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Article

Experimental and Theoretical Study on the Reactivity of the R-CN/H_2O_2 System in the Epoxidation of Unfunctionalized Olefins

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A reatividade da acetonitrila, tricloroacetonitrila, benzonitrila, *m*-clorobenzonitrila, 3-cianopiridina, 1-naftonitrila e 9-antracenonitrila na geração *in situ* do respectivo ácido peroxicarboximídico foi estudada por cálculos de OM, utilizando o método AM1, e experimentalmente na epoxidação do cicloexeno e *R*-(+)-limoneno. Os resultados experimentais mostraram que a reatividade do sistema Cl_3CCN/H_2O_2 foi semelhante ao MCPBA na epoxidação de olefinas não-funcionalizadas, quando o solvente utilizado foi uma mistura bifásica CH_2Cl_2/H_2O.

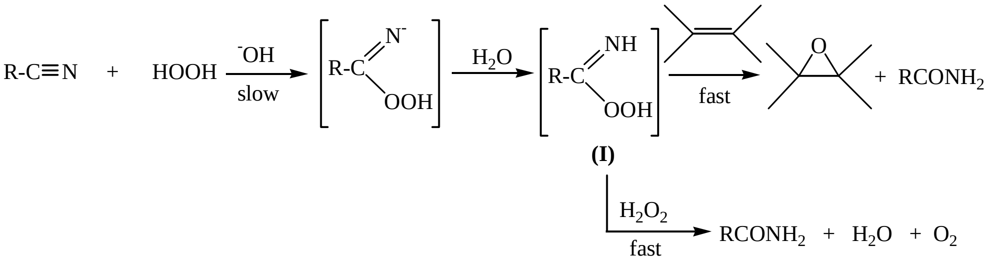
A study on the reactivity of peroxycarboximidic acids *in situ* generated from acetonitrile, trichloroacetonitrile, benzonitrile, *m*-chlorobenzonitrile, 3-cyanopyridine, 1-naphthonitrile and 9-anthracenenitrile was performed by semiempirical AM1 method and experimentally in the epoxidation of cyclohexene and R-(+)-limonene. Experimental results showed that the reactivity of Cl_3CCN/H_2O_2 was quite similar to MCPBA in the epoxidation of unfunctionalized olefins when a biphasic mixture CH_2Cl_2/H_2O was employed as solvent.

Keywords: epoxidation, alkenes, peroxycarboximidic acid

Introduction

Many reagents have been utilized to epoxidize unfunctionalized olefins, among them peracids are the most widely used. The structurally related peroxycarboximidic acids[1] have been much less explored in spite of non-acidic conditions and good yields obtained with peroxybenzimidic acid (Payne epoxidation)[2a-d]. The acid (**I**) is a highly reactive species which has not yet been isolated. It reacts with an alkene leading to epoxide and amide (Scheme 1). In the absence of the alkene, it reacts with a second mole of hydrogen peroxide affording oxygen, water and an amide.

The activation of the nitrile by hydrogen peroxide[3] to form a peroxycarboximidic acid (**I**) occurs in methanol as solvent and basic medium. An interesting variation of Payne epoxidation was introduced by Bach and coworkers[4]. These authors utilized trichloroacetonitrile instead of benzonitrile and a biphasic mixture of dichloromethane/water (1:1) as solvent in the epoxidation of some olefins. This work was preceded by a theoretical study of the structural and electronic features of peroxyformic and peroxyformimidic acids using *ab initio* level calculations[5]. The results suggested that the reactivity of both species would be quite similar and that the presence of an electron withdrawing



Scheme 1.

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substituent should enhance the reactivity of the peroxycarboximidic acid on the epoxidation. To our knowledge, no other study has been put forward to investigate the effect of the nitrile substituent in the epoxidation of unfunctionalized olefins.

In this context, we studied the theoretical and experimental reactivity of the acetonitrile (**1a**), trichloroacetonitrile (**1b**), benzonitrile (**1c**), 3-chlorobenzonitrile (**1d**), 3-cyanopyridine (**1e**), 1-naphthonitrile (**1f**) and 9-anthracenenitrile (**1g**) in the epoxidation of cyclohexene (**2a**) and R-(+)-limonene (**2b**). Our goal was to develop a reagent based on hydrogen peroxide that could compete with MCPBA in cost and reactivity.

In the experimental study we employed some different solvents as methanol, a biphasic mixture of dichloromethane/ water (1:1) and water as depicted in the Scheme 2.

A theoretical study was carried out at the AM1[6a] level implemented by MOPAC program[6b] in order to investigate the conformational features and intrinsic properties of each peroxycarboximidic acid.

Experimental

General

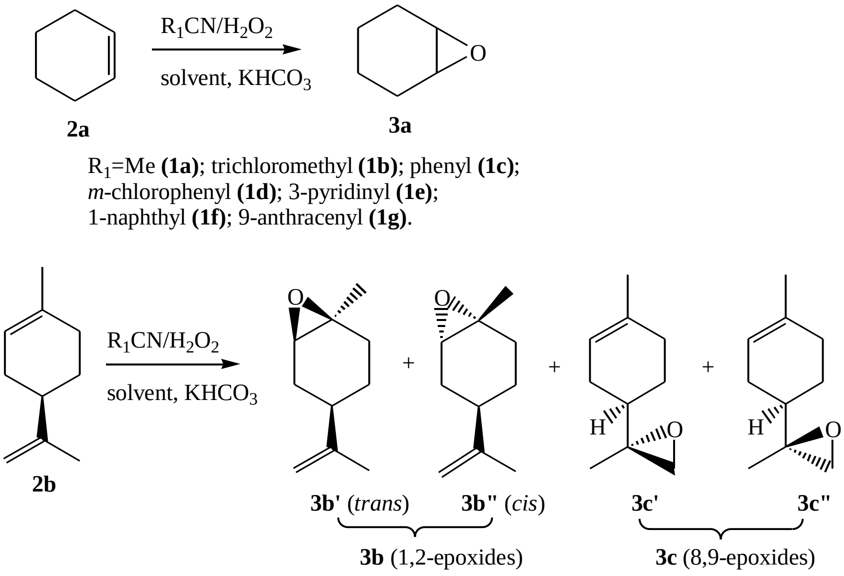
Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. R-(+)-limonene was distilled prior to use. Flash column chromatography was carried out using 230-400 mesh silica gel. ^1H NMR spectra were obtained with a Varian VXR-200 spectrometer. Proton-decoupled ^{13}C-spectra were obtained at 50MHz with the same instrument. GC analyses were carried out using a capilar column HP-1 (50m x 0.2mm x 0.11 μm). Theoretical calculations were performed at Cray Y-MP2E/ 232 computer employing the AM1 method implemented by MOPAC 7.0 program. The energy minimization was realized with respect to all geometrical parameters from an appropriate region of the Potential Energy Surface (PES).

Typical procedure for the epoxidation of **2a** *or* **2b** *with nitriles* **(1a, 1c-g)**/H_2O_2:

In a typical run, olefin (**2a** or **2b**, 10 mmol), nitrile (**1a**, **1c-g**, 10 mmol) and $KHCO_3$ (2 mmol) were dissolved in methanol (20 cm^3). The mixture was treated with hydrogen peroxide (30% wt. solution in water, 10 mmol) dropwise. The stirring was continued for 24 hours at room temperature. The mixture was diluted with water (5 cm^3) and extracted three times with dichloromethane (10 cm^3). The organic layer was washed with 20% aq. solution of $NaHSO_3$ and dried over $MgSO_4$. The yield of epoxide was determined by GC analysis based on internal standard (n-decane). The respective amide was isolated by filtration, washed with hexane and dried in vacuo. Purification by column chromatography on silica gel (10% EtOAc/hexane, v/v) afforded epoxides **3a** or **3b-c** (yields are indicated in Table 1). Compounds **3a**, **3b** and **3c** were isolated as chromatographically pure materials and exhibited acceptable ^1H NMR, ^{13}C NMR, IR and MS spectral data, which were identical with those reported in the literature[7].

Typical procedure for the epoxidation of **2a** *or* **2b** *with* Cl_3CCN/H_2O_2:

To a solution of olefin (**2a** or **2b**, 10 mmol) and Cl_3CCN (**1b**, 10 mmol) in CH_2Cl_2 (10 cm^3) was added 10 cm^3 of



Scheme 2.

Table 1. Results for the epoxidation of **2a** and **2b** with RCN **(1a-1g)**/H_2O_2.

Entry	Nitrile	Olefin	Solvent	Product (ratio), yield	Amide[d]
1	**1a**	**2a**	MeOH	**3a**, 45%[a]	-
2	**1a**	**2b**	MeOH	**3b:3c** (1:1), 51%[a]	-
3	**1b**	**2a**	CH_2Cl_2/H_2O	**3a,** 76%[a]	71 %
4	**1b**	**2b**	CH_2Cl_2/H_2O	**3b:3c** (13:1),72%[a]	70 %
5	**1b**	**2b**	H_2O	**3b:3c** (9:1)[b],12%[c]	52%
6	**1c**	**2a**	MeOH	**3a,** 60%[a]	48 %
7	**1c**	**2b**	MeOH	**3b:3c** (1:1), 65%[a]	50 %
8	**1d**	**2a**	MeOH	**3a,** 35%[c]	63 %
9	**1d**	**2b**	MeOH	**3b:3c** (1:1), 40%[c]	68 %
10	**1e**	**2a**	MeOH	**3a,** 20%[c]	30 %[e]
11	**1e**	**2b**	MeOH	**3b:3c** (2:1), 24%[c]	13%[e]
12	**1f**	**2a**	MeOH	**3a,** 10%[c]	16 %
13	**1f**	**2b**	MeOH	**3b:3c** (2:1), 10%[c]	12%
14	**1g**	**2a**	MeOH	-[f]	-[f]

a. Yields are reported after purification of the crude mixture by column chromatography; **b.** Ratio **3b**':**3b**" (*trans:cis)* of 10:1, determined by ^{1}H NMR, as indicated in reference 11; **c.** Yields were determined by GC relative to an internal standard (n-decane); **d**. Isolated yields after the filtration of the crude mixture; **e**. Nicotinamide N-oxide was isolated. **f.** Nitrile was recovered.

0.2 mol. dm^{-3} aqueous solution of $KHCO_3$. The biphasic mixture was cooled to 0°C and treated with hydrogen peroxide (30% wt. solution in water, 10 mmol) dropwise under vigorous stirring. The mixture was vigorously stirred for 24 hours at room temperature. The organic layer was separated, the aqueous layer was three times extracted with dichloromethane (10 cm^3), and dried over $MgSO_4$. The solvent was removed under vacuum and trichloroacetamide was isolated by filtration. Purification by column chromatography on silica gel (10% EtOAc/hexane, v/v) afforded epoxides **3a** or **3b-c** in 76% and 72% yield, respectively. In the aqueous condition, 10 cm^3 of dichloromethane was replaced by 10 cm^3 of water.

Results and Discussion

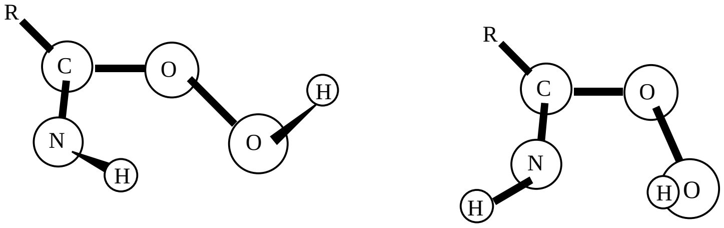
The epoxidation of cyclohexene (**2a**) and R-(+)-limonene (**2b**) with nitriles (**1a-g**), mediated by H_2O_2 and $KHCO_3$ was carried out. The results described in Table 1 were obtained after 24 hours at room temperature (standard procedure).

Epoxides were obtained in 10-65% yields with nitriles **1a**, **1c-f** (entries 1-2, 6-13, Table 1) using methanol as solvent. Trichloroacetonitrile (**1b**) did not furnish epoxides or amide in methanol. In this case, methyl trichloroacetimidate was isolated as result of the nucleophilic attack of the solvent at the nitrile carbon. The trichloroacetimidic acid was formed only when a biphasic mixture of dichloromethane/water (1:1) (entries 3 and 4) or water (entry 5) were used as solvent. Interestingly, nitriles **1a**, **1c-g** did not furnish epoxides or amides using the biphasic mixture of solvent. An amide/epoxide ratio superior to 1.0 was observed in some cases (entries 5, 8-10, and 12-13) and suggested that the peroxycarboximidic acid reacted with hydrogen peroxide in the fast step[8]. It is important to consider that the reduction of reactive intermediate can be promoted by the olefin or the hydrogen peroxide, as represented in the Scheme 1.

The epoxidizing system Cl_3CCN/H_2O_2 showed high chemoselectivity in the epoxidation of the more nucleophilic double bond of R-(+)-limonene (entries 4-5) in spite of the unselective behavior of the other systems RCN/H_2O_2 studied[9]. A 13:1 ratio of **3b:3c** (Scheme 2) was obtained in CH_2Cl_2/H_2O (entry 4) and 9:1 in water (entry 5), which were quite similar with results obtained in the epoxidation of R-(+)-limonene with MCPBA[10]. Besides, when the reaction was carried out in water (entry 5) the product **3b'** *(trans)* was obtained in 82% d.e. (ratio *trans:cis* of 10:1, determined by ^{1}H NMR). In this case the diastereoselectivity was attributed to a deleterious effect of the aqueous 0.1mol. dm^{-3} solution of $KHCO_3$ on the *cis* stereoisomer which resulted an enriched mixture of *trans* isomer in only 12% yield. Jones and coworkers[11] verified the same effect when an aqueous 1mol. dm^{-3} solution of $NaHSO_3$ was employed. They noted that the oxirane ring opening in the *cis* isomer was faster than in the *trans* isomer.

The experimental reactivity order observed in the olefin epoxidation with nitriles **1a**, **c-g** using a standard procedure and methanol as solvent, was **1c** > **1a** > **1d** > **1e** > **1f** > **1g**. This experimental behavior is not in accordance with LUMO energies of nitriles **1a-g** calculated by AM1 method[12]. Besides, it is important to consider that Cl_3CCN (**1b**) was not included in the above order because good results only were attained when methanol was replaced by CH_2Cl_2/H_2O.

In order to attempt rationalize these results, a conformational analysis and intrinsic properties calculations of the conformers of each peroxycarboximidic acids (**5a-g**, Figure 1) were performed[13]. The two most stable conformers of the eight possible[5] were *Z* (C=N geometry), s-*cis* (C-O bond), antiperiplanar and *E* (C=N geometry), s-*cis* (C-O bond), synperiplanar as represented in Figure 1.



Z (E_{rel}=0) ***E***

Figure 1. Representations of the geometry of the two most stable conformers of the peroxycarboximidic acids **5a-g** (values of relative energies are summarized in Table 2).

We calculated the relative energies and dipole moment values of the corresponding *E* and *Z* conformers of the peroxycarboximidic acids **5a-g**. The results are summarized in Table 2.

Table 2. Calculated values of the intrinsic properties of *E* and *Z* conformers of the peroxycarboximidic acids (**5a-g**).

Entry	Conformer	E_{rel} (kcal/mol)	Dipole moments (D)
1	***5a-Z***	0.0	1.72
2	***5a-E***	3.54	2.59
3	***5b-Z***	0.0	2.12
4	***5b-E***	1.19	1.50
5	***5c-Z***	0.0	1.80
6	***5c-E***	2.81	2.90
7	***5d-Z***	0.0	2.54
8	***5d-E***	2.25	1.68
9	***5e-Z***	0.0	2.35
10	***5e-E***	3.20	2.98
11	***5f-Z***	0.0	1.85
12	***5f-E***	1.88	2.88
13	***5g-Z***	0.0	1.74
14	***5g-E***	1.37	2.74

The calculations showed that *Z* is the conformer of minimum energy with an internal hydrogen bond between *H* imidic and hydroxyl group. The *E* conformer is an analog of the peracids with an *anti* imine structure containing an internal hydrogen bond between nitrogen atom and *H* hydroperoxide. Both conformers showed a minimum conformation when *H* hydroperoxide was out of plane formed by the functional group (Figure 1).

The *butterfly* mechanism is usually accept for Payne epoxidation[14]. In this context, it was postulated that only the *E* conformer has an adequate geometry to react with an olefin[5]. However, we assumed that *Z* conformer could be able to react with hydrogen peroxide in the fast step.

We observed an unusual selectivity of trichloroacetimidic acid in the epoxidation of the more substituted double bond of R-(+)-limonene, which was comparable with that observed by peracids. Since the formation of the peroxycarboximidc acid is usually accepted as the rate-determining step we believed that, in this particular case, the strong electron-withdrawing effect of the trichloromethyl group could be affecting the kinetics of the reaction. Unfortunately, it was impossible to compare the reactivity of all RCN/H_2O_2 systems studied in the same solvent. Further additional kinetics studies would be needed to understand the different reactivity showed by these systems.

Conclusion

In conclusion, the choice of a nitrile for olefin epoxidation mediated by hydrogen peroxide could not be carried out through a simple analogy between the peroxycarboximidic acid, *in situ* generated, and the structurally related peracid.

Moreover, we concluded that the reactivity of benzonitrile, 3-chlorobenzonitrile and acetonitrile were quite similar in the epoxidation of unfunctionalized olefins, mediated by hydrogen peroxide and $KHCO_3$ in methanol as solvent. Trichloroacetonitrile showed the best results in this study. In the epoxidation of R-(+)-limonene, the Cl_3CCN/H_2O_2 system presented a chemoselective behavior similar to MCPBA. Besides, the utilization of a biphasic mixture of solvent makes the purification of oxiranes easier and avoids acidic conditions, which makes the Cl_3CCN/H_2O_2 system an excellent alternative method to MCPBA epoxidation.

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12. We calculated the LUMO energies of nitriles **1a-g** by AM1 method. However, we cannot correlate the theoretical reactivity order, based in the LUMO energies of nitriles with the experimental reactivity order observed. (a) von Holleben, M. L. A.; Schuch, C. M.; Livotto, P.R. *5th European Symposium on Organic Reactivity (ESOR V),* Santiago de Compostela, Spain, **1995**, 95. (b) Schuch, C. M. *Dissertação de Mestrado,* Universidade Federal do Rio Grande do Sul, Brazil, 1996.
13. Geometrical Parameters for Peroxycarboximidic acids **5a-5g**: *Z* Conformers: (O-O): 1.291 Å (**5a**, **5f**); 1.290 Å (**5b**, **5c**, **5d**, **5e**); 1.292 Å (**5g**). (O-H): 0.986 Å (**5b**, **5e**, **5f**); 0.985 Å (**5a**, **5c**, **5d**, **5g**). (C-O): 1.434 Å (**5a**); 1.440 Å (**5c**); 1.438 Å (**5d**); 1.437 Å (**5e**, **5f**, **5g**); 1.433 Å (**5b**). (C=N): 1.279 Å (**5a**, **5f**); 1.278 Å (**5b**); 1.282 Å (**5c**, **5e**); 1.280 Å (**5d**, **5g**). (N-H): 0.998 Å (**5a**); 1.000 Å (**5b**, **5e**, **5g**); 0.999 Å (**5c**, **5d**, **5f**). (C-R): 1.499 Å (**5a**); 1.525 Å (**5b**); 1.480 Å (**5c**); 1.479 Å (**5d**); 1.474 Å (**5e**); 1.482 Å (**5f**); 1.484 Å (**5g**). (O-C-R): 106.9º (**5a**); 108.5º (**5b**); 108.2º (**5c**); 108.4º (**5d**); 108.3º (**5e**); 107.1º (**5f**); 107.6º (**5g**). (O-C=N): 127.2º (**5a**); 127.3º (**5b**); 126.6º (**5c**); 126.5º (**5d**); 126.8º (**5e**); 127.0 (**5f**); 127.1º (**5g**). (C=N-H) 116.1º (**5a**, **5b**); 115.8º (**5c**, **5e**, **5f**, **5g**). (O-O-C): 114.2º (**5a**, **5c**, **5f**); 113.6º (**5b**); 114.1º (**5d**, **5g**). (O-O-H): 107.2º (**5a**, **5b**, **5e**, **5f**); 107.3º (**5c**); 107.4º (**5d**); 107.1º (**5g**). *E* Conformers: (O-O): 1.286 Å (**5a, 5d, 5f, 5g**); 1.284 Å (**5b**); 1.290 Å (**5c**); 1.285 Å (**5e**). (O-H): 0.985 Å (**5a**, **5f**, **5g**); 0.986 Å (**5c**, **5d**); 0.987 Å (**5b**, **5e**). (C-O): 1.420 Å (**5a**); 1.422 Å (**5b**, **5d**, **5f**, **5g**); 1.430 Å (**5c**); 1.423 Å (**5e**). (C=N): 1.284 Å (**5a**, **5f**, **5g**); 1.277 Å (**5b**); 1.286 Å (**5c**); 1.285 Å (**5d**, **5e**). (N-H): 0.996 Å (**5a**, **5e**); 0.997 Å (**5b**, **5c**, **5d**, **5f**, **5g**). (C-R): 1.499 Å (**5a**); 1.530 Å (**5b**); 1.480 Å (**5c**, **5d**); 1.475 Å (**5e**); 1.483 Å (**5f**); 1.485 Å (**5g**). (O-C-R): 107.4º (**5a**); 108.3º (**5b**); 108.8º (**5c, 5e**); 108.5º (**5d**); 108.1º (**5g**); 108.7º (**5g**). (O-C=N): 121.4º (**5a,5g**); 121.3º (**5b**); 121.0º (**5c**, **5e**); 121.1º (**5d**); 121.5º (**5f**). (C=N-H) 115.2º (**5a**); 117.6º (5b); 115.3º (**5c**, **5f**); 115.4º (**5d**, **5g**); 115.5º (**5e**). (O-O-C): 117.5º (**5a**); 116.4º (**5b**); 117.1º (**5c**, **5f**); 117.0º (**5d**, **5g**); 117.2º (**5e**). (O-O-H): 108.9º (**5a**, **5d**, **5f**, **5g**); 108.8º (**5b**); 109.0º (**5c**); 109.1º (**5e**).
14. In the olefin epoxidation, the electrophilic mechanism occurs in the cyclic transition state (*Butterfly*) or in the opened transition state. For discussion see: Rebek, J. *Heterocycles* **1981**, *15*, 517.

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