Alc-t

2

2.6.2.Experimental and computational methods

2.6.2.1. Ozonation and contacting procedures

Ozonations were performed with 30 L/h of a gas stream obtained submitting dioxygen to a 200 mA electric discharge using an ozone generator from Ozono Elettronica Internazionale, Muggio', Italy. The diffusion of the gas in the liquid phase was obtained through a Pasteur pipette 2 mm wide.

2.6.2.2. Oxidations in aqueous solution

2.6.2.2.1. Cyclodecane

The substrate was suspended in the required amount of water, adjusted at pH 3 for sulphuric acid and ozonized. After 30 minutes at 25 °C the mixture was extracted three times with 10 mL portions of methylene chloride, the collected organic extracts were then dried over sodium sulphate and the solvent was evaporated under a nitrogen stream and analysed by GLC-MS.

2.6.2.2.2. n-decane

The substrate was suspended in the required amount of water, adjusted at pH 3 for sulphuric acid and ozonized. After 30 minutes at 25 °C the mixture was extracted three times with 10 mL portions of methylene chloride, the collected organic extracts were then dried over sodium sulphate and the solvent was evaporated under a nitrogen stream and analysed by GLC-MS.

2.6.2.2.3. 18-crown-16 ether

The substrate was suspended in the required amount of water, adjusted at pH 3 for sulphuric acid and ozonized. After 30 minutes at 25 °C the mixture was extracted three times with 10 mL portions of methylene chloride, the collected organic extracts were then dried over sodium sulphate and the solvent was evaporated under a nitrogen stream and analysed by GLC-MS.

2.6.2.3. Oxidations in pure organic liquid

2.6.2.3.1. Cyclodecane

8 mL of substrate were ozonized at 25 °C. After 30 minutes the resulting mixture was dissolved in dichloromethane and analyzed by GLC-MS.

2.6.2.4. Oxidations in dichloromethane

2.6.2.4.1. Cyclodecane

The substrate was dissolved in the required amount of dichloromethane and ozonized at 25 °C and 0 °C. After 30 and 60 minutes, respectively, the solution was evaporated under nitrogen stream and analysed by GLC-MS.

2.6.2.4.2. Cyclododecane

The substrate was dissolved in the required amount of dichloromethane and ozonized at 25 °C. After 90 minutes the solution was evaporated under nitrogen stream and analysed by GLC-MS.

2.6.2.4.3. n-decane

The substrate was dissolved in the required amount of dichloromethane and ozonized at 25 °C. After 90 minutes the solution was evaporated under nitrogen stream and analysed by GLC-MS

2.6.2.4.4. 18-crown-16 ether

The substrate was dissolved in the required amount of dichloromethane and ozonized at 25 °C. After 90 minutes the solution was evaporated under nitrogen stream and analysed by GLC-MS.

2.6.2.4.5. Dibenzylether

The substrate was dissolved in the required amount of dichloromethane and ozonized at 25 °C. After 90 minutes the solution was evaporated under nitrogen stream and analysed by GLC-MS.

2.6.2.5. Oxidations in dichloromethane or acetonitrile

2.6.2.5.1. Naphthalene

The substrate was dissolved in the required amount of dichloromethane or acetonitrile to obtain a 4 x 10^{-1} M concentration, kept at the required temperature and treated with a stream of ozonized oxygen. After the required time 5 mg of zinc were added, the solution filtered, evaporated under a nitrogen stream and the residue was purified by silica gel flash chromatography (R = 100), eluting with dichloromethane: ethyl acetate 9:1. The individual fractions were analysed by GLC-MS.

2.6.2.5.2. N-phenylmorpholine

The substrate was dissolved in the required amount of dichloromethane or acetonitrile to give a 4 * 10-2 M solution and ozonized at the required temperature. After the required time the solution was evaporated under a nitrogen stream and the residue was separated by flash chromatography over silica gel (R = 100) eluting with dichloromethane-ethyl acetate 9:1. The individual fractions were analysed by GLC-MS, IR ^{1}H NMR and ^{13}C NMR.

2.6.2.5.3. Cyclohexane

The substrate was dissolved in the required amount of dichloromethane or acetonitrile to obtain a 4 x 10^{-1} M concentration, kept at the required temperature and treated with a stream of ozonized oxygen. After the required time 5 mg of zinc were added, the solution filtered, evaporated under a nitrogen stream and the residue was purified by silica gel flash chromatography (R = 100), eluting with dichloromethane: ethyl acetate 9:1. The individual fractions were analysed by GLC-MS.

2.6.2.5.4. Cis-decalin

The substrate was dissolved in the required amount of dichloromethane or acetonitrile to obtain the required concentration, kept at the required temperature and treated with a stream of ozonized oxygen. After the required time the mixture was analysed by GLC-MS.

2.6.2.5.5. Trans-decalin

The substrate was dissolved in the required amount of dichloromethane or acetonitrile to obtain a 4×10^{-1} M concentration, kept at the required temperature and treated with a stream of ozonized oxygen. After the required time the solution was evaporated under nitrogen stream and analysed by GLC-MS.

2.6.2.6. Determination of the content in acidic material

Extraction of the dichloromethane solution containing the mixture of reaction products with saturated sodium hydrogen carbonate solution allowed recovering the acidic fraction, which was isolated by acidification and extraction with dicloromethane and analysed by GLC-MS after methylation with methanol and sulphuric acid.

2.6.2.7. Oxidations with a limited amount of ozone in acetonitrile

Ozone was bubbled for 15 min in 1 L of acetonitrile at -25 °C. The content of ozone was then measured by iodometric titration. The solution was then added of naphthalene (1) in the amount appropriate for a 1:1 stoichiometry with ozone. After 1 h reaction 5 mg of solid zinc were added and the suspension was filtered, evaporated at reduced pressure. The residue was then suspended in 10mL of water, extracted three times with portions of 20 mL of dichloromethane, washed three times with brine, dried over anhydrous sodium sulphate, evaporated under reduced pressure and separated by silica gel chromatography.

For the determination of the content in acidic material, the dichloromethane solution was extracted with saturated sodium hydrogen carbonate solution (3 x 25 mL). The combined aqueous phases were acidified, extracted three times with 20 mL portions of dichloromethane and the collected organic phases were dried over anhydrous sodium sulphate, filtered, and evaporated under reduced pressure.

2.6.2.8. Computational methods

All calculations have been performed in the framework of the Density Functional Theory (DFT) [10] by using the hybrid three parameters B3LYP exchange and correlation functional, [11] and the valence triple-ζ basis set with polarization on all atoms cc-pVTZ[1]. Stationary points of the energy hypersurface (minima and saddle points) have been located by means of energy gradient techniques using the quantum mechanical Gaussian 03 suite[2]. Transition states

---

[1] Dunning, T.H. Jr. *J. Chem. Phys*. 90, 1007 (1989);

[2] Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M.

have been characterized by a full vibrational analysis. Geometry optimizations to minima and transition states have been performed in *vacuum* as well as in the two solvents employed in the experiments (dichloromethane and acetonitrile). The effect of the solvents (dichloromethane ε = 8.93; acetonitrile, ε = 35.688) has been evaluated according to the Polarizable Continuum Model (PCM) approach of Tomasi et al.[3] as implemented in Gaussian 03. Due to the nature of the reaction investigated, individual spheres on hydrogen atoms, with UFF radius, have been used in the definition of the polarisable cavity. The wavefunctions of the transition states was tested for an internal and external stability[4], and in all cases the wavefunctions resulted to be stable.

W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, (2004);

[3] Cancès, E., Mennucci, B., Tomasi, J. J. Chem. Phys., 107, 3032-3041 (1997); Mennucci, B., Cancès, E., Tomasi, J., J. Phys. Chem. B, 101, 10506-10517 (1997); Cossi, M., Barone, V., Cammi, R., Tomasi, J. Chem. Phys. Lett. 255, 327−335 (1996); Barone, V., Cossi, M., Tomasi, J. *J. Comput. Chem*., 19, 404−417 (1998);

[4] Bauernschmitt, R., Ahlrichs, R. J. *Chem. Phys*., 104, 9047-52 (1996).

3. Synthesis and reactions of oxazolidinediones

3.1. Introduction

3.1.1. Cyclic carbonates

The chemistry of the cyclic carbonates has been recently reviewed. Their reactivity appears to be controlled by the hard-soft properties of reagents. Hence, the reaction of cyclic carbonates with soft nucleophiles such as thyols, aromatic amines or phenols occurs at the carbon located next to the oxygen, followed by a decarboxylation. However, hard bases such as aliphatic amines or alcohols, attack the trigonal carbon of the carboxylic group leading to 2-hydroxicarbamate and 2-hydroxicarbonate.

The reaction of the cyclic carbonates with amines has been largely described[1] [2]. This reaction produces compounds which can be useful to obtain polyurethanes resistant to oxidation, light exposure or hydrolysis.

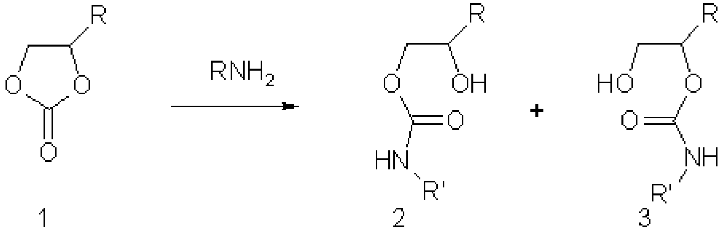
---

[1] Clements, J.H., Reactive Applications of Cyclic Alkylene Carbonates, www.huntsman.com;

[2] Shaikh, A.A.G.; Sivaram, S.,*Chem.Rev.*, **1996**, *96*, 951-976.

The reactivity of aliphatic amines and asymmetric cyclic carbonates has been recently studied[3].

Several cyclic carbonates (1) were used for the reaction with n-hexylamine, a mixture of the primary alcohol (3) and the secondary alcohol (2) were obtained. However, the reacticity changes when R is an electrondonor.



In case R= methyl primary alcohol vs secondary alcohol ratio is 0.82, while when R= trifluoromethyl only secondary alcohol is formed.

3.1.2. *The oxazolidine-2,4-diones*

---

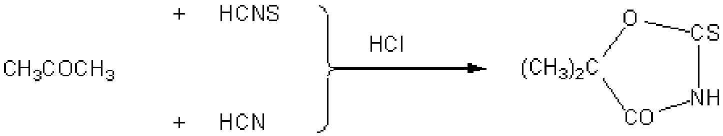
[3] Tomita, H., Sanda, F., Endo, T., J. Polymer Sci., Part A, Polymer Chemistry 2001, 39, 3678-3685;

Oxalidin-2,4-diones are important drugs. 3-methyl-2,4-ossazolidindione is an analgesic and anticonvulsive.

The new procedure proposed is interesting because is, in some respects, a green procedure but also because, differently than what is found in literature[4] (see below), it is a noble method that uses easily available products.

3.1.2.1. 2-thio-4-oxazolidones oxidation

Acetone, potassium cyanide and potassium thiocyanate together with concentrated hydrochloroc acid produce 5,5-dimetil-2-tio-4-ossazolidone[5].



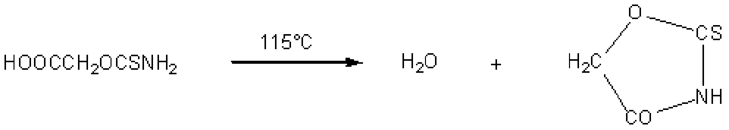
This reaction was also carried out using formaldehyde, acetaldehyde, benzaldehyde and ethylmethyl ketone. However, the reaction does not work when higher ketones are used.

---

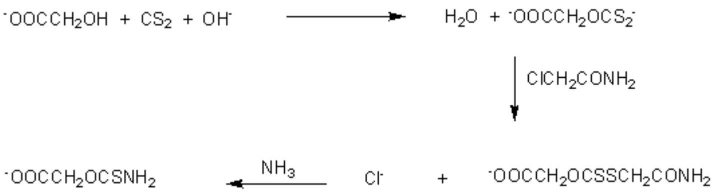
[4] Galliani G., Orlandi M., Rindone B., Terraneo A., PCT Int. Appl. WO2006122782A1, **2006**, *Chem.Abs.* **2006**, *145, 505969;*

[5] Urek, F., Ber.6, 1113-17 (1873)

When $HOOCCH_2OCSNH_2$ is heated at 115°C during 30 minutes the 2-thio-4-oxazolidone is obtained[6].



The acid is synthesized from sodium glycolate.



The conversion from 2-thio-4-oxazolidone to 2,4.oxazolidinedione can be achieved by:

a) bubbling of chlorine into a H_2O/CCl_4 solution of the thio compound;

b) oxidation using hydrogen peroxide at 70-100 ºC;

c) oxidation using permanganate;

d) oxidation with nitric acid.

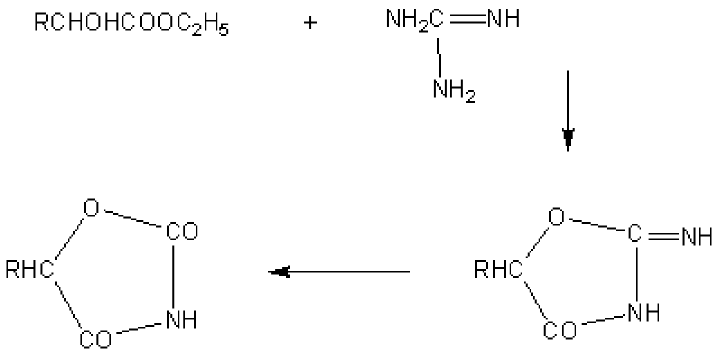
---

[6] Alhqvist, A., J. Pratk. Chem. **99**, 50-6 (1919);

3.1.2.2. Hydrolysis of 2-imino-4-oxazolidone

The condensation of esters of α-hydroxylacids with guanidine, produce 2-imino-4-oxalidindione.

The imino compounds are then hydrolyzed to 2,4-oxazolidinedione[7].

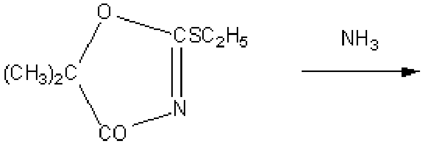


The 2-imino-5,5,dimethyl-4-oxazolidindione can be synthesized by reaction of 2-ethylthio-5,5-dimethyloxazol-4-one with an ammonia solution [8].

---

[7] Traube, W., ando Ascher, R., Ber. **46**, 2077-84 (1913);

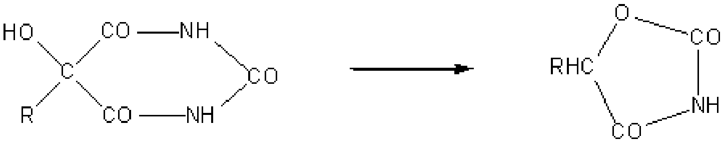
[8] Davies, J. S. H., Hook, W. H., and Long, F., J. Chem. Soc. **1950**, 36-41;



2-imino-4-oxazolidindione hydrolyzes to produce 2,4-oxazolidinedione. This hydrolysis is fast when mineral acidic solutions are used.

3.1.2.3. Alkaline hydrolysis of dialuric acids

2,4-oxazolidinedione are synthesized by reaction of dialuric acid in a sodium hydroxide solution at room temperature or during 20-30 minutes at 100 °C. Furthermore, crystallization of 2,4-oxazolidinedione is frequently observed[9].

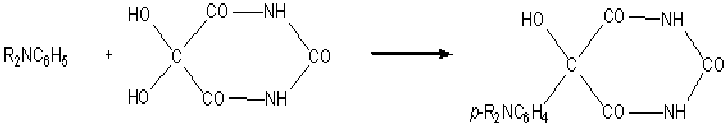


---

[9] King, F. E., and Clark-Lewis, J. Chem. Soc. **1951**, 3077-9;

The alloxane hydride reacts with aromatic amines[10] [11] [12] such as aniline, methylaniline and dimethylaniline, leading to 5-p-aminophenyldialuric, phenols and phenolethers[13].

The substitution is obtained in para position to the amine group. However, if this position is not available (i.e. p-toluidine), the reaction does not occur. Nevertheless, if phenols or phenolethers are used orto substitution is obtained.



3.1.2.4. Condensation of the ester of a-hydroxylacids with urea.

2,4-oxazolidindione are produced by condensation of α-hydroxylacids and urea with sodium ethoxide. Reaction yield reach

---

[10] King, F. E., and Clark-Lewis, J. Chem. Soc. **1951**, 3077-9;

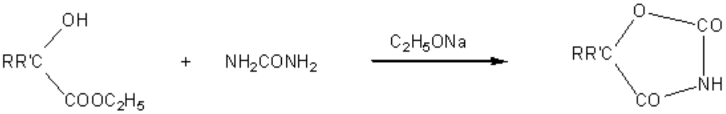
[11] Chemische Fabrik Boehringer & Söhne, German patent 112, 174 (May 7, 1900);

[12] Pellizzari, G., Gazz. Chim. Ital., **17**, 409-24 (1887);

[13] Széki, T.: Ber. **56**, 2464-8 (1923);

80% [14]. This method has been widely used since the 2,4oxazolidindiones are used in medicine. The method allows to obtain a wide range of 2,4-oxazolidindione-5-monosubstituted and 5,5-disubstituted.

The interaction between urea, ester of α-hydroxyacids and C_2H_5ONa were noticed in 1908. However, 2,4-oxazolidinedione was found to be the obtained thirty years later. Furthermore, the reaction yield was optimized using equimolecular amount of the starting materials[15] [16].



---

[14] Stoughton, R. W., J. Am. Chem. Sox. **63**, 2376-9 (1941);

[15] Aspelund, H., Acta Acad. Aboensis, Math. Et Phys. **11**, No. 7, 4 pp. (1938); Chem. Abstracts **33**, 6802 (1939);

[16] Aspelund, H., Acta Acad. Aboensis, Math. Et Phys. **11**, No. 14, 14 pp. (1938); Chem. Abstracts **33**, 6802 (1939);

3.1.2.5. Condensation of the amides of the a-hydroxyacids with alkyl carbonates or chloroformates.

The amide from an α-hydroxyacids is condensed with alkyl chloroformate[17] [18] or with dialkyl carbonates[19] [20] producing the corresponding 2,4-oxazolidindione.

In order to obtain 2,4-oxazolidinedion can be used:

a) alkyl chloroformate and the amide of the α-hydroxyacid heated together;

b) a solution (inert solvent required) containing acyl chloroformate, the amide and potassium carbonate.

---

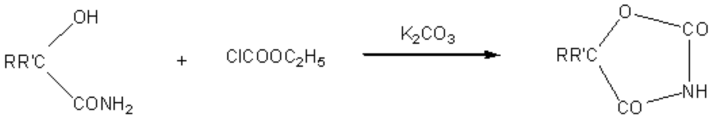
[17] Altwegg, J., and Ebin, D, U. S. patent 1,375,949 (April 26, 1921); Chem. Abstracts **15**, 2641 (1921) ;

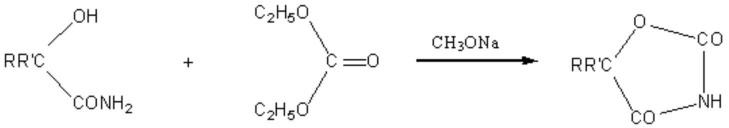
[18] Société Chimique des Usines du Rhône, Anciennement Gillard, P. Monnet et Cartier, British patent 159,153 (June 5,1920); Chem. Abstracts 15, 1965 (1921);

[19] Wallingford, V. H., U. S. patent 2,338,220 (january 4, 1944); Chem. Abstracts **38**, 3666 (1944);

[20] Wallingford, V. H., Thorpe, M. A. and Stoughton, R. W., J. Am. Chem. Soc. **67**, 522-3 (1945)

When dialkyl carbonates are used, the conditions are similar to those used for esters and urea condensation. Furthermore, higher yield are obtained when sodium methoxide is used.



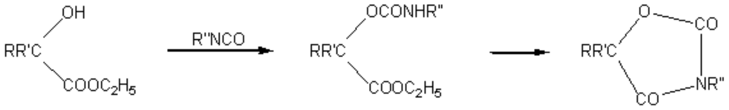


3.1.2.6. Cyclization of urehanes of hydroxyacids and esters.

The interaction between alkyl or aryl isocyanates with esters of α-hydroxyacids produces urethanes, which cyclize to 2,4-oxazolidindiones by heating[21].

---

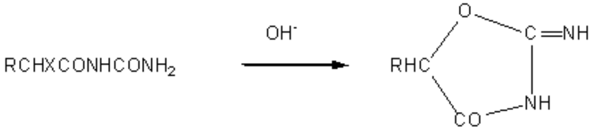
[21] Koninklijke Pharmaceutische fabriken voor Brocades-Stheeman & Pharmacia, Duch patent 69,840 (April 15, 1952); Chem. Abstracts **47**, 1745 (1953);



The main advantage of this procedure is that 3-alkyl-2,4-oxazolidindione is directly formed. The substituent bound to nitrogen depends from the isocyanate used.

3.1.2.7. Preparation using ester of halogens acids and 5-bromobarbituric acids.

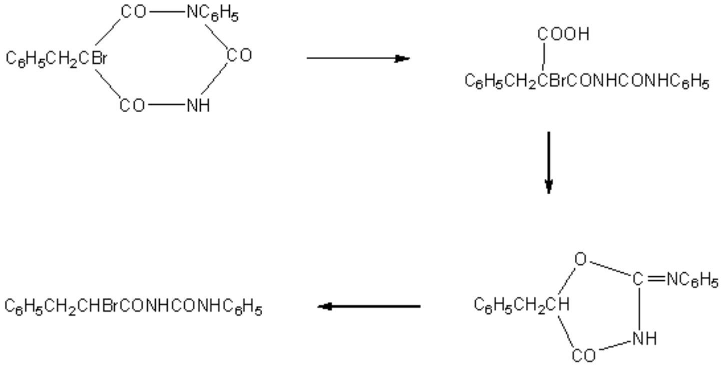
The cyclization of the a-halogenoureidi to 2-imino-4-oxazolidone is induced by the use of bases. Thus, 2-imino-4-oxazolidones can be transformed to 2,4-oxazolidinediones.



5-bromobarbituric acids treated with aqueous alkali produces the intermediate bromourea. The following condensation with the ester of α-halogenacids leads into 2-imino-4-oxazolidones[22].

---

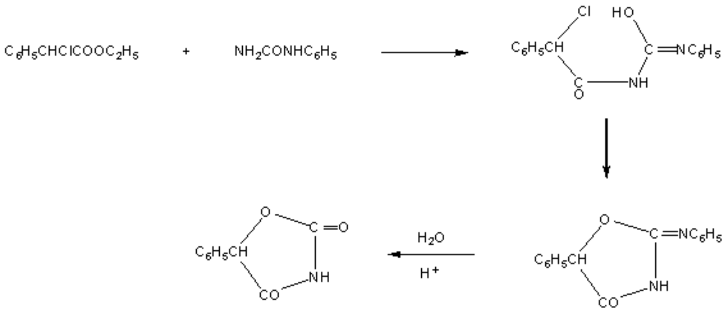
[22] Aspenlund, H., Finska Kemistsamfundets Medd. **49**, 49-8 (1940); Chem. Abstracts **35**, 3634 (1941);



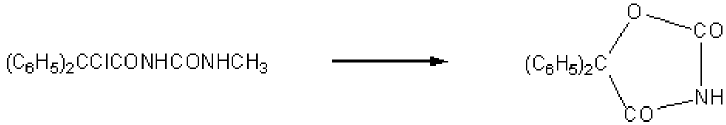
The reaction of α-chlorine ester with urea or substituted ureas produce 2-imino-4-oxazolidone[23] and also minor amounts of 2,4-oxazolidinediones which are formed by basic hydrolysis of the 2-imino compound.

---

[23] Aspenlund, H., Acta. Acad. Aboensis, Math. Et Phys. **10**, No. 9, 7 pp. (1936);



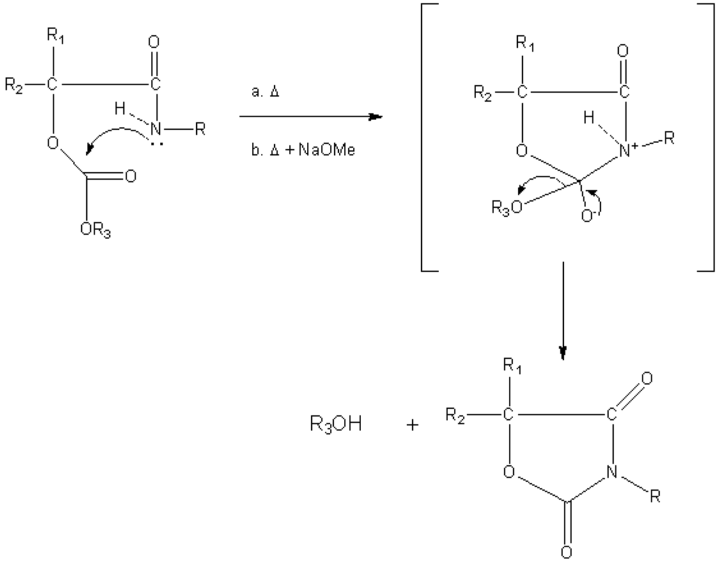
1-diphenylchloroacetyl-3-methylurea in pyridine and benzene is converted into 5,5-diphenyl-2,4-oxazolidinediones. A 91% yield is obtained.



3.1.2.8. Pyrolisis of carbamates.

The oxazolidinediones are obtained in good yield when temperature is in the range 150-230 ºC. When traces of sodium methoxide are used, lower reaction temperatures are needed. The R groups do not interfere in the reaction rate. However, when basic catalysts are not used R1 and R3 influence the reaction rate. When R= *p*-ClC_6H_4-, R_1= H, R_2= CH_3-, and R_3 is CH_3-, C_2H_5-, *n*-C_3H_7-,

$ClCH_2CH_2$-, $ClCH_2CH_2CH_2$- the reaction temperatures observed are: 150-152°C, 180°C, 188-190°C, 205°C and 205-210°C respectively[24].



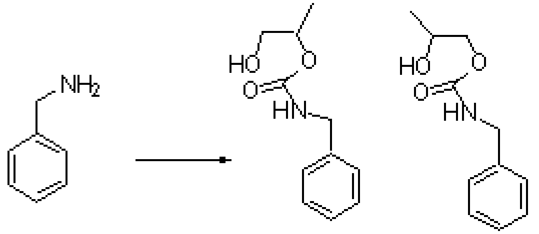
3.1.2.9. 2,4-oxazolidinediones synthesis from benzylamine and cyclic carbonates.

3.1.2.9.1. Adduct synthesis

---

[24] Holmberg, G. A., Acta Chem. Scand. **6**, 502-7 (1952);

The eequimolecolar solventless reaction between propilenecarbonate (X) and benzylamine (13) leads into a mixture of two adducts (14,15). These adducts, a primary and a secondary alcohol, are constituted by a carbamate and an alcohol function. The reaction is achieved by heating at 80 ºC during 24 hours or irradiating by microwaves for a few minutes[25].



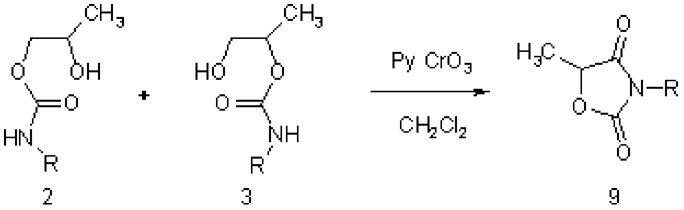
(13) (14) (15)

The oxidation of 14 and 15 using CrO_3-pyridine[26] leads to the corresponding 3-alkyl-2,4-oxalodinediones. 85% yields were obtained.

---

[25] Galliani G., Orlandi M., Rindone B., Terraneo A., PCT Int. Appl. WO2006122782A1, **2006**, *145, 505969;*

[26] Ratclffe, R.; Rodehorst, R., *J.Org.Chem.,* **1970**, *35,* 4000-402;



3.1.3. *Features of the 2,4-oxazolidinediones*

The physico-chemical properties and the reactivity of the 2,4-oxazolidinediones have been incompletely studied several decades ago. The more significant features are reported below.

2,4.oxazolidinediones with aliphatic substituent are crystal with low melting points (30-100 ºC). However, the N-alkyl derivates are oils. These oils can be distilled under reduced pressure without decomposition.

The melting point of 5-aryl-2,4-oxalidinediones is high (100-200 ºC). They crystallize easily in hot water.

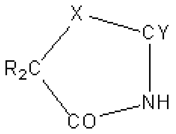
3-aryl-derivatives are sparingly soluble in water, 3-alkyl-2,4-oxazolidinediones are very soluble in aprotic solvents.

2,4-oxazolidinediones containing a free imidic hydrogen are weak acid (pKa=6.0). They can form salts when mixed with organic bases. Furthermore, they form salts when mixed with metal ions such as:

calcium, magnesium, copper, mercury or silver[27]. Sodium and potassium salts are used for the alkylation of 2,4-oxazolidinediones.

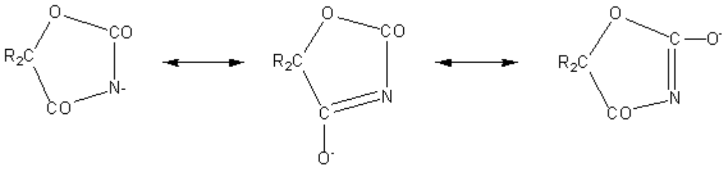
Acidity decreases following the order:

-SCSNH- > -OCONH- > -SCONH- > -NHCONH-



Oxazolidinediones are stable when in aqueous solution. However, they transform into amides and later to α-hydroxyacid when mixed with an alkaline solution.

The stability of the salt is explained by resonance structures.



---

[27] Clemmensen, E., and Heitman, A. H. C., Am. Chem. J. **40**, 280-302 (1908);

2,4-oxazolidindiones are a cyclic urethane (1,2,3 position), a cyclic amide (3,4,5 position), therefore hydrolysis of the ring produce amides or urethanes[28].

Hydrolysis of 3-alkyl-2,4-oxazolidinediones breaks down a-b bond leading to an amide[29] [30]. However, the breakdown of the c bound is rarely produced to obtain urethanes[31] [32] [33].

---

[28] Fisher, E., and Fisher, H. O. L., Ber. **47**, 780 (1914);

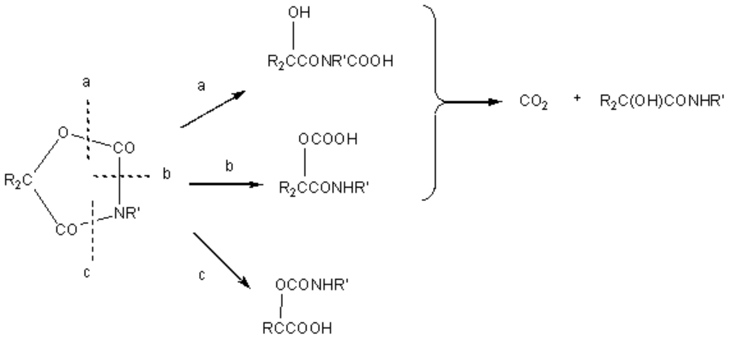
[29] Davies, J. S. H., and Hook, W. H., J. Chem. Soc. **1950**,30-4;

[30] Spielman, M. A., J. Am. Chem. Soc. **66**, 1244 (1944);

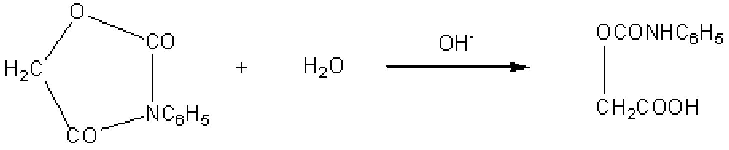
[31] Lambling, E., Compt. Rend. **127**, 188-90 (1898);

[32] Lambling, E., Bull. Soc. Chim. [3] **27**, 441-51 (1902);

[33] Lambling, E., Bull. Soc. Chim. [3] **27**, 606-11 (1902);



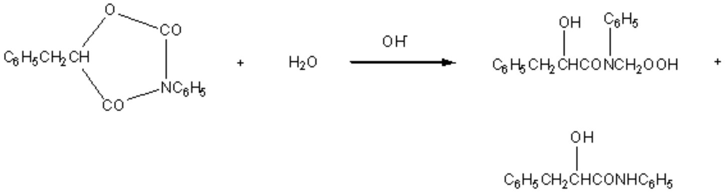
The basic hydrolysis of 3-phenyl-2,3-oxazolidinediones produces phenylurethanes of glycolic acid.

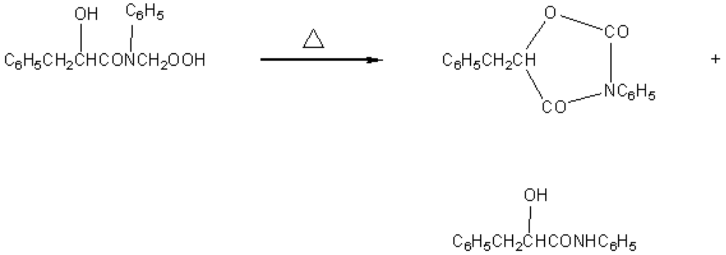


The hydrolysis of 5-benzyl-3-phenyl-2,4-oxazolidinediones produces a mixture of anilide and carbamic acid[34]. The pyrolisis of the acid produces the anilide and a small amount of oxazolidinedion.

---

[34] Aspenlund, H., Acta. Acad. Aboensis, Math. Et Phys. **10**, No. 14, 29 (1937);





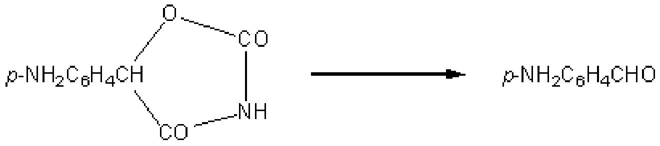
Alloxane and an aromatic amine produce the respective 5-p-aminophenyl-2,3-oxazolidinediones by basic hydrolysis.

Dialuric acid or oxazolidinediones stirred with sulfuric acid at 150-160 ºC during 10 minutes lead into aromatic aldehyde[35] [36].

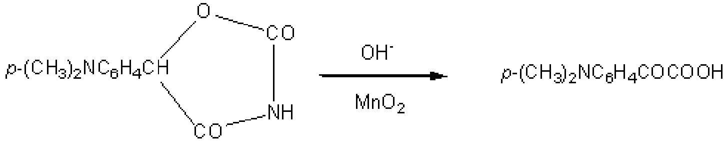
---

[35] Chemische Fabrik Boehringer & Söhne, German patent 108, 026 (October 30, 1899);

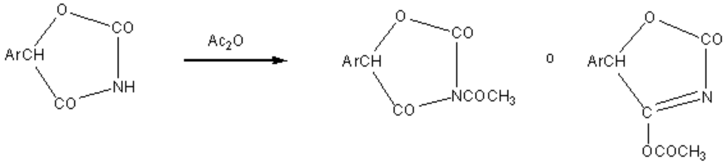
[36] Ferguson, L. N., Chem. Revs. **38**, 232 (1946)



The aromatic aldehydes are also formed by hydrolysis of 2,4-oxazolidinediones using a weak oxidant in the media.



An acetylderivative can be obtained by reaction of 5-(2,4-dimethoxyphenyl)-2,3-oxazolidindiones with acetic anhydride. Furthermore, the product is not soluble in basic media.



3.1.4. DBU chemistry

DBU is a guanidinic base (strong nitrogenated organic bases) which can be used in organic synthesis in processes such as dehydrohalogenation[37], condensation promoter[38], and catalyst in methylation[39].

Iwani et al[40] and Perez et al[41] observed the formation of a zwitterionic stable adduct which precipitates when a DBU solution in acetonitrile, is bubbled with CO_2.

Jessop[42] reported that such adduct is just formed when water is present into the solvent. Furthermore, its spectroscopic (X-ray

---

[37] Reed D. J., Snedecor, T. G., **The Dow Chemical Company :** U.S. PATENT , 4 pp. CODEN: USXXAM US 5210344 A 19930511 CAN 119:138716 AN 1993:538716;

[38] Jiang N., Wang J., *Tetrahedron Letters,* **2002,** 43, 1285–1287;

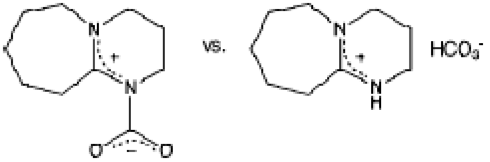
[39] Shieh W-C., Dell S., Repic O., *Organic letters* , **2001,** vol 3, n 26, 4279 4281;

[40] Iwani M.; Kudo K. , Sugita N. , Takezaki y. , *Sekiyu Gakkaishi* **1978**, 21, 290-296;

[41] Perez E.R. , da Silva M.O. ; Costa V. C. , Rodrigues-Filho U. P. , Franco D. W. ; *Tetrahedron Lett.* **2002,** 43, 4091- 4093;

[42] Heldebrant D.J, .Jessop P.G, Thomas C.A., Eckert C. A., Liotta C.L. *J. Org. Chem* **2005,** 70, 5335-5338;

crystallography, ^{1}H and ^{13}C NMR) and conductimetric data show that bicarbonate salt is the obtained product.



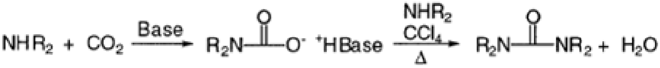
DBU acts as a promoter during the formation of a carbamic salt in the reaction of amines and CO_2[43]. DBU is more involved when the amine is not basic enough to shove the reaction itself.

$PhNH_2 + CO_2 + B \rightarrow [BH][O_2CNHPh]$

An urea is obtained when dehydrating or redducing agents are used[44]. However, a carbamate is obtained when an alkylating reagent is used.

---

[43] Jeremy L.P., Andreatta, R.,Horvey L. K,. Edie C F,, Luco A.L., Mirchandani A, Darensbourg D J., Jessop P. G ., *J. Org. Chem.,* **2008,** 73, 127-132;



---

[44] Cooper, C. F.; Falcone, S. J. *Synth. Commun.* **1995**, 25, 2467–2474;

3.2. Adducts, obtained from cyclocarbamates and phenylamines, oxidation using oxygen and catalyzed by TEMPO and copper and manganese nitrates.

Greener approaches for oxazolinediones synthesis were design by our group (see below).

In order to avoid the use of CrO_3, 5 bar of oxygen (98%), a catalytic amount of 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO) (3), $Cu(NO_3)_2$, $Mn(NO_3)_2$ in acidic media (acetic acid and p-toluensulfonic acid) at 50 ºC were mixed with the adducts formed by method 8 during 24 hours. 3-benzyl-2,4-oxazolidinediones (5) was obtained with a 20% yield.

3.3. Synthesis of oxazolidinediones using primary amines, CO_2 and DBU.

In this chapter is presented a greener methodology for the synthesis of oxazolinediones using CO_2.

Following Perez et al[45] experience, a first protocol was proposed. The DBU-CO_2 adduct was expected to be obtained by bubbling of CO_2 into a DBU-acetonitrile solution under atmospheric pressure.

---

[45] Aspelund, H., *Acta Acad. Aboensis, Math. Et Phys*. **1939,** 11, No. 7.Chem. Abstracts 33, 6802;

Metallic sodium was used in order to obtain a Williamson like intramolecolar cyclization. However, such a procedure leads into the only formation of side products. However, it was observed that the reaction was accomplished after three days under stirring. (Fig 1)

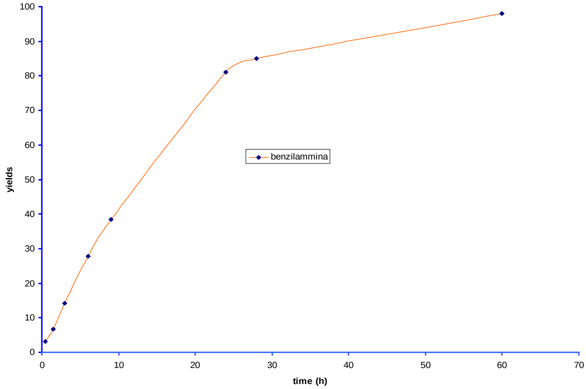
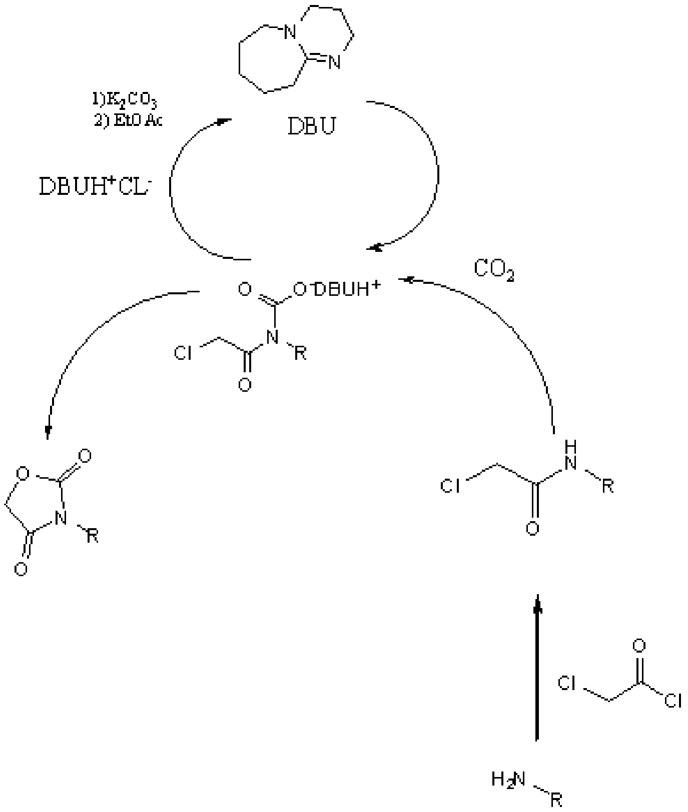


Figure 1. Reaction evolution during three days

The reaction was unsuccessfully carried out using water as solvent, and under solventless conditions. No reaction was observed when water was used and low reaction yields were observed in solventless condition.

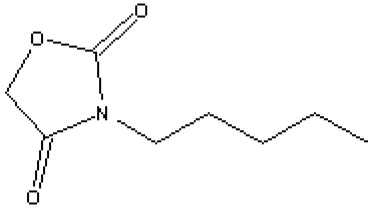
The reaction was finally performed under CO_2 pressure. Scheme 3 summarizes the reaction steps.

N-benzyl-oxazolinedione (**2**) was obtained when N-benzyl-chloroacetamine (obtained by the reaction of equimolecular amounts of benzylamine and chloroacetylchloride, catalyzed by piperidine) was kept with DBU under pressure of CO_2.

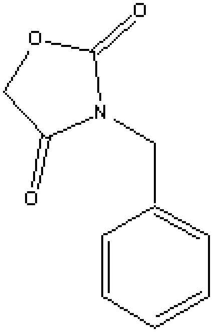


Schema 3. Synthesis of 3-alkyl-2-4-oxazolidinedione.

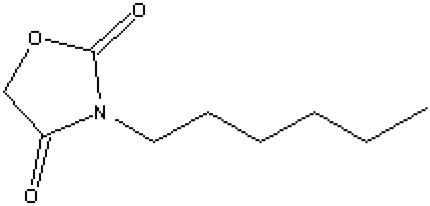
The same reaction path and similar products (1, 3, 4, 5, 6 and 7) yields were obtained when n-penthyl, n-hexyl, cyclohexyl, isopropyl, allyl and methyl-benzylamine were used (Table 2). However, just traces of the corresponding oxazolidinedione (8 and 9) were obtained when aniline and adamantylamine were used. This suggests that features such as alkalinity and steric hindrance of the amines could have an important role during the reaction.



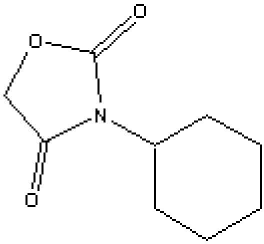
1



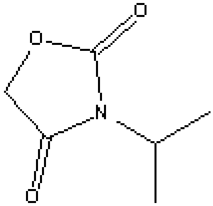
2



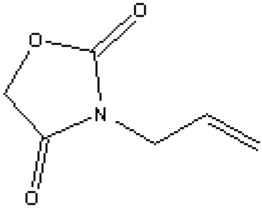
3



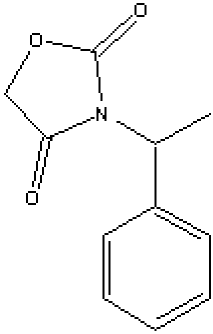
4



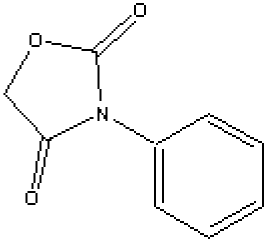
5



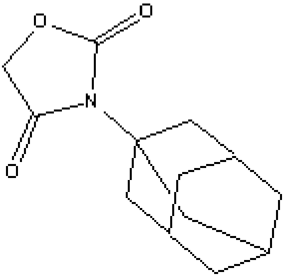
6



7



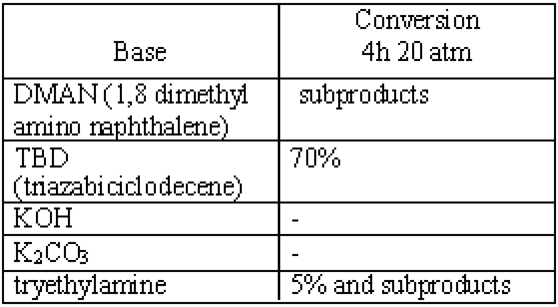
8



9

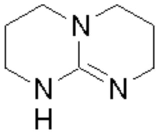
3.3.1. *Experimental*

0.01 mol of amine hydrochloride were kept under 20 atm of CO_2 with an equimolecular amount of DBU during 4 hours at 80 ºC. Oxazolidinediones were purified using a silica gel column and a 1:1 dichloromethane: ethyl acetate as eluent. Reaction products were then analyzed using GC-MS.

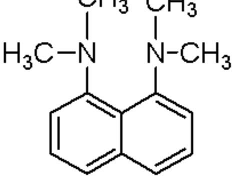


Base	Conversion 4h 20 atm
DMAN (1,8 dimethyl amino naphthalene)	subproducts
TBD (triazabiciclodecene)	70%
KOH	-
K_2CO_3	-
tryethylamine	5% and subproducts

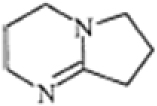
Table 1. Obtained yields for the different primary bases used.



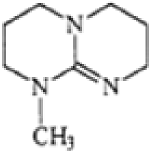
DMAN



TBD



DBN



MTBD

Primary amine	Oxazolinedione yield (%)
Benzylamine	97
n-pentylamine	95
n-hexylamine	97
Cyclohexylamine	87
Allyamine	86
Isopropylamine	88
Benzyl-methylamine	82
Anilina	traces
Adamantylamine	traces

Table 2. Obtained yields for the different primary amines used.

3.4. Reaction of 4-benzyl-5-methyl-1,3-oxazolidine-2,4-diones with Grignard reagents and lithium alkyls to give O-acyl-N-benzyllactamides

3.4.1. Introduction

1,3-oxazolidine-2,4-diones are useful intermediates for the preparation of biologically active compounds[1]. These compounds are hydrolyzed in alkaline conditions by attack to the three available bonds, namely the amide C-N bond and the two carbamate C-O and C-N bonds, depending on substrate and reaction conditions. No further data on their reactivity with nucleophiles are available. Recently, we found that 3,5-dialkyl-1,3-oxazolidine-2,4-diones (1) react with primary aliphatic amines to give N-lactylureas (2) (Scheme 1). Reactions are performed in solventless conditions, rates being enhanced by microwaves[2]. The carbamate carbonyl is attacked by the amine nitrogen and the carbon-oxygen bond is broken during the reaction.

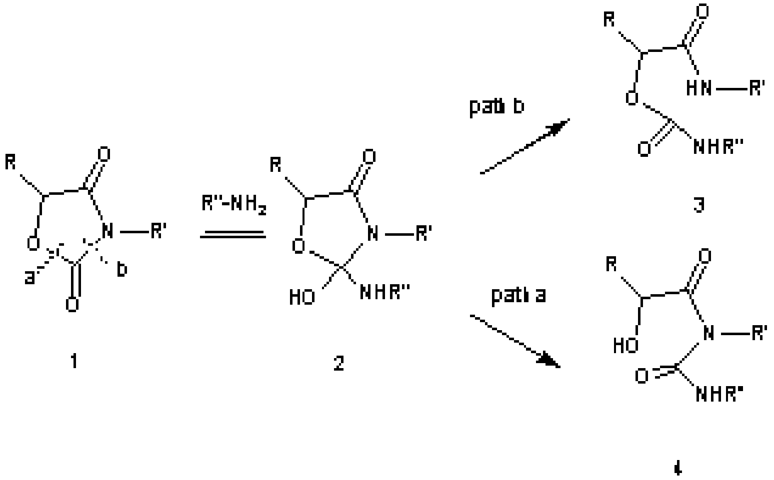
---

[1] Clark-Lewis, J.W *Chem. Rev.*, **1958**, *58,* 63-99;

[2] Galliani, G.; Orlandi, M.; Rindone, B.; Terraneo, A. WO2006122782A1; *Chem. Abs.* **2006**, *145,* 505969;

3.4.2. Discussion and results

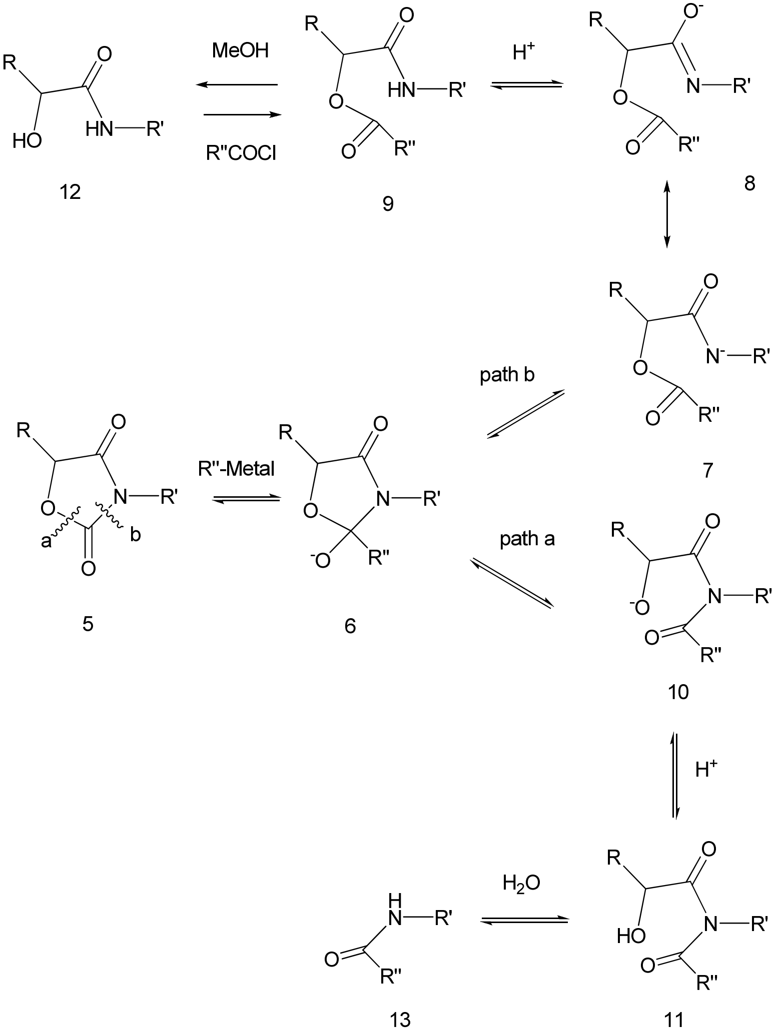
In search for additional data on the reactivity of 3,5-dialkyl-1,3-oxazolidine-2,4-diones with nucleophiles, 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione (1: R = Me; R' = Bz) was reacted with several carbon centered nucleophiles. The starting material was prepared by reaction of a mixture of urea and ethyl lactate with sodium ethoxide in ethanol, followed by N-alkylation[3].



---

[3] Stoughton, R.W. *J.Am.Chem.Soc.*, **1941**, *63*, 2376-2379

With Grignard reagents and with lithium alkyls, the reaction product obtained at low temperature (-30°C) was identified as an O-acyl-N-benzyllactamide (3: R = Me; R’ = Bz). No reaction was observed with either nitromethane anion sodium anion or with the enolate of ethyl acetoacetate sodium salt. The reacting carbonyl was again the carbamate carbonyl but, unlike in the case of primary aliphatic amines, the carbon-nitrogen bond was broken during the reaction, as shown in scheme 1.



Scheme 1. Reaction of 3,5-dialkyl-1,3-oxazolidine-2,4-diones (1) with nucleophiles.

Table 1 (entries a-g) reports the yields obtained after flash chromatography of the crude reaction mixture which contained only the reaction product and starting material. Yields are not optimized. The reaction products were identified by IR, LC-MS, ^{1}H- and ^{13}C-NMR[4]. Their structure was confirmed by methanolysis in the presence of a catalytic amount of sodium methoxide. In these conditions N-benzyllactamide (3) was formed, identified with a sample prepared by a literature method[8] (Scheme 2). Moreover, the structure of compounds (3) in entries a-c was confirmed by acylation of N-benzyllactamide (3) to the correspondig O-acyl-N-benzyllactamide (3: R = Me; R’ = Bz).

Reactions of 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione (1: R = Me; R’ = Bz) with these carbon centered nucleophiles in refluxing tetrahydrofuran gave mixtures of O-acyl-N-benzyllactamide (3: R = Me; R’ = Bz). and of another product. Its LC-MS suggested that it was an isomer of O-acyl-N-benzyllactamides (3: R = Me; R’ = Bz). The same products were obtained by raising the temperature of the reaction performed at –30°C to reflux temperature before quenching and work-up or by reacting O-acyl-N-benzyllactamides (3: R = Me; R’ = Bz). with one equivalent of any Grignard reagent at reflux

---

[4] Ratchford, W.P., Fisher, C.H. *J.Org.Chem.* **1950**, *15*, 317-325

temperature in tetrahydrofuran. O-acyl-N-benzyllactamides (3: R = Me; R’ = Bz) did not undergo any reaction when treated in refluxing tetrahydrofuran in the absence of a base.

The new products were identified as N-acyl-N-benzyllactamides (5: R = Me; R’ = Bz). The comparison of ^{1}H- and ^{13}C-NMR spectra of O-acyl-N-benzyllactamides (3: R = Me; R’ = Bz) and of the corresponding N-acyl-N-benzyllactamides (5: R = Me; R’ = Bz) confirmed the structure of these compounds[5], which is similar to the ring opening of 1,3-oxazolidine-2,4-diones with primary amines[2]. For instance, when R = methyl[4,5], the shift of the quartet of C-H (lactate) from 4.35 □ to 4.49 □ indicates the change from an acetate to a free hydroxyl group, and the shift from 4.01 □ (singlet) to 3.71 □ (broad) indicates the change from a N-H proton to a hydroxyl proton.

N-acyl-N-benzyllactamides (5: R = Me; R’ = Bz) are much less stable than the corresponding N-lactylureas (2), as they are easily hydrolyzed to N-benzylamides during aqueous work-up.

4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione (1: R = Me; R’ = Bz) reacts with nucleophiles as shown in Scheme 1. Both nitrogen and carbon nucleophiles attack the carbamate carbonyl to give presumably

---

[5] Fein, M.L., Filachione, E.M. *J.Am.Chem.Soc.* **1953**, *75*, 2097-2099;

the adduct (5) and eventually its anion (6). This fragments via path a) to give lactylureas (2), via path b) to give N-acyllactamides (3). Compound (3) was calculated by ab initio B3LYP STO-31G* to be 10 kcal mol^{-1} more stable than compound (2). Hence, when the nucleophile is an amine thermodynamic control occurs in the reaction at 80 °C and the most stable product is formed.

When the nucleophile is a strong base such as Grignard or organolithium reagents the equilibrium system contains also the anion (6), corresponding to the initial adduct (5), the resonance-stabilized nitrogen-centered anion (7) and the oxygen-centered anion (8). Also in this case thermodynamic control occurs in the reaction at -30 °C and the most stable anion is formed.

Raising the temperature of this reaction to refluxing tetrahydrofuran or adding a base resulted in the formation of mixtures of (4), which derive from the alkaline hydrolysis of (3), and (2). This is probably a temperature effect on the composition of the equilibrium.

The reaction of Grignard reagents and lithium alkyls with 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione at –30°C seems to have a broad synthetic application. In fact, 4-benzyl-5-n-butyl-1,3-oxazolidine-2,4-dione, 4-n-hexyl-5-methyl-1,3-oxazolidine-2,4-dione, and 4-n-pentyl-5-methyl-1,3-oxazolidine-2,4-dione gave the corresponding O-acyl-N-substituted lactamides under the same experimental conditions (Table 1, entries h,i,j)

The present method is an alternative to the preparation of O-acyl-N-alkyllactamides, which is currently performed by direct acylation of the corresponding N-alkyllactamides[6]. The method is particularly valuable when the acyl moiety is not available and should be obtained by homologation of a shorter chain, for instance by reacting a Grignard reagent with carbon dioxide. The present method is actually a way to extend a Grignard reagent by a C_1 unit. The advantage of the method is easily seen by observing entries f and g of Table 1, where simple acylation cannot be performed.

3.4.3. References

7.Typical Procedure for addition of either Grignard Reagents or Lithium Alkyks. 2.0 g of 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione (9.75 mmoles) were dissolved in 40 mL of anhydrous tetrahydrofuran. The solution was cooled at –40°C under nitrogen. 3.25 mL of methyl magnesium chloride 3 M in tetrahydrofuran (9.75 mmoles) were dropped into the solution, by keeping the temperature below –30°C. The temperature was then raised from –30°C to 5°C in 5 hours, this final temperature being maintained for an additional

---

[6] Kamimura, A., Omata, Y., Kakehi, A.,Shirai, M. *Tetrahedron*, **2002**, *58*, 8763-8770

hour. After quenching with 200 mL of a saturated aqueous solution of ammonium chloride, the mixture was extracted with methylene chloride (2 x 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with n-hexane/ethyl acetate 4:1.

(b) **Reaction with the lithium derivative of the sodium enolate of methyl acetoacetate (entry f).** 1.8 mL of methylacetoacetate (17 mmoles) are added dropwise in a suspension of 0.41 g of sodium hydride (17 mmoles) in 200 mL of dry tetrahydrofuran at –15°C under nitrogen atmosphere. The mixture was stirred for 40 minutes, then 6.8 mL of 2.5 M butyl lithium in tetrahydrofuran (17 mmoles) were added dropwise at the same temperature. A solution of 2.0 g of 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione in 30 mL of dry tetrahydrofuran was added at –15°C. The mixture was then allowed to reach 0°C during 2 hours. Work-up as in reference 4a.

Reaction with the lithium derivative of 2-methyl-1,3-dithiane (entry g). 0.93 mL of 2.5 M butyl lithium in tetrahydrofuran (10 mmoles) were added dropwise into a solution of 2-ethyl-1,3-dithiane (1.5 mL, 12.5 mmoles) in 100 mL of dry tetrahydrofuran at –20°C under argon atmosphere. After stirring for 30 minutes at the same temperature, a solution of 2.0 g of 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione in 30 mL of dry tetrahydrofuran was added dropwise at –

20°C. The mixture was allowed to reach 20°C. Work-up as in reference 4b.

Spectroscopic Data for Reaction Products (Table 1). All products where analyzed by LC/MS (column Gemini C18, 5 micron, 4.6 x 150 mm, 80% ammonium acetate 0.01M pH 3.5, 20% acetonitrile, 30°C) giving a peak at the corresponding M+1 (positive ionization). For all ^{1}H-NMR and ^{13}C-NMR: 400 MHz, CDCl$_3$.

(1) Compound **2a**: IR (KBr): 3275, 1718, 1702, 1640 cm^{-1}. ^{1}H-NMR: δ = 7.33 (t, *j* = 2.4 Hz, 4H), 7.26 (d, *j* = 2.8 Hz, 1H), 4.50 (AB, *j* = 16.0, 1H), 4.47 (AB, *j* = 16.0 Hz, 1H), 4.35 (q, *j* = 8.0 Hz, 1H), 4.08 (s, 1H), 1.41 (d, *j* = 8.0 Hz, 3H), 1.29 (s, 3H). ^{13}C-NMR: δ = 158.8 (C=O), 138.3 (C=O), 129.1 (CH), 128.1 (CH), 128.0 (CH), 88.5 (C), 80.6 (CH), 43.8 (CH$_2$), 24.2 (CH$_3$), 13.1 (CH$_3$).

(2) Compound **2b**: IR: 3280, 1720, 1702, 1645 cm^{-1}. ^{1}H-NMR: δ = 7.28-7.18 (m, 5H), 4.39 (AB, *j* = 16.0 Hz, 1H), 4.35 (AB, *j* = 16.0 Hz, 1H), 4.41 (s, 1H), 4.37 (q, *j* = 6.8 Hz, 1H), 1.65 (ddd, *j* = 7.6, 14.4, 22.0 Hz, 1H), 1.48 (ddd, *j* = 7.6, 12.0, 22.0 Hz, 1H), 1.35 (d, *j* = 6.8 Hz, 3H), 0.63 (t, *j* = 7.6 Hz, 3H). ^{13}C-NMR: δ = 159.1 (C=O), 138.4 (C=O), 128.8 (CH), 127.9 (CH), 127.6 (CH), 90.7 (C), 78.5 (C), 43.9 (CH$_2$), 30.7 (CH$_2$), 14.6 (CH$_3$), 8.0 (CH$_3$).

(3) Compound **2c**: IR(KBr): 3260, 1722, 1695, 1650 cm^{-1}. ^{1}H-NMR: δ = 7.36-7.25 (m, 5H), 4.46 (AB, *j* = 16.0 Hz, 1H), 4.42 (AB, *j* = 16.0 Hz, 1H), 4.44 (q, *j* = 6.4 Hz, 1H), 4.39 (s, 1H), 1.72 – 1.44 (overlapping, 2H), 1.41 (d, *j* = 6.4 Hz, 3H), 1.29-1.04 (m, 2H), 1.00-0.87 (m, 2H), 0.70 (t, *j* = 7.2 Hz, 3H). ^{13}C-NMR: δ = 159.1 (C=O), 138.3 (C=O), 128.7 (CH), 128.2 (CH), 127.6 (CH), 90.6 (C), 78.6 (CH), 43.9 (CH$_2$), 37.2 (CH$_2$), 25.8 (CH$_2$), 22.8 (CH$_2$), 14.4 (CH$_3$), 13.9 (CH$_3$).

(4) Compound **2d**: IR(KBr): 2295, 2231, 1730, 1715 cm^{-1}. ^{1}H-NMR: δ = 7.36-7.25 (m, 5H), 4.46 (AB, *j* = 16.0 Hz, 1H), 4.42 (AB, *j* = 16.0 Hz, 1H), 4.44 (q, *j* = 6.4 Hz, 1H), 4.39 (s, 1H), 1.72 – 1.44 (overlapping, 2H), 1.41 (d, *j* = 6.4 Hz, 3H),

1.29-1.04 (m, 2H), 1.00-0.87 (m, 2H), 0.70 (t, *j* = 7.2 Hz, 3H) ^{13}C-NMR: δ = 157.3 (C=O), 137.6 (C=O), 128.8 (CH), 128.4 (CH), 127.8 (CH), 84.9 (C), 83.6 (C), 81.0 (CH), 75.1 (CH), 45.1 (CH_2), 12.9 (CH_3), 3.6 (CH_3).

(5) Compound **2e**: IR(KBr): 3250, 1731, 1697, 1644 cm^{-1}. ^{1}H-NMR: δ = 7.37-7.25 (m, 5H), 5.47 (dd, *j* = 7.2, 17.2 Hz , 1H), 5.04 – 4.96 (overlapping, 2H), 4.50 (AB, *j* = 16.0 Hz, 1H), 4.46 (AB, *j* = 16.0 Hz, 1H), 4.61 (s, 1H), 4.46 (q, *j* = 6.0Hz, 1H), 2.50 – 2.21 (overlapping, 2H), 1.39 (d, *j* = 6.0 Hz, 3H). ^{13}C-NMR: δ = 157.3 (C=O), 137.6 (C=O), 131.5 (CH), 128.8 (CH), 128.4 (CH), 127.8 (CH), 120.0 (CH_2), 89.7 (CH), 78.8 (C), 44.0 (CH_2), 42.6 (CH_2), 14.1 (CH_3).

(6) Compound **2f**: IR (KBr): 3875, 1746,1713, 1695, 1660 cm^{-1}. ^{1}H-NMR: δ = 7.38-7.28 (m, 5H), 5.11 (s, NH), 4.54 (AB, *j* = 16.0 Hz, 1H), 4.49 (AB, *j* = 16.0 Hz, 1H), 4.53 (q, *j* = 6.5 Hz, 1H), 3.70 (s, 3H), 3.05 (d, *j* = 6.5 Hz, 2H), 2.80 (AB, *j* = 16.9 Hz, 1H), 2.77 (AB, *j* = 16.9 Hz, 1H),1.42 (d, *j* = 6.5 Hz, 3H). ^{13}C-NMR: δ = 202.5 (C), 167.2 (C), 158.0 (C), 137.8 (C), 129.3 (CH), 129.2 (CH), 128.2 (CH), 88 (C), 79.7 (CH), 52.9 (CH_3), 49.8 (CH_2), 49.3 (CH_2), 44.2 (CH_2), 14.3 (CH_3) Compound **2g:** IR(KBr): 3280, 1712, 1688, 1640 cm^{-1}. ^{1}H-NMR: δ = 7.46 (d, *j* = 7.3 Hz, 2H), 7.33 (dd, *j* = 7.1, 7.7 Hz, 2H), 7.28(d, , *j* = 7.3 Hz, 1H), 4.93 (AB, *j* = 15.7, 1H), 4.91 (AB, *j* = 15.7,1H), 4.83 (q, *j* = 6.4 Hz, 1H), 3.77 (s, 1H), 3.42 (ddd, *j* = 7.4, 10.4, 13.6 Hz, 1H), 3.18 (ddd, *j* = 7.6, 10.8, 13.8 Hz, 1H), 2.71 (ddd, *j* = 3.4, 6.7, 8.3 Hz, 1H), 2.63 (ddd, *j* = 3.2, 5.3, 8.9 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.95 – 1.88 (m, 1H), 1.47 (d, *j* = 6.4 Hz, 3H), 1.42 (s, 3H); ^{13}C-NMR: δ = 158.5 (N-$\underline{C}$=O), 138.9 (O-$\underline{C}$=O), 128.8 (CH), 128.2 (CH), 97.5 (C), 78.2 (CH), 46.1 (C), 29.3 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 25.6(CH_3), 24.8 (CH_2), 16.7(CH_3).

(7) Compound **2h:** IR(KBr): 3264, 1720, 1695**.** ^{1}H-NMR: δ = 7.35 (d, *j* = 4.0 Hz, 2H), 7.32 – 7.27 (m, 3H), 4.52 (AB, *j* = 16.0, 1H), 4.48 (AB, *j* = 16.0, 1H), 4.19 (q, *j* = 4.0 Hz, 1H), 4.03 (s, 1H), 1.87 – 1.83 (m, 1H), 1.73 – 1.70 (m, 1H), 1.47 – 1.44 (m, 1H), 1.42 – 1.38 (overlapping, 3H), 1.32 (s, 3H), 0.93 (t, *j* = 7.2 Hz, 3H); ^{13}C-NMR: δ = 158.9 (C=O), 138.5 (C=O), 129.0 (CH), 128.0 (CH), 127.8 (CH), 88.6

(C), 84.7 (CH), 43.9 (CH_2), 28.4 (CH_2), 28.1 (CH_2), 24.8 (CH_3), 22.9 (CH_2), 14.3 (CH_3).

(8) Compound **2i:** IR(KBr): 3260, 1732, 1710, 1650 cm^{-1}. ^{1}H-NMR: δ = 4.61 (s, 1H), 4.60 (q, *j* = 6.8 Hz, 1H),), 3.34 (t, *j* = 7.6 Hz, 2H), 1.75 – 1.69 (m, 2H), 1.58 (5, *j* = 7.2 Hz, 3H), 1.48 – 0.91 (overlapping, 8H), 0.89 – 0.87 (overlapping, 6H); ^{13}C-NMR: δ = 157.5 (C=O), 83.7 (C=O), 80.9 (CH_3), 75.3 (CH_2), 42.1 (CH_2), 31.8 (CH_2), 29.0 (CH_2), 27.0 (CH_2), 18.2 (CH_2), 14.4 (CH_3), 13.0 (CH_3), 13.0 (CH_3).

(9) Compound **2j:** IR(KBr): 3306, 1727, 1705, 1642 cm^{-1}. ^{1}H-NMR: δ = 5.76 (ddt, *j* = 7.2, 9.6, 16.1 Hz, 1H), 5.20 – 5.16 (overlapping, 2H), 4.39 (s, 1H); 4.39 (q, *j* = 6.5 Hz, 1H), 3.20 (t, *j* = 7.5 Hz, 2H), 2.63 – 2.57 (ABX, j_{AB} = 14.3 Hz, 1H), 2.46 – 2.40 (ABX, j_{AB} = 14.3 Hz, 1H), 2.01 – 1.98 (m, 1H), 1.68 – 1.58 (m, 1H), 1.38 – 1.30 (overlapping, 7H), 0.91 (t, *j* = 6.7 Hz, 3H); ^{13}C-NMR: δ = 158.5 (C=O), 131.9 (CH), 120.1 (CH_2), 89.6 (C=O), 78.5 (CH), 42.3 (CH_2), 40.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 22.7 (CH_2), 14.4 (CH_3), 14.2 (CH_3).

7. **A typical preparation of an N-acyl-N-benzyllactamide**: 2.0 g of 4-benzyl-5-methyl-1,3-oxazolidine-2,4-dione (9.75 mmoles) were dissolved in 40 mL of anhydrous tetrahydrofuran. 3.25 mL of methyl magnesium chloride 3 M in tetrahydrofuran (9.75 mmoles) were dropped into the solution blanketed with nitrogen, by keeping the temperature below 10°C. The temperature was then raised to reflux and maintained at such temperature for three hours. After quenching with 200 mL of a saturated aqueous solution of ammonium chloride, the mixture was extracted with methylene chloride (2 x 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography,

eluting with n-hexane/ethyl acetate 4:1. In addition to 0,9 g of N-benzyllactamide, 1,1 g of N-acetyl-N-benzyllactamide were recovered, showing the following spectroscopic data: IR: 3380 (broad), 1723, 1655, 1620 cm^{-1}; ^{1}H-NMR: δ = 7.36-7.25 (m, 5H), 4.56 (AB, *j* = 15.6 Hz, 1H), 4.40 (AB, *j* = 15.6 Hz, 1H), 4.49 (q, *j* = 6.6 Hz, 1H), 3.71 (broad, 1H), 1.31 (d, *j* = 6.6 Hz, 2H), 1.27 (s, 3H); ^{13}C-NMR: d = 166.5 (C=O), 138.0 (C=O), 128.7 (CH), 127.5 (CH), 89.4 (C), 82.2 (CH), 43.4 (CH_2), 20.9 (CH_3), 16.8 (CH_3).

Entry	**R_1**	**R_2**	**R_3**	**M**	**Yield (%)**
A	Benzyl	Methyl	Methyl	MgBr	76
B	Benzyl	Methyl	Ethyl	MgBr	80
C	Benzyl	Methyl	n-Butyl	Li	47
D	Benzyl	Methyl	Propynyl	MgCl	64
E	Benzyl	Methyl	Allyl	MgBr	64
F	Benzyl	Methyl	2-methyl-1,3-Dithian-2-yl	Li	44
G	Benzyl	n-Butyl	Methyl	MgBr	62
H	n-Pentyl	Methyl	Ethyl	MgBr	83
I	n-Hexyl	Methyl	Allyl	MgBr	75

4. Avoiding phosgene: Preparation of carbamates and ureas via cobalt-catalyzed oxidative carbonylation of aromatic or aliphatic primary amines and aliphatic amines

4.1.1. Introduction

Phosgene ($COCl_2$) is prepared by reaction of carbon monoxide with chlorine over activated carbon at high temperature[1]. It is a very toxic gas (b.p 7.56 °C) to eyes and nose even at 3 ppm.

The reaction of phosgene with amines is one of the most important industrial methods for the formation of isocyanates, carbamates and ureas[2]. In particular, isocyanates are starting materials for the production of polyurethanes[3].

---

[1] W. Schneider, W. Diller, Ulmann's Encyclopedia of Industrial Chemistry, 5th edition, 1991, A19, 411;

[2] Kirk-Othmer, Third Edition, Wiley Interscience, Vol. 13, p. 799; L. H. Vogt, H. M. Faigenbau, E. Wiberley, Chem. Rev., 63, (1963), 269

[3] K. Weissermel, H. J. Arpe, Industrial Organic Chemistry, 2nd Edition, WCH, Weinheim, 1993, 373;

The environmental risk connected with the use of phosgene encouraged efforts for alternative methods with low environmental impact. For example, dialkyl carbonates react with amines in the presence of lead catalysts[4], sodium hydride catalyst[5], phosphorous acid[6] to form urethanes. However, dialkyl carbonates are usually prepared by reaction of phosgene with an alcohol. More recently, the carbonylation of methanol in gas phase in the presence of a Co or a Cu catalyst has been reported to give dimethyl carbonate in high yields and selectivity[7].

---

[4] Z. H. Fu, Y. Ono, J. Mol. Cat., 91, (1994), 399;

[5] E. Angeles, A. Santillan, I. Martinez, A. Ramirez, E. Moreno, M. Salmon, R. Martinez, Synth. Comm., 24, (1994), 2441;

[6] M. Aresta, C. Barloco, E. Quaranta, Tetrahedron, 51, (1995), 8073;

[7] F. Rivetti, U. Romano, D. Delledonne in P. T. Anastas, T. C. Williamson eds, Green Chemistry, Designing Chemistry for the Environment, ACS Symp. 626, Washington, D. C., (1996), preprints A.C.S. Div. Environ. Chem, 34, (1994), 332 and references therein;

Carbamates may also be obtained by carboxylation of amines. A titanium catalyst[8], dehydrating agents[9] or a tertiary base are needed[10]. Thermal cracking of carbamates forms isocyanates[11].

An alternative to the use of phosgene is the metal-catalyzed oxidative carbonylation of amines to form ureas or carbamates (using

---

[8] M. Aresta, E. Quaranta, Chemtech, 27, (1997), 32; A. G. Shaikh, S. Sivaram, Chem. Rev., 96, (1996), 951

[9] W. D. McGhee, M. Paster, D. Riley, K. Ruettiman, J. Solodar, T. Waldman in P. T. Anastas, T. C. Williamson eds, Green , Designing Chemistry for the Environment, ACS Symp. 626, Washington, D. C., (1996), preprints A.C.S. Div. Environ. Chem, 34, (1994), 206 and references therein;

[10] G. Galliani, B. Rindone, F. Saliu, Tetrahedron Letters, in the press;

[11] S. Fukuoka, M. Chono, M. Kohno, CHEMTECH, 670, (1984), 670 and references therein;

an alcohol as the solvent). This topic has been recently reviewed[12] [13]. Also sulphur[14] or periodate[15] have been used in a metal-free approach.

Cobalt is a relatively non toxic group VIII metal, when compared with second and third row group VIII metals. Hence it was used by us as a catalyst in the oxidative carbonylation of amines. In previous experiments the treatment of aniline derivatives with carbon monoxide (1 bar) and dioxygen (1 bar) in methanol in the presence of N,N-bis(salicylidene)ethylenediaminocobalt(II) (1) (Scheme 1) as the catalyst led to the formation of azo derivatives, deriving from an oxidation reaction; carbamates and ureas, deriving from oxidative carbonylation. The selectivity in the oxidative carbonylation reaction

---

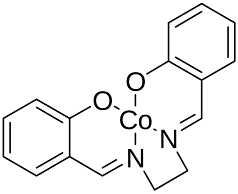
[12] B. Gabriele, G. Salerno, M. Costa, Topics in Organometallic Chemistry (2006), 18 (Catalytic Carbonylation Reactions), 239, Springer GmbH;

[13] D. J. Diaz, A. K. Darko, L. McElwee-White, European Journal of Organic Chemistry (2007), (27), 4453;

[14] T. Mizuno, T. Nakai, M. Mihara, Heteroatom Chemistry (2009), 20(1), 64-68; T. Mizuno, M. Mihara, T. Iwai, T. Ito, Y. Ishino, Synthesis (2006), (17), 2825;

[15] P. A. Shelton, Y. Zhang, Y., T. H. H. Nguyen, L. McElwee-White, Chemical Communications (2009), (8), 947;

was not high. An isocyanate was intermediate in these reactions, and could be evidenced by performing the oxidative carbonylation in methylene chloride[16]. At higher dioxygen and carbon monoxide partial pressures, ureas were formed in good yields, with only small amounts of carbamates and azo derivatives. Aromatic amines having certain ortho-substituents also gave cyclic ureas via a metal-induced oxidative carbonylation-cyclisation pathway[17].



(1)

---

[16] F. Benedini, M. Nali, B. Rindone, S. Tollari, S.Cenini, G. La Monica, F. Porta, J. Mol. Catal., 34 (1986), 155;

[17] A. Bassoli, B. Rindone, S. Tollari, J. Mol. Catal., 60, (1990), 41;

The generality of this reaction was checked submitting five groups of ortho-, meta- and para-substituted anilines to the cobalt-catalyzed oxidative carbonylation. Reaction products were isocyanates and carbamates in the ortho- and the meta-substituted substrates. The para substituted substrates formed mainly ureas[18].

Adamantylamine, an aliphatic primary amine lacking α-hydrogens was also submitted to oxidative carbonylation and gave moderate amounts of the corresponding carbamate[19].

Cobalt porphyrinates have been also used in the oxidative carbonylation of aromatic and aliphatic primary amines to isocyanates in the presence of sodium iodide as a co-catalyst[20].

Hence, the cobalt-catalyzed oxidative carbonylation of primary amines is complementary to other synthetic methods for the

---

[18] E. Bolzacchini, S. Meinardi, M. Orlandi, B. Rindone, J. Mol. Cat., 111 (1996), 281;

[19] G. Maddinelli, M. Nali, B. Rindone, S. Tollari, S. Cenini, G. La Monica, F. Porta, J. Mol. Catal., 39 (1987) 71;

[20] T. W. Leung, B. D. Dombeck, J. Chem. Soc. Chem. Commun, (1992), 205;

preparation of ureas and isocyanates such as the Pd-[21] or the W-catalyzed[22] oxidative carbonylation of amines, the use of dimethylcarbonate[23] the ruthenium-catalyzed reductive carbonylation of aromatic nitroderivatives[24], the indirect electrochemical carbonylation of aromatic amines with a palladium catalyst[25].

---

[21] B. Gabriele, G. Salerno, R. Mancuso, M. Costa, J. Org. Chem., 69, (2004), 4741; S. Fukuoka, M. Chono, M. Kohno, J, Chem. Soc., Chem. Commun., (1984) 399; S. Fukuoka, M. Chono, M. Kohno, J. Org. Chem., 49 (1984) 1460; E. W. Stern and M. L. Spector, J. Org. Chem., 31 (1966) 596;

[22] F. Qian, J. E. McCusker, Y. Zhang, A. D. Main, M. Chlebowski, M. Kokka, L. McElwee-White, J. Org. Chem. 67, (2002), 4086;

[23] M. L. Quesada, R. H. Schlessinger, J. Org. Chem, 43, (1978), 3468; U. Romano, G. Fornasari, S. Di Gioacchino, Ger. Offen, 320, (1982), 2690;

[24] S. Cenini, C. Crotti, M. Pizzetti, F. Porta, J. Org. Chem., 53 (1988) 243; C. Crotti, S. Cenini, B. Rindone, S. Tollari, F. Demartin, J. Chem. Soc., Chem. Commun., (1986) 784 , G. La Monica, G. Ardizzoia, G. Maddinelli, S. Tollari, J. Mol. Catal., 38 (1986) 327; G. La Monica, C. Monti, S. Cenini, B. Rindone, J. Mol. Catal., 23 (1984) 89;

4.1.2. Results and discussion

4.1.2.1. Oxidative carbonylation of primary aromatic amines

An aniline derivative (2a-f) was submitted to the cobalt-catalyzed oxidative carbonylation in methanol. The results are shown in Table 1.

---

[25] F. W. Hartstock, D. G. Herrington, L. B. McMahon, Tetrahedron Letters, 35, (1994), 8761;

Table 1 Conversion and yields in the oxidative carbonylation of primary amines with [substrate]:[catalyst] (r) = 10

	T (°C)	Solvent	Reaction time (h)	Conversion %	Isocyanate %	Carbamate %	Urea %	Azoderivative %
4-bromoaniline (2a)	100	MeOH	24	70	9	80	-	-
	60	“	48	16	-	1	88	1
	100	CH_2Cl_2	24	50	28	-	-	-
4-chloroaniline (2b)	100	MeOH	24	100	6	84	-	-
	60	“	48	13	-	1	85	1
	100	CH_2Cl_2	24	100	29	-	-	-
aniline (2c)	100	MeOH	24	99	1	87	1	1
	100	CH_2Cl_2	24	100	42	-	-	-
4-fluoroaniline (2d)	100	MeOH	24	97	1	88	-	1
	60	“	48	96	-	3	80	1
	100	CH_2Cl_2	24	100	39	-	-	-
4-methylaniline (2e)	100	MeOH	24	100	4	85	-	-
	60	“	48	92	-	9	64	4
	100	CH_2Cl_2	24	100	65	-	-	-
4-methoxyaniline (2f)	100	MeOH	24	100	18	70	-	-
	60	“	48	100	43	2	53	1
	100	CH_2Cl_2	24	100	68	-	-	-
1-methylbenzylamine (7)[a]	100	MeOH	24	98	8	48	38	-
i-propylamine (11)	100	MeOH	24	100	-	-	95	-

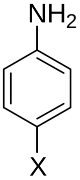
Conversions and selectivity in methyl carbamate (4) were very high in all but one case. Isocyanate (3) was also present in low amounts. The diarylurea (5) and the azoderivative (6) were also occasionally present (Scheme 1) according to the reactions:

$$\text{Ar-NH}_2 + \text{CO} + 0.5\ \text{O}_2 \rightarrow \text{Ar-N=C=O} + \text{H}_2\text{O}$$

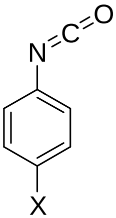
$$\text{Ar-NH}_2 + \text{CO} + 0.5\ \text{O}_2 + \text{CH}_3\text{OH} \rightarrow \text{Ar-NH-COOCH}_3 + \text{H}_2\text{O}$$

$$2\ \text{Ar-NH}_2 + \text{CO} + 0.5\ \text{O}_2 \rightarrow \text{Ar-NH-C(O)-NH-Ar} + \text{H}_2\text{O}$$

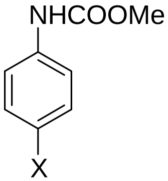
$$2\ \text{Ar-NH}_2 + \text{O}_2 \rightarrow \text{Ar-N=N-Ar} + 2\ \text{H}_2\text{O}$$



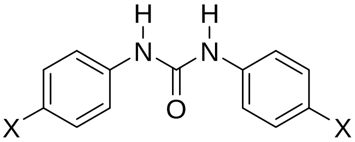
(2)



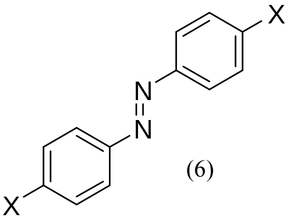
(3)



(4)



(5)



(6)

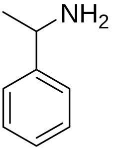
a: X = Br
b: X = Cl
c: X = H
d: X = F
e: X = Me
f: X = OMe

A comparison with the results obtained using a reaction temperature of 60 °C and a reaction time of 48 h [16] (Table 1) shows that at the lower temperature the diarylurea (5) was the major reaction product, and the methyl carbamate (4) was present in lower amounts. Hence, the reaction at 100 °C in methanol for 24 h has preparative value for methyl carbamates (4).

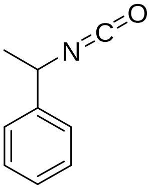
In the oxidative carbonylation of aromatic amines (2a-f) in dichloromethane (Table 1) a nearly quantitative conversion was obtained with all substrates but 4-bromoaniline (2a). The isocyanate (3) was the only reaction product isolated in moderate yields.

The primary benzylic amine 1-methylbenzylamine (7) was then submitted to oxidative carbonylation in the same conditions. A nearly quantitative conversion was obtained. The main reaction product was the carbamate (9), but also the urea (10) was formed in significant yields, together with moderate amounts of the isocyanate (8) and the formamide (11), deriving from carbonylation of the substrate according to the reaction:

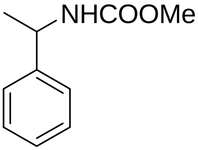
$$\text{Ar-NH}_2 + \text{CO} \rightarrow \text{Ar-NH-CHO}$$



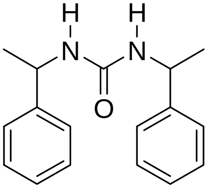
(7)



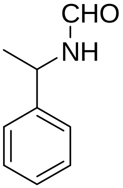
(8)



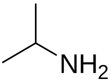
(9)



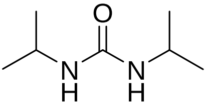
(10)



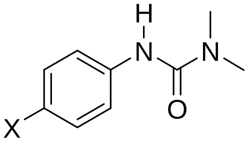
(11)



(12)



(13)



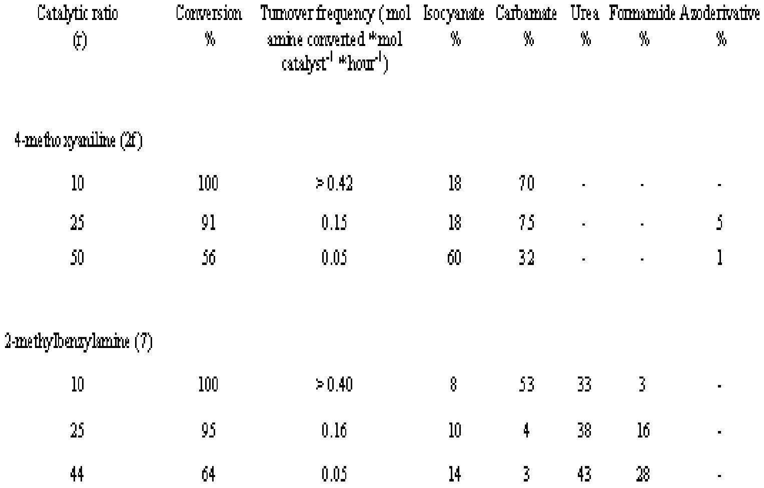
(14)

The primary amine i-propylamine (12) in the same conditions gave the corresponding urea (13) in almost quantitative yields.

In order to have information about the efficiency of the catalyst, the effect of the ratio substrate:catalyst was checked performing the oxidative carbonylation of 4-methoxyaniline (2f) with r = 10, 25, 50.

Table 2 shows the results thus obtained. The reaction was efficient also with lower amounts of catalyst, and the turnover frequency, defined as [mol amine converted * mol catalyst^{-1} * hour^{-1}] was increasingly lower with higher substrate:catalyst ratio, ranging from > 0.42 to 0.05.

Differences were also noticed in the distribution of products. More carbamate (4f) than isocyanate (3f) was formed with the lower catalytic ratio.



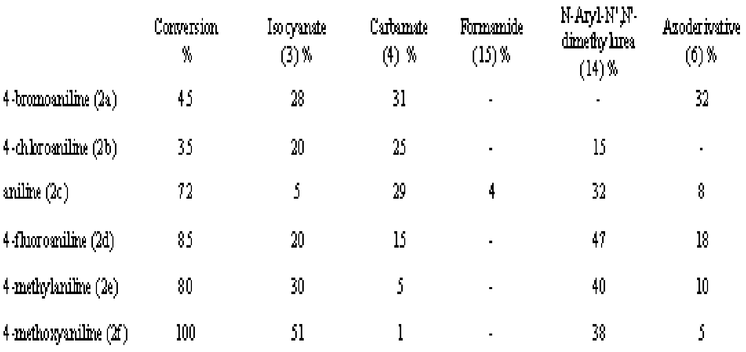
Catalytic ratio (r)	Conversion %	Turnover frequency (mol amine converted *mol catalyst^{-1} *hour^{-1})	Isocyanate %	Carbamate %	Urea %	Formamide %	Azoderivative %
4-methoxyaniline (2f)							
10	100	> 0.42	18	70	-	-	-
25	91	0.15	18	75	-	-	5
50	56	0.05	60	32	-	-	1
2-methylbenzylamine (7)							
10	100	> 0.40	8	53	33	3	-
25	95	0.16	10	4	38	16	-
44	64	0.05	14	3	43	28	-

Table 2 Conversion, turnover frequency and yields in the oxidative carbonylation of 4-methoxyaniline (2f) and 2-methylbenzylamine (7) in methanol with various [substrate]:[catalyst] (r) ratios

A similar experiment was performed using 1-methylbenzylamine (7) as the substrate. Again, more carbamate (9) than isocyanate (8) was formed with the lower catalytic ratio, but the yield in urea (10) was not affected by the catalytic ratio. The yield in formamide (11) was high with the higher catalytic ratio. The turnover frequency was similar to that observed with 4-methoxyaniline (2f) and ranged from > 0.40 to 0.05.

In search of unsymmetrical ureas, an aqueous 50% solution of dimethylamine was added in 4:1 excess over the aromatic amine substrate (2a-f) and the oxidative carbonylation was performed in the usual conditions. Here, N,N'-diarylureas (5) were completely replaced by N-aryl-N',N'-dimethylureas (14) (Table 3) according to the reaction:

$$\mathrm{Ar\text{-}NH_2 + CO + 0.5\ O_2 + (CH_3)_2NH \rightarrow Ar\text{-}NH\text{-}CO\text{-}N(CH_3)_2 + H_2O}$$

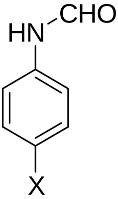


	Conversion %	Isocyanate (3) %	Carbamate (4) %	Formamide (15) %	N-Aryl-N',N'-dimethylurea (14) %	Azoderivative (6) %
4-bromoaniline (2a)	45	28	31	-	-	32
4-chloroaniline (2b)	35	20	25	-	15	-
aniline (2c)	72	5	29	4	32	8
4-fluoroaniline (2d)	85	20	15	-	47	18
4-methylaniline (2e)	80	30	5	-	40	10
4-methoxyaniline (2f)	100	51	1	-	38	5

Table 3 Conversion and yields in the oxidative carbonylation of aromatic amines (2a-f) in methanol in the presence of dimethylamine

Carbamates (4) and azoderivatives (6) were present in the reaction mixture. A small amount of formamide (15) was observed in one case (X = H). Also tetramethylurea was observed and derived from the reaction:

$$2\ Me_2NH + CO + 0.5\ O_2 \rightarrow Me_2N\text{-}C(O)NMe_2 + H_2O$$

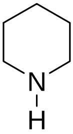


(15)

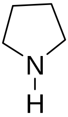
Significant amounts of azoderivative (6) were formed in the presence of dimethylamine. These compounds were present only in trace amounts in the absence of dimethylamine in the same conditions. Hence, the presence of the secondary amine seems to switch the reaction from the oxidative carbonylation to a simple oxidation.

4.1.2.2. Oxidative carbonylation of secondary aliphatic amines

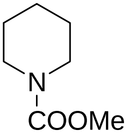
Piperidine (16) and pyrrolidine (17) were submitted to oxidative carbonylation in the usual conditions. The corresponding carbamates (18-19) in good yield and formamides (20-21) in small amounts were obtained in methanol. The ureas (22-23) and small amounts of formamides (20-21) were obtained in dichloromethane (Table 4).



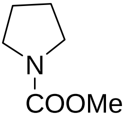
(16)



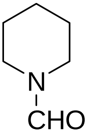
(17)



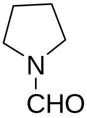
(18)



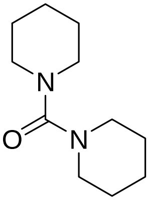
(19)



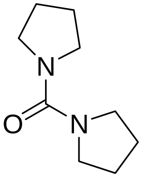
(20)



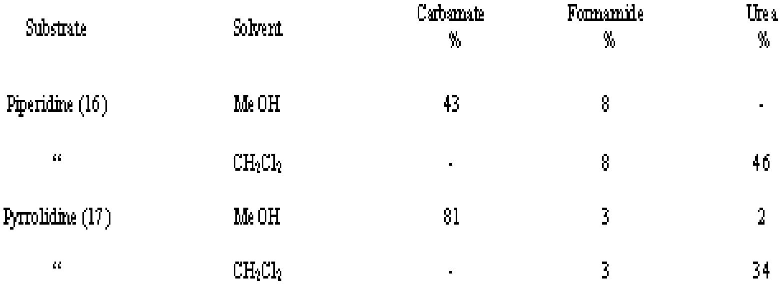
(21)



(22)



(23)

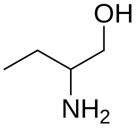


Substrate	Solvent	Carbamate %	Formamide %	Urea %
Piperidine (16)	MeOH	43	8	-
"	CH_2Cl_2	-	8	46
Pyrrolidine (17)	MeOH	81	3	2
"	CH_2Cl_2	-	3	34

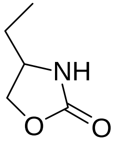
Table 4 Yields in the oxidative carbonylation of secondary aliphatic amines

4.1.2.3. Oxidative carbonylation of 2-aminobutan-1-ol (24)

2-aminobutan-1-ol (24) was submitted to oxidative carbonylation in methanol at 70 °C, in the presence of Co(II) salen (1) (r = 10) with dioxygen (1 bar) and carbon monoxide (10 bar) for 24 h. 4-ethyl-1,3-oxazolidin-2-one (25) was isolated in 32 % yield after chromatographic separation (Scheme 2). Turnover frequency = 0.133 . When this reaction was repeated in dioxane at 120 °C for 4 h with a catalytic ratio r = 200 with dioxygen (1 bar) and carbon monoxide (10 bar) 4-ethyl-1,3-oxazolidin-2-one (25) was isolated in 90 % yield after chromatographic separation. Turnover frequency = 50.



(24)



(25)

4.1.3. Conclusions

In conclusion, the cobalt-catalyzed oxidative carbonylation of primary and secondary amines in methanol gives carbamates mildly and selectively. Unsymmetrical ureas are prepared in the presence of dimethylamine. In dichloromethane moderate amounts of isocyanate are isolated. This procedure seems to be “greener” than that using phosgene or toxic group VIII metals or high pressure of carbon monoxide.

4.1.4. Experimental

Amines were commercial grade reagents. All solvents were distilled before use. The catalyst N,N-bis(salicylidene)ethylenediaminocobalt(II) hydrate (Cosalen) was a commercial product (Aldrich Inc.). Carbon monoxide and dioxygen were high purity grade. GC-MS analyses were performed with a Hewlett Packard 5890A instrument, (split/splitless injector, capillary column SPB-5, 30 m, 0.32 mm I.D.).

4.1.4.1. Reaction procedure

A 5 * 10-2 M solution of the substrate in the appropriate solvent and the appropriate amount of catalyst to result in a [substrate]:[catalyst] ratio 1:10 was put in a glass liner, fitted in an autoclave, charged with dioxygen (2 bar) and carbon monoxide (10 bar) and heated at 100 °C for 24 h in a thermoregulated oil bath. The autoclave was then allowed to cool to room temperature and outgassed. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel Merck 0.05-0.2 mm (R = 20), using dichloromethane-ethyl acetate 1:1 as the eluting mixture. The fractions were then analysed by GLC-MS. Yields were calculated on the converted material unless otherwise stated.

5. General Procedures

5.1. Thin-layer chromatography (TLC)

Thin-layer chromatography (TLC) was performed on Silica Gel 60F254 plates (merk) with UV detection.

5.2. Flash column chromatography

Flash column chromatography was performed on Silica Gel 230-400 mesh (Merk), following procedure described in literature[1]

5.3. Gas chromatography Mass detection (GC-MS)

Mass spectra were recorded on a HEWLETT PACKARD 5890 instrument equipped with a MSD-HP 5971 mass spectrophotometer. A SUPECCO SPB-5 30 m. long, I.D. 0.25 mm, 0.25um thick 95 % dimethylpolyxyloxane column was used.

---

[1] J.Org.Chem., 1979,93,14.

5.4. Nuclear magnetic resonance (NMR)

^{1}H and ^{13}C NMR spectra were recorded on a Varian 400MHz MERCURY instrument at 300 K. Chemical shifts are reported in ppm downfield from MS as internal standard.

5.5. Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra were recorded using a FT-IR AVATAR 360 instrument. Compounds were analyzed on KI disks.

6. Communications

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Isocyanates using procedures not involving phosgene”. 237th National ACS meeting in Salt Lake City, USA. 2009. Poster;

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Functionalization of the unactivated carbon-hydrogen bond via ozonation”. 237th National ACS meeting in Salt Lake City, USA. 2009. Oral;

Galliani Guido, Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, Alberto Terraneo, “Reaction of a 1,3-oxazolidine-2,4-dione with carbon nucleophiles”. National ACS meeting in Salt Lake City, 2009. USA. Oral;

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Oxidative carbonylation of Amino groups for synthetic purposes”. XVII National Congress of industrial chemistry division of the Italian Chemical Society in Genova, Italy. 2008 Poster;

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Funzionalizzazione del legame carbonio-idrogeno non attivato mediante ozonizzazione”. XXXI National Congress of the Organic Chemistry division of the Italian Chemical Society in Rende, Italy. 2007. Poster;

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Preparazione e reattività di 3,5-dialchilossazolidin-2,4-dioni”. XXXI National Congress of the Organic Chemistry division of the Italian Chemical Society in Rende, Italy. 2007. Poster;

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Functionalization of the unactivated carbon- hydrogen via ozonation”. 3rd International Conference on Green-Chemistry in Delft, Netherlands. 2007. Poster.

7. Papers

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Functionalization of the unactivated carbon-hydrogen bond via ozonation” Ozone Science & Engineering Vol 30, Issue 2 2008, 165-171.

Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “The synthesis of phthalic anhydride via ozonation of naphthalene” Ozone Science & Engineering, Submitted;

Guido Galliani, Bruno Rindone,Ricardo Suarez-Bertoa, Francesco Saliu, Alberto Terraneo, Reaction of 4-Benzyl-5-methyl-1,3-oxazolidine-2,4-dione with Grignard Reagents and Lithium Alkyls to give O-Acyl-N-benzyllactamides, Tetrahedron Letters, Submitted;

Maurizio Bruschi, Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “The ozonation of n-phenylmorpholine: products and reaction mechanism” Ozone Science & Engineering, Submitted;

Benedetto Putomatti, Bruno Rindone, Francesco Saliu, Ricardo Suarez-Bertoa, Avoiding phosgene: Preparation of carbamates and ureas via cobalt-catalyzed oxidative carbonylation of aromatic or aliphatic primary amines and aliphatic amines, Royal Society of Chemistry, Submitted**.**

Maurizio Bruschi, Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Metal free oxidations: the ozonation of cis- and trans-decalin. A mechanistic approach” Ozone Science & Engineering, Submitted;

Maurizio Bruschi, Rindone Bruno, Saliu Francesco, Suarez-Bertoa Ricardo, “Metal free oxidations: the ozonation of cyclohexane. A mechanistic approach” Ozone Science & Engineering, Submitted.

Maurizio Bruschi, Marco Orlandi, Michol Rindone, Bruno Rindone, Francesco Saliu, Ricardo Suarez-Bertoa, Eva Liisa Tollpa, Luca Zoia” Podophyllotoxin and antitumor synthetic aryltetralines. Toward a biomimetic preparation”. Molecules. Submitted.

8. Fellowships

2008-2009 Barrie de la Maza Fellowship

2009 IIC Fellowship

Agradecementos Agradecimientos Ringraziamenti Acknowledgments

During these three years I have come across with a lot people. Most of them meant nothing but fortunately few of them have meant and still mean a lot to me. Maybe some of them did not collaborate directly to this thesis but they influence the way I see or think about things *ergo* the way I have carried out the research. This few people are the ones I have more things to thank for.

Como era de esperar, os meus maiores agradecemotos van para mila nai. Sen o seu apoio incodicional, e a completa liberdade na que me educou no poderia estar a escribir estas letras. Grazas tamen a meus irmans e irmas os cales, cada un a sua maneira, respetaron sempre as miñas decisions e nunca dubidaron das miñas eleccions.

Devo ringraziare anche le mie due guide scientifiche, Bruno e Maurizio, che mi hanno formato nel mondo della scienza e della politica universitaria. Senza di voi questo lavoro non sarebbe stato possibile.

Grazas os amigos de galicia, Alberto, Oscar, Sergio, Diana, Marcos, Silvia, Cintia, Tony, Ali, por estar no sitio xusto no momento xusto cada vez que necesitei de vos. Gracias a los pucelanos, catalanes, charnegos, extremeños, gallegos, vascos y maños (Mario, Sergio y Laura, Maria y Carlos, Eva, Guille e Ixone) que en cada lugar del mundo me han hecho sentir en casa.

Grazie a tutti quelli che durante questi anni sono stati i miei colleghi di lavoro, e non tesisti come alcuni vi chiamano: Ale, Alessia, Cecilia, Fede, Conti e Bagnato, Gio, Giusy, Jere, Luca, Maria, Loca e Stefano, grazie. Grazie anche a Carmine non solo per il lavoro che abbiamo svolto assieme, ma anche per tutte le ore di calcetto assieme. Grazie ai ragazzi di scienze ambientali (Fede, Ale, Jacopo, Marghe, Brandi, Luca…e anche a Gabriele il somaro) per tutte quelle ore di svago fatte in università e non solo. Grazie a Robi, la coinquilina perfetta per tutte quelle belle pappe, birre e risate, ma anche per avermi fatto capire che l’amicizia va oltre al credo e a pensieri politici, almeno la nostra (qui vai ringraziato anche te, biondo).

Grazie alla mia coinquilina Italiana. Grazie a te (al destino, la noia, la voglia di cambiamenti e tutto quello che ci puó passare per la testa) ho iniziato questa avventura. Se qualcuno ha sempre, indiscutibilmente, scommesso per me, quella sei stata tu. Questo mi ha dato coraggio e voglia di continuare, cercando di essere ogni giorno un po’ piú bravo (però poco… non esageriamo). Grazie per il tuo appoggio incondizionato, la tua fiducia e per esserci sempre nella giusta misura. Semplicemente Grazie.