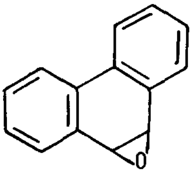
Tetrahedron Letters No. 16, pp 1369 - 1372, 1977. Pergamon Press. Printed in Great Britain.

THE FORMATION OF ARENE OXIDES BY DIRECT OXIDATION OF ARENES USING CARBODIIMIDES AND HYDROGEN PEROXIDE[1]

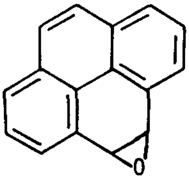
S. Krishnan, David G. Kuhn, and Gordon A. Hamilton*
Department of Chemistry, The Pennsylvania State University
University Park, PA 16802 USA

(Received in USA 28 February, received in UK for publication 9 March 1977)

Presently there exists a large body of evidence that implicates arene oxides or their subsequent metabolic products as the intermediates responsible for the carcinogenicity and mutagenicity of polycyclic aromatic hydrocarbons.[2] Biologically, the arene oxides are formed by the direct oxidation of arenes but non-enzymically they have usually been prepared by other methods.[3] Although arene oxides have been proposed as intermediates in some non-enzymic oxidations of arenes,[4] in only one reported case (from a photochemical reaction) has an arene oxide been isolated from a direct oxidation.[5] We would like to report that phenanthrene 9,10-oxide and pyrene 4,5-oxide can be isolated in yields approaching 30% (based on the amount of unrecovered arene) from direct oxidation reactions involving commercially available materials and mild conditions.

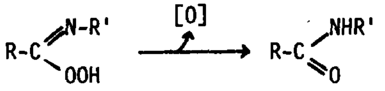


phenanthrene 9,10-oxide



pyrene 4,5-oxide

This study arose from our continued interests in the mechanism of biological oxygen atom transfer or "oxenoid" reactions,[6] the reactions apparently involved in the enzymic conversion of arenes to arene oxides. One of the species we have suggested[6] as a possible oxenoid reagent in some enzymic reactions is a peroxycarboximidic acid (1), a species which is isoelectronic with a peroxyacid, and which is known to be more reactive than the corresponding peroxyacid in alkene epoxidation.[7] It occurred to us that compounds such as 1 or similar compounds might be useful reagents for converting arenes to arene oxides because the by-product formed on oxygen atom transfer (eq. 1) is neutral, thereby avoiding further reactions of the initially formed arene oxide.[8] Peroxycarboximidic acids have been generated in situ by the reaction of nitriles with



(1)

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hydroperoxide ion,[7,10] but because this reaction requires hydroxylic solvents, elevated temperatures, and/or long reaction times, it is unsuitable for the arene oxide synthesis. While investigating methods for generating compounds similar to 1 under milder conditions, we have found that the reaction of aliphatic carbodiimides with hydrogen peroxide apparently readily forms 1 (R=alkylamino, R'-alkyl) because this system can be used for the direct oxidation of arenes to arene oxides.

In a typical reaction, 0.71 g (4 mmol) of phenanthrene, 1.01 g (8 mmol) diisopropylcarbodiimide, 0.54 g (16 mmol) 98% H_2O_2, and 0.118 g (8 mmol) acetic acid in 10 ml ethyl acetate were maintained for 4 hr in a room temperature water bath. Following filtration (to remove the urea precipitate) and addition of 10 ml of $CHCl_3$, the organic solution was washed twice with 15 ml portions of cold 5% Na_2CO_3 solution and twice with 15 ml of cold water, dried (anhydrous K_2CO_3) and evaporated to dryness at room temperature. After dissolution in 3 ml of $CHCl_3$, the material was subjected, in 1 ml portions, to high pressure liquid chromatography (Varian 8500) using a cyanosilica column (50 cm x 8 mm, Varian Micropak CN-10) and eluting (200 ml/hr) at room temperature with 10 vol % CH_2Cl_2 in hexane. The material eluting at 7.5 min was collected and evaporated to dryness to give 22.3 mg of pure phenanthrene 9,10-oxide. The material eluting at 3 min was also collected and upon evaporation to dryness yielded 0.64 g phenanthrene. Thus, the isolated yield of phenanthrane 9,10-oxide is 28% of the reacted phenanthrene and 2.9% of that initially present. The oxide recrystallized from methylene chloride-cyclohexane, has a mp of 124-125° and is identical by TLC (3 different solvent systems) to an authentic sample of phenanthrene 9,10-oxide obtained from Dr. D.M. Jerina. It also has the same melting point, IR, UV, and NMR spectra as the compound prepared in these laboratories by two published procedures.[3d,11]

Under similar reaction conditions, pyrene is converted to pyrene 4,5-oxide in 27% yield (based on reacted pyrene). The oxide, recrystallized from methylene chloride-cyclohexane, has a mp of 176-177° (lit[12] mp 177-180°) and gives the same IR, mass spectrum (parent ion 218) and TLC (R_f = 0.34 on silica gel plates using 85:15 (v/v) cyclohexane:dioxane as the solvents) characteristics as reported.[12]

In addition to the oxide, more polar compounds are also formed in the reactions as evidenced by additional spots on TLC. In the phenanthrene reaction, three of these, which have been shown to be 9,10-phenanthraquinone, 9,10-dihydrophenanthrene-9,10-diol, and 2,2'-biphenyl dicarboxylic acid, are formed in only minor amounts in the initial stages of the reaction but build up if the reaction mixture is allowed to sit for an extended period of time.

Control experiments indicate that all four components (arene, carbodiimide, H_2O_2, and acid) are required for the reaction. It is not necessary to use 98% H_2O_2; approximately the same yield of oxide is formed when 30% H_2O_2, in conjunction with a four-fold relative increase in the carbodiimide concentration, is used. Acetic acid may be replaced with silica gel, Dowex 50W-X8 or diphenylphosphinic acid, and the oxide is still formed. However, little if any oxide is formed when HCl, H_2SO_4, or polyphosphoric acid is used. Peroxyacetic acid is not the epoxidant in the reaction catalyzed by acetic acid because replacement of the H_2O_2 by peroxyacetic acid under the same reaction conditions leads to no detectable amounts of phenanthrene 9,10-oxide.

In most of our experiments diisopropylcarbodiimide was used but the arene oxides are also formed if dicyclohexylcarbodiimide or cyclohexylbenzylcarbodiimide replace the diisopropyl compound. However, no appreciable quantities of oxide are formed under similar reaction conditions when di(p-tolyl)-, phenyl-p-toluenesulfonyl-, and cyclohexyl-p-toluenesulfonylcarbodiimides are used. The amount of oxide formed depends on the solvent, the temperature, the time of reaction, and the relative ratios of reactants; these results will be presented in the full paper.

The procedure described represents only the second reported example of the isolation of an arene oxide following direct epoxidation of an arene. Since the biological epoxidations appear to proceed by a mechanism (the oxenoid mechanism) similar to that presumably involved in the present work, it seems likely that the present model system would mimic somewhat the reactivity of certain monooxygenases. Therefore, an investigation of the products given by more complex arenes, along with studies directed toward the improvement of the yield of arene oxides, is in progress. In addition to its use in the arene oxide synthesis, the carbodiimide-H_2O_2 system may be useful for simple alkene epoxidations under mild conditions.[13] Preliminary experiments in these laboratories[15] and elsewhere[14c] indicate that this is the case.

Acknowledgement. The authors thank Dr. D.M. Jerina for supplying an authentic sample of phenanthrene 9,10-oxide.

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