

endo/exo Isomerism in Norcarane and 2-Norcaranol Hydrotrioxides (ROOOH)

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Abstract: Ozonation of norcarane (**1**) yielded *endo* and *exo* norcarane hydrotrioxides (**2a**, **2b**), as characterized by ¹H and ¹³C NMR spectroscopy. Further ozonation of the primary decomposition products of these hydrotrioxides, i.e., 2-norcaranols (**3**), produced the corresponding isomeric 2-norcaranol hydrotrioxides (**4a**, **4b**), and hydrogen trioxide (HOOOH).

During the past 2 decades, research on polyoxides has intensified.¹ Hydrogen trioxide (HOOOH) and its organic derivatives, i.e., alkyl hydrotrioxides (ROOOH), are currently at the focus of intense investigations. Namely, these species have recently been shown unambiguously to be involved as unstable intermediates in the low-temperature ozonation of alcohols and ethers by using ¹⁷O-enriched ozone (¹⁷O NMR).² Recent research even showed that hydrogen trioxide is most likely produced in biological systems from singlet oxygen and water by antibodies,³ as well as in the reactions of hydrogen peroxide with ozone (peroxone chemistry).⁴

We have recently reported experimental and theoretical evidence for the formation of alkyl hydrotrioxides (ROOOH) and hydrogen trioxide (HOOOH) in the ozonation of some saturated hydrocarbons, i.e., cumene and triphenylmethane.⁵

In this work we report for the first time an unambiguous structural assignment of *endo/exo* isomerism in norcarane and norcaranol hydrotrioxides. The possibility of structural isomerism in norcarane hydrotrioxide has

already been proposed by de Meijere et al.,^{1b,6} but no detailed structural assignment could be made at that time.

Low-temperature ozonation of norcarane (**1**)^{7,8} (0.3–0.8 M) in acetone-*d*₆, methyl acetate, and *tert*-butyl methyl ether at –78 °C produced two isomeric alkyl hydrotrioxides (**2a** and **2b**), characterized by a typical OOOH ¹H NMR absorptions at δ = 13.29 and 13.39 ppm downfield from TMS (–60 °C, acetone-*d*₆) in molar ratio 1:0.06 (Figures 1 and 2).⁹

The structural assignment of the hydrotrioxide absorptions of isomers **2a** and **2b** was confirmed by the corresponding signals in the aliphatic region of the ¹H NMR spectra, two sets of signals in the ¹³C NMR spectra, and by 2D NMR (HMQC, NOESY) correlation (Table 1. See also Supporting Information).¹⁰

Besides the corresponding OOOH absorptions of **2a** and **2b**, still another downfield absorption at δ = 13.46 ppm (–60 °C, acetone-*d*₆, TMS) was observed in the ¹H NMR spectra (Figure 1). This hydrotrioxide absorption was assigned to HOOOH on the basis of ¹H NMR spectra of independently prepared samples of this polyoxide.^{11,12}

Our previous studies of the ozonation of isopropyl alcohol² showed the formation of significant amounts of HOOOH in these reactions. We suspected, therefore, that

(6) Zarth, M.; de Meijere, A. *Chem. Ber.* **1985**, *118*, 2429.

(7) Norcarane was prepared by using the Simmons–Smith reaction: Friedrich, E. C.; Lunetta, S. E.; Lewis, E. J. *J. Org. Chem.* **1988**, *54*, 2388.

(8) (a) Although we have not studied in the present work the details of the mechanism of the ozonation of **1**, the exclusive attack of ozone at the C-2(H) position (rather than at the C-5(H)) would seem to indicate that the free radical mechanism, involving the formation of the radical pair, R[•]•OOH, is the first step of this reaction (see ref 5a). However, no reaction products that would indicate the cyclopropyl-ring opening in the initially formed norcaranyl radical (R[•]) were detected in the reaction mixtures. (b) Pryor et al. have suggested that transition states for the ozonation of C–H bonds in saturated systems might have contributions ranging from radical to ionic resonance forms, depending on the substrate and the experimental conditions used.^{5b} See also: Giamalva, D. H.; Church, D. F.; Pryor, W. A. *J. Am. Chem. Soc.* **1986**, *108*, 7678. (c) For use of norcarane as a probe for radicals in cytochrome P450 catalyzed hydroxylation reactions, see: Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 6020. Newcomb, M.; Shen, R.; Lu, Y.; Coon, M. J.; Hollenberg, P. F.; Koop, D. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 6879.

(9) GC–MS analysis of the reaction mixture after the decomposition of **2a** and **2b** gave the same ratio of isomeric *endo*- and *exo*-2-norcaranol (**3a**:**3b** = 1:0.06), which are, in addition to 2-norcaranone (**6**), the main decomposition products (54 mol %).

(10) (a) For comparison, we have prepared a mixture of *endo*- and *exo*-2-hydroperoxynorcarane (**5a**:**5b** = 5:1) from mixtures of isomeric 2-norcaranols (**3a** and **3b**) by catalytic nucleophilic substitution.^{10b} In a typical reaction, 2-norcaranol (**3**, 3.4 g, 0.025 mol) in 40 mL of methanol was added to a precooled (0 °C) solution of concentrated H₂O₂ (70%, 47 mL, 1.0 mol) in 55 mL of methanol. A few drops of HClO₄ were added, and the reaction was allowed to run at room temperature until **3** disappeared. The reaction was quenched by washing with NaHCO₃, and the product was isolated by an extractive workup (diethyl ether). The hydroperoxide **5** was distilled in a vacuum: yield 1.06 g (29%), 96% purity by GC–MS (*m/z* M⁺ = 128). For NMR spectroscopic data of **5a** and **5b**, see Table 1. (b) Davies, A. G.; Foster, R. V.; White, J. M. *J. Chem. Soc.* **1953**, 1541. (c) For a recent review on alkyl hydroperoxides (ROOH), see: Porter, N. A. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; pp 101–156.

(11) An independent preparation of HOOOH was made by low-temperature ozonation of 1,2-diphenylhydrazine (hydrazobenzene), and characterized by ¹H and ¹⁷O NMR spectroscopy.² For a complete study of the ozonation of hydrazines, see: Plesničar, B.; Tuttle, T.; Cerkovnik, J.; Koller, J.; Cremer, D. *J. Am. Chem. Soc.* **2003**, *125*, 11553.

(1) (a) Plesničar, B. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; pp 479–533. (b) de Meijere, A.; Wolf, F. In *Organische Peroxo-Verbindungen*; Kropf, H., Ed.; Houben-Weyl Methoden der Organischen Chemie, Vol. E13; George Thieme Verlag: Stuttgart and New York, 1988; pp 971–990.

(2) (a) Plesničar, B.; Cerkovnik, J.; Tekavec, T.; Koller, J. *J. Am. Chem. Soc.* **1998**, *120*, 8005. (b) Plesničar, B.; Cerkovnik, J.; Tekavec, T.; Koller, J. *Chem. Eur. J.* **2000**, *6*, 809. (c) Wu, A.; Cremer, D.; Plesničar, B. *J. Am. Chem. Soc.* **2003**, *125*, 9395 and references therein.

(3) (a) Wentworth, P., Jr.; Jones, L. H.; Wentworth, A. D.; Zhu, X.; Larsen, N. A.; Wilson, I. A.; Xu, X.; Goddard, W. A., III; Janda, K. D.; Eschenmoser, A.; Lerner, R. A. *Science* **2001**, *293*, 1806. (b) Xu, X.; Muller, R. P.; Goddard, W. A., III. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3376. (c) Wentworth, P., Jr.; McDunn, J. E.; Wentworth, A. D.; Takeuchi, C.; Nieva, J.; Jones, T.; Bautista, C.; Ruedi, J. M.; Gutierrez, A.; Janda, K. D.; Babiior, B. M.; Eschenmoser, A.; Lerner, R. A. *Science* **2002**, *298*, 2195. (d) Wentworth, P., Jr.; Wentworth, A. D.; Zhu, X.; Wilson, I. A.; Janda, K. D.; Eschenmoser, A.; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 1490.

(4) Xu, X.; Goddard, W. A., III. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 15308 and references therein.

(5) (a) Cerkovnik, J.; Eržen, E.; Koller, J.; Plesničar, B. *J. Am. Chem. Soc.* **2002**, *124*, 404. (b) For the previous studies on the involvement of hydrotrioxides in the ozonation of cumene and some other saturated hydrocarbons, see: Pryor, W. A.; Ohto, N.; Church, D. F. *J. Am. Chem. Soc.* **1983**, *105*, 3614. Giamalva, D. H.; Church, D. F.; Pryor, W. A. *J. Org. Chem.* **1988**, *53*, 3429.

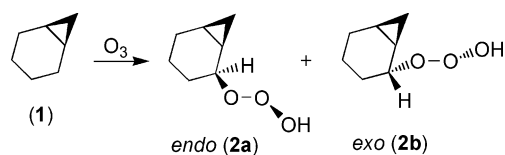


FIGURE 1. Isomeric hydrotrioxides formed in the ozonation of norcarane (**1**).

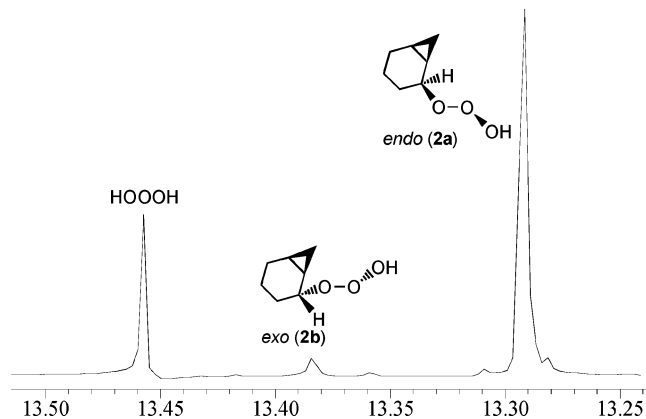


FIGURE 2. Segment of the ^1H NMR spectrum of the ozonized solution of norcarane (**1**) in acetone- d_6 (0.5 M) at -60°C .

TABLE 1. Selected ^1H and ^{13}C NMR Chemical Shifts of Isomeric Hydrotrioxides of Norcarane (**2a** and **2b**) and Some Homologous Compounds in Acetone- d_6 at -60°C^a

(species) R	^1H NMR				^{13}C NMR	
	C(2)-R		C(2)-H		C(2)	
	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>	<i>endo</i>	<i>exo</i>
(2) OOOH ^{b,c}	13.29	13.39	4.93	4.69	77.02	77.42
(5) OOH	11.10	11.35	4.41	4.14	79.70	80.54
(3) OH	5.46	5.74	4.22	4.07	67.15	67.03

the presence of HOOOH in the reaction mixtures after the ozonation of norcarane (**1**) was the result of further ozonation of 2-norcaranol (**3**), which was formed as the primary decomposition product of **2a** and **2b**. Therefore, we have studied the ozonation of pure *endo*-2-norcaranol (**3a**)^{13a} and found that in this reaction HOOOH was

(12) The preferred formation of the “*endo*” hydrotrioxide **3a** might be due to the interaction of the electrophilic ozone with the “nucleophilic” cyclopropane ring of **1**. (de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809. *The Chemistry of the Cyclopropyl Group*; Rapoport, Z., Ed.; Wiley: Chichester, 1995; Part II.)

(13) (a) *endo*-2-Norcaranol (**3a**) was prepared by stereoselective magnesium-promoted cyclopropanation of 2-cyclohexenol. Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* **1997**, *38*, 7349. (b) 2-Norcaranol (**3**) was prepared as a mixture of **3a** and **3b** from LAH reduction of 2-norcaranone (**6**). For preparation of **6**, see: Dauben, E. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468.

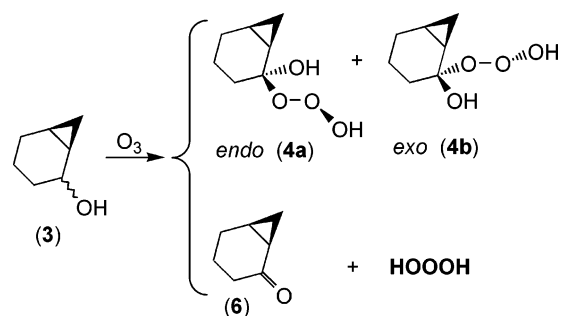


FIGURE 3. Isomeric hydrotrioxides formed in the ozonation of 2-norcaranol (**3**).

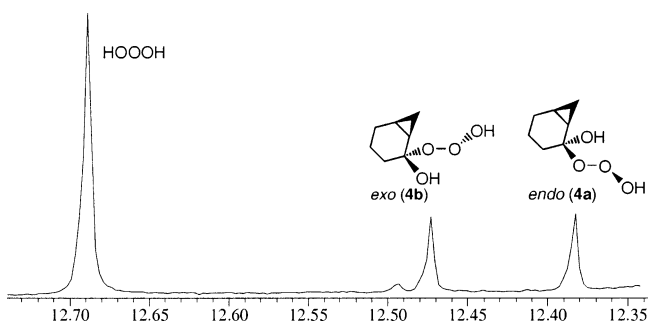


FIGURE 4. Segment of ^1H NMR spectrum of the ozonized solution of 2-norcaranol (**3**) in methyl acetate (0.2 M) at -20°C .

indeed formed (in addition to **4b**) as the main reaction product. For comparison, ozonation of mixtures of *endo*- and *exo*-2-norcaranol (**3a:3b** = 65:35)^{13b} produced HOOOH as the main reaction product also^{14–16} (Figures 3 and 4, Table 1).

To additionally confirm the identity of the species under investigation, we have studied the kinetics of the decomposition of **4a**, **4b**, and HOOOH by following the disappearance of the corresponding OOOH absorptions. We found that hydrotrioxides **4a** and **4b** decomposed at approximately the same rate (first-order kinetics [k_1 (-25°C), **4a**, $0.43 \times 10^{-4} \text{ s}^{-1}$; **4b**, $0.48 \times 10^{-4} \text{ s}^{-1}$ (OOH); **4a**, $0.35 \times 10^{-4} \text{ s}^{-1}$; **4b**, $0.40 \times 10^{-4} \text{ s}^{-1}$ (H_1 -cyclopropyl ring); $E_a = 21.0 \pm 1.5 \text{ kcal mol}^{-1}$ ($22.0 \pm 1.5 \text{ kcal mol}^{-1}$, with radical inhibitor, see Supporting Information); $\log A = 13.5 \pm 1.0$ (14.2 ± 1.0); temperature range from -25 to 0°C , acetone- d_6]), while the kinetics of the decomposition of HOOOH was in agreement with our previous kinetic

(14) As a result of relatively long reaction times necessary for the conversion of **1** into the corresponding hydrotrioxides **2a** and **2b**, considerable amounts of these polyoxides decomposed to **3a** and **3b** even at -60°C . Norcaranols **3a** and **3b** reacted with ozone much faster than norcarane, and thus we were not able to detect them by low-temperature ^1H NMR (-60°C). It should be pointed out that an excess of ozone (relative to **1**) was used in all experiments.

(15) Molar ratio HOOOH, **4a:4b** = 1.0:0.20:0.16.

(16) (a) Norcarane hydrotrioxides (**2a**, **2b**) decomposed to norcaranols **3a** and **3b** and norcaranone (**6**), whereas norcaranol hydrotrioxides (**4a**, **4b**) yielded **6** as the end decomposition product. Oxygen and hydrogen peroxide were also detected among the decomposition products. (b) It should be pointed out that water was always present in the ozonized solutions of norcarane and 2-norcaranols, most likely due to the reaction of ozone with the hydrotrioxides **2a**, **2b**, **4a**, **4b**, HOOOH, and HOOH.^{2a,b,4} (c) For the proposed mechanism of the decomposition of the hydrotrioxides of saturated hydrocarbons, alcohols, and HOOOH, see refs 2, 4, 5, and 11.

results on this polyoxide [k_1 ($-25\text{ }^\circ\text{C}$), $0.60 \times 10^{-4}\text{ s}^{-1}$, $E_a = 17.2 \pm 0.5\text{ kcal mol}^{-1}$ ($17.7 \pm 0.5\text{ kcal mol}^{-1}$), $\log A = 10.8 \pm 0.5$ (11.2 ± 0.5), temperature range from -25 to $0\text{ }^\circ\text{C}$, acetone- d_6]. Although the measurements of the decomposition of **2b** were somewhat less accurate than those for **2a** [k_1 ($-25\text{ }^\circ\text{C}$), $3.87 \times 10^{-4}\text{ s}^{-1}$, $E_a = 13.5 \pm 1.0\text{ kcal mol}^{-1}$ (12.2 ± 0.5), $\log A = 8.5 \pm 0.5$ (7.9 ± 0.5), temperature range from -35 to $-10\text{ }^\circ\text{C}$, acetone- d_6], it was obvious that both species decomposed with ap-

(17) The hydrotrioxides **4a** and **4b** are more stable than hydrotrioxides **2a** and **2b**, most probably because of a possibility of intramolecular hydrogen bonding in the former. See ref 2c.

proximately the same rate also (Tables S1 and S2 in Supporting Information).¹⁷

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Supporting Information Available: Tables S1 and S2, containing a complete set of kinetic and activation data for the decomposition of **2a**, **4a**, **4b**, and HOOOH. Segments of HMQC and NOESY NMR spectra of the ozonized solutions of **1** (Figures S1 and S2). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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