brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the crude product, which was eluted with diethyl ether through a short silica-gel column, which gave after evaporation of the solvent 4.16 g (91%) of sulfone **21**: IR 3027, 2958, 1446, 1290, 1143, 1083 cm^{-1}; ^1H NMR δ 7.88–7.81 and 7.64–7.46 (m, 5 H, Ar), 6.13–6.02 (m, 1 H, H-1), 5.76 (dd, J = 10.2, 2.1 Hz, 1 H, H-2), 5.01 (d, J = 10 Hz, 1 H, H-2), 2.36–1.84 (m, 4 H, allylic H-4, and one of H-5), 1.67–0.97 (m, 10 H, $(CH_2)_3$, one H-5, and Me on ring), 0.96–0.83 (t (distorted), 3 H, Me on chain); ^{13}C NMR 139.09, 136.40, 135.32, 134.68, 133.13, 133.07, 130.57, 130.35, 128.30, 128.22, 125.24, 125.47, 72.63, 71.32, 41.54, 33.32, 32.41, 32.36, 29.32, 28.97, 27.80, 26.90, 26.06, 25.79, 25.70, 15.12, 24.71, 23.57, 23.24, 23.08; MS (CI, isobutane) 293. Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27. Found: C, 69.73; H, 8.17.

3,4-Dimethyl-3-(phenylsulfonyl)cyclohexene (22). The same reaction conditions as for the preparation of **21** were applied, but MeI was used as the alkylating reagent instead of *n*-BuBr. This afforded the desired sulfone **22** as a mixture of diastereomers (88:12) in 95% yield: IR 3029, 2932, 1446, 1298, 1145, 1071 cm^{-1}; ^1H NMR (major diastereomer) δ 7.95–7.85 and 7.72–7.50 (m, 5 H, Ar), 5.97–5.89 (m, 1 H, H-1), 5.67 (dq, J = 10.1, 1.4 Hz, 1 H, H-2), 2.15–1.56 (m, 4 H, H-6, H-4, and one H-5), 1.42 (s, 3 H, allylic Me), 1.42–1.23 (m, 1 H, one of H-5), 1.15 (d, J = 6.6 Hz, 3 H, homoallylic Me); ^{13}C NMR δ 136.20, 133.32, 133.12, 130.42, 128.42, 126.73, 68.09, 31.62, 27.95, 24.34, 17.11, 16.16; MS (CI, isobutane) 251. Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 66.95, H, 7.10.

3-Methyl-4-*n*-butyl-3-(phenylsulfonyl)cycloheptene (23). Sulfone **19** was alkylated by using the same reaction conditions as for the preparation of **20**. This gave the desired sulfone **23** as a 4:1 mixture of diastereoisomers in 94% yield: IR 3029, 2928, 1446, 1300, 1144, 1072 cm^{-1}; ^1H NMR (major diastereomer) δ 7.90–7.83 and 7.65–7.47 (m, 5 H, Ar), 5.98 (dt, J = 12, 6 Hz, 1 H, H-1), 5.45 (d, J = 12 Hz, 1 H, H-2), 2.40–2.26 (m, 1 H, one of H-7), 2.24–1.96 (m, 3 H, one of H-7 and H-4), 1.94–1.48 (m, 4 H, H-6 and H-5), 1.39 (s, 3 H, allylic Me), 1.42–1.08 (m, 6 H, $(CH_2)_3$), 0.91 (t, J = 7 Hz, 3 H, Me in chain); ^{13}C NMR δ 138.54, 136.22, 133.20, 130.36, 129.80, 128.49, 72.23, 44.88, 31.22, 30.15, 29.68, 28.07, 24.90, 24.50, 22.78, 14.21. Anal. Calcd for $C_{18}H_{26}O_2S$: C, 70.55; H, 8.55. Found: C, 70.31; H, 8.52.

Dienes **24–27** were prepared from sulfones **21–23**, respectively, utilizing the same reaction conditions as described for **13**.

4-Methyl-5-*n*-butyl-1,3-cyclohexadiene (24):[23] yield, 410 mg (60%); IR 3040, 2928, 1445 cm^{-1}; ^1H NMR δ 5.85–5.78 (m, 1 H, H-2), 5.64 (d, J = 5.2 Hz, 1 H, H-3), 5.58–5.51 (m, 1 H, H-1), 2.42–2.28 (m, J_{gem} = 17.5, 8.6 Hz, 1 H, H-6_{ax}), 2.14 (ddd, J_{gem} = 17.5, 5, 5 Hz, 1 H, H-6_{eq}), 1.94 (m, 1 H, H-5), 1.80 (s, 3 H, Me on ring), 1.48–1.16 (m, 6 H, $(CH_2)_3$), 0.91 (t (distorted), 3 H, Me in chain); ^{13}C NMR δ 140.03, 124.29, 121.70, 118.82, 37.28, 29.67, 29.58, 27.21, 22.94, 22.01, 14.05.

5-Methyl-4-*n*-butyl-1,3-cyclohexadiene (25): yield, 1.14 g (60%); IR 3040, 2927, 1456 cm^{-1}; ^1H NMR δ 5.88–5.81 (m, 1 H, H-2), 5.62–5.52 (m, 2 H, H-1 and -3), 2.44–2.32 (m, J = 17, 9 Hz, 1 H, H-6_{ax}), 2.20–1.93 (m, 4 H, allylic), 1.53–1.23 (m, 7 H, Me on ring and $(CH_2)_2$), 0.94 (t (distorted), 3 H, Me on chain); ^{13}C NMR δ 145.09, 124.10, 121.66, 117.36, 34.81, 31.01, 30.49, 30.47, 22.55, 16.97, 13.97; HRMS calcd for $C_{11}H_{18}$ 150.1408, found 150.1409.

4,5-Dimethyl-1,3-cyclohexadiene (26): yield, 370 mg (62%); spectral data are in accord with those reported in the literature for **26**;[24] IR 2928, 1446 cm^{-1}; ^1H NMR δ 5.484–5.77 (m, 1 H, olefinic), 5.64–5.53 (m, 2 H, olefinic), 2.44–2.31 (m, J = 17.6, 8 Hz, 1 H, H-6_{ax}), 2.12 (sextet, J = 7 Hz, 1 H, H-5), 1.96 (dt, J = 17, 5.5 Hz, H-6_{eq}), 1.77 (s, 3 H, vinylic Me), 0.97 (d, J = 7 Hz, 3 H, allylic Me); ^{13}C NMR δ 140.60, 124.08, 121.82, 118.50, 32.02, 30.96, 21.47, 16.96.

4-Methyl-5-*n*-butyl-1,3-cycloheptadiene (27): yield, 155 mg (83%); IR 3012, 2925, 1448 cm^{-1}; ^1H NMR 5.67–5.64 (m, 2 H, H1 and H2), 5.53–5.48 (m, 1 H, H3), 2.37–2.21 (m, 3 H, allylic), 1.85 (s, 3 H, vinylic Me), 1.73–1.61 (m, 1 H, one of H6), 1.50–1.42 (m, 1 H, one of H6), 1.40–1.18 (m, 6 H, $(CH_2)_3$), 0.89 (t (distorted), 3 H, Me in chain); ^{13}C NMR δ 147.17, 131.59, 124.07, 119.54, 44.17, 30.14, 28.96, 27.13, 26.55, 22.91, 22.34, 14.09; MS (EI) 164.

3-Methylene-4-*n*-butyl-1-ethylcyclohexene (30). Sulfone **20** was rearranged under acidic conditions ($HOAc/H_2O$ (3/2), 100 °C, 1 h) to 2-methyl-3-*n*-butyl-6-(phenylsulfonyl)cyclohexene (**28**) in 80% yield.[11a] Deprotonation with *n*-BuLi at −78 °C and alkylation with ethyl bromide gave 2-methyl-3-*n*-butyl-6-ethyl-6-(phenylsulfonyl)cyclohexene (**29**) in 94% yield. The sulfone was then eliminated under the same reaction conditions as described for **13**. This afforded **30** in 62% yield: ^1H NMR δ 5.86 (s, 1 H, H2), 4.69 (d, J = 11.5 Hz, 2 H, exocyclic olefin), 2.36–1.88 (m, 5 H, allylic), 1.82–1.52 (m, 2 H, H5), 1.46–1.18 (m, 6 H, $(CH_2)_3$), 1.03 (t, J = 7.4 Hz, 3 H, Me in ethyl chain), 0.90 (br t, 3 H, Me in butyl chain); ^{13}C NMR δ 147.84, 143.00, 122.63, 108.29, 38.89, 32.34, 30.30, 29.47, 27.54, 25.87, 22.89, 14.14, 12.06.

5-Methyl-1,3-cyclohexadiene (31). 4-Methyl-3-(phenylsulfonyl)cyclohexene[8b] was eliminated under the same reaction conditions as described for **13**. This gave the desired diene and the 1-substituted isomer **16**, in a 95:5 ratio and 45% yield. Diene **31** was identified by comparison with an authentic sample:[3a] IR 3031, 2958, 1456, 680 cm^{-1}; ^1H NMR δ 5.92–5.60 (m, 4 H, olefinic), 2.50–2.16 (m, 2 H, one of H6 and H5), 2.02–1.02 (m, 1 H, one of H6), 1.04 (d, J = 6.9 Hz, 3 H, Me); ^{13}C NMR δ 133.20, 125.89, 123.89, 123.37, 30.58, 27.76, 19.79; MS (EI) 94.

5-*n*-Butyl-1,3-cyclohexadiene (32).[25] 4-*n*-Butyl-3-(phenylsulfonyl)cyclohexane[8b] was eliminated under the same reaction conditions as described for **13**. This gave the desired diene **32** and the 1-substituted isomer **13** in a 94:6 ratio and 73% yield: IR ($CDCl_2$) 3035, 2928, 1466 cm^{-1}; ^1H NMR δ 5.90–5.68 (m, 4 H, olefinic), 2.32–2.18 (m, 2 H, allylic, H5, and one of H6), 2.03–1.87 (m, 1 H, one H6), 1.48–1.20 (m, 6 H, $(CH_2)_3$), 0.92 (t (distorted), 3 H, Me); ^{13}C NMR δ 131.88, 126.01, 123.98, 123.44, 34.26, 32.87, 29.13, 28.70, 22.86, 14.10.

Acknowledgment. Financial support from the Swedish Natural Science Research Council, the National Science Foundation (USA), and the National Institutes of Health (USA) is gratefully acknowledged. We thank Mr. Niklas Plobeck for helpful discussions.

(23) Bandara Ratnayake, B. M.; Birch, A. J.; Khor, T.-C. *Tetrahedron Lett.* **1980**, 3625.

(24) Marvell, E. N.; Caple, G. Schatz. B.; Pippin, W. *Tetrahedron* **1973**, *29*, 3781.

(25) Brieger, G.; Anderson, D. W. *J. Chem. Soc., Chem. Commun.* **1970**, 1325.

Analysis of (α-Hydroxybenzyl)tetrahydroisoquinoline Stereoisomers by Pirkle Column HPLC: Correlation of Absolute Configuration with Order of Elution

Kathleen S. Rein and Robert E. Gawley*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received June 8, 1990

The analysis of absolute configuration by chiral stationary-phase HPLC is becoming ever more important to synthetic chemists as the number of compound classes separable by this method grows.[1] We have recently begun as investigation of enantiofacial selectivity in the addition of chiral organometallics to aldehydes,[2] a process that generates two new stereocenters in one step. The initial

(1) (a) Pirkle, W. H.; Finn, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, Chapter 6, pp 87–124. (b) Souter, R. W. *Chromatographic Separations of Stereoisomers*; CRC Press: Boca Raton, FL, 1985. (c) *Chromatographic Chiral Separations*; Zief, M., Crane, L. J., Eds.; Chromatographic Science Series; Marcel Dekker: New York, 1988; Vol. 40. (d) Allenmark, S. G. *Chromatographic Enantioseparation: Methods and Applications*; Ellis Horwood Ltd.: Chichester, UK, 1988.

(2) Rein, K. S.; Gawley, R. E. *Tetrahedron Lett.* **1990**, *31*, 3711–3714. Rein, K. S.; Gawley, R. E. *J. Org. Chem.*, in press.

0022-3263/91/1956-0839$02.50/0

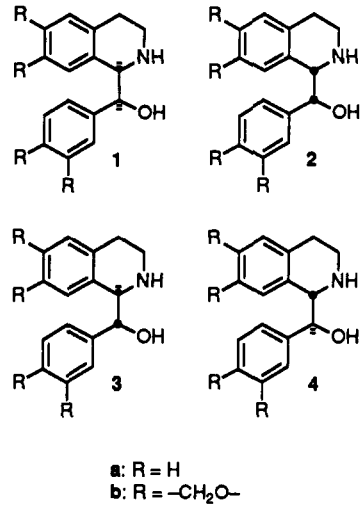
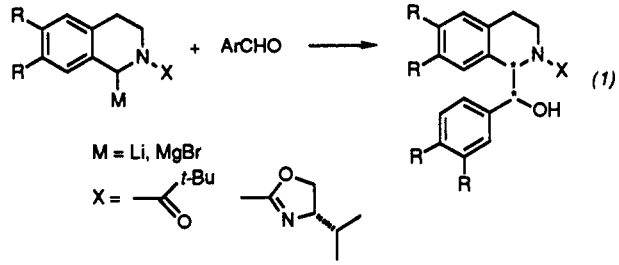


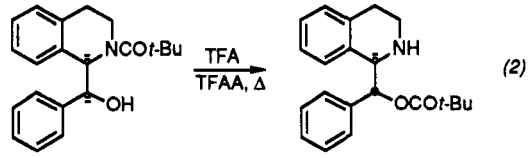
Figure 1. (α-Hydroxybenzyl)tetrahydroisoquinoline stereoisomers.

stages of this study involve the elaboration of metalated tetrahydroisoquinolines for the synthesis of phthalide isoquinoline alkaloids (eq 1).[3] As part of this effort, we



have established a correlation between absolute configuration and order of elution on a Pirkle column[4] for the erythro enantiomers (**1a,b, 2a,b**) and the threo enantiomers (**3a,b, 4a,b**) shown in Figure 1 and report the results herein.

The syntheses of the (hydroxybenzyl)isoquinolines were accomplished as illustrated in eq 1. The racemic compounds were made by metalation of the tetrahydroisoquinoline pivalamides and addition to the corresponding aldehyde,[5] while the nonracemic compounds were made similarly using an oxazoline auxiliary and resolution.[2] It was established in 1984 that the organomagnesium pivalamides afford the erythro isomers exclusively, and that the threo isomers are available by the inversion process shown in eq 2.[5] The lithiated amides and oxazolines afford mixtures of both erythro and threo addition products.[6]



After removal of the pivaloyl or oxazoline group, treatment of the amino alcohols with α-naphthoyl chloride affords the corresponding naphthamides with no esterification observed. Figure 2 shows the separation of the erythro (**1,2a**) and threo (**3,4a**) pairs. Table I lists the separability factors, α, and the capacity ratios, κ'_1, for the eight compounds **1-4a,b**.

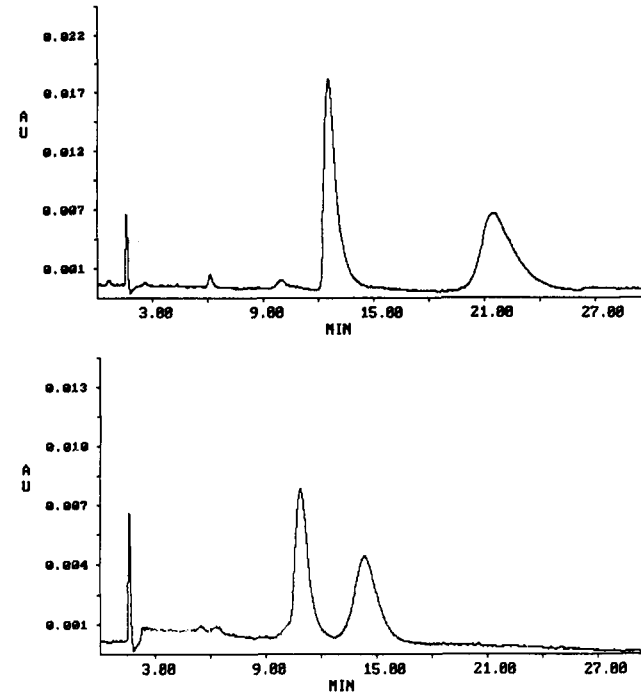


Figure 2. Pirkle chromatograms of **1,2a** (top) and **3,4a** (bottom).

Table I. Resolution of (α-Hydroxybenzyl)tetrahydroisoquinoline Enantiomers on a Pirkle Column

compounds	α[a]	κ'_1[b]	% IPA[c]	retained enantiomer
1-2a	1.87	5.55	15	1*R*,9*S*
3-4a	1.40	4.59	15	1*R*,9*R*
1-2b	1.24	7.52	35	1*R*,9*S*
3-4b	1.40	5.82	35	1*R*,9*R*

[a] The chromatographic separability factor, $\alpha = \kappa'_2/\kappa'_1$, where κ'_2 and κ'_1 are the capacity ratios of the two enantiomers. [b] The capacity ratio, $\kappa'_1 = T_r/T_0$, where T_r and T_0 are the retention times of the analyte and an unretained eluent, respectively. [c] The percent of isopropyl alcohol, in hexane, of the mobile phase.

The absolute configuration of the major isomer of a 2:1 mixture of erythro compounds **1a** and **2a** was established by hydrogenolysis to the corresponding benzylisoquinolines[7] and Pirkle analysis.[8] Conversion of this **1-2a** mixture to a mixture of **3a** and **4a** (eq 2) established the absolute configuration of the major enantiomer of the latter mixture as well. The absolute configuration of the oxygenated series, **1-4b**, was established by conversion of **1b** to (+)-bicucullinediol and of **3b** to (+)-adlumidinediol.[9]

Summary. The retained enantiomer of both the erythro and the threo series of (α-hydroxybenzyl)tetrahydroisoquinolines on a Pirkle column has the C_1 hydrogen α (*R* configuration). This is the same configuration as the retained enantiomer of the simpler 1-alkyl-substituted compounds, although in the latter case the C_1 α-hydrogen

(3) Blaskó, G.; Gula, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105-122.

(4) Bakerbond DNBPG (Covalent) Chiral column, J. T. Baker Co. The chiral stationary phase is (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine.

(5) (a) Seebach, D.; Syfrig, M. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 248-249. (b) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1-13.

(6) The erythro and threo isomers are readily differentiated by the coupling constants between the two methine protons. See: Rozwadowska, M. D.; Brossi, A. *J. Org. Chem.* **1989**, *54*, 3202-3205 and references cited therein.

(7) Battersby, A. R.; Spenser, H. *J. Chem. Soc.* **1965**, 1087-1092.

(8) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504-2506. In addition to the chromatographic resolution of α-alkyl heterocyclic amines, these authors reported the resolution of erythro and threo (α-hydroxybenzyl)tetrahydroquinolines, but did not establish the absolute configuration of the retained enantiomer in either case.

(9) Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1975**, *23*, 294-298. The details of these conversions will be published elsewhere (see ref 2).

has the *S* configuration due to the difference in Cahn-Ingold-Prelog priorities of the two systems. Our interpretation of these observations with regard to the chiral recognition models[10] is as follows: (i) although both chiral amides and chiral benzylic alcohols may interact with the chiral stationary phase,[1] the binding of the amide appears to predominate over binding of the benzylic alcohol; (ii) there may be some secondary effects due to the benzylic alcohol, as evidenced by the changes in α in going from erythro to threo, but these effects are minor and unpredictable.[11,12]

Experimental Section

HPLC analysis was performed on a Varian Vista 5000 LC, using a Groton PF1 diode array detector coupled to a Hewlett-Packard 3392A integrator. The stationary phase was a Bakerbond chiral DNBPG covalent Pirkle column,[4] and the flow rate was 2.0 mL/min.

Preparation of the Naphthamides. Naphthoyl chloride (1.5 equiv) was added to a solution of the amino alcohol and triethylamine (1.5 equiv) in methylene chloride at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solution was washed with 10% HCl and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The product was purified by radial chromatography eluting with 50:50 hexane and ethyl acetate.

Acknowledgment. K.S.R. thanks the University of Miami for a Maytag Fellowship. This work was supported by the National Institutes of Health (GM-37985).

(10) (a) Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1984**, *49*, 138-140. (b) Lipkowitz, K. B.; Demeter, D. A.; Zegarra, R.; Larter, R.; Darden, T. *J. Am. Chem. Soc.* **1988**, *110*, 3446-3452. (c) Topiol, S.; Sabio, M.; Moroz, J.; Caldwell, W. B. *Ibid.* **1988**, *110*, 8367-8376. (d) Pirkle, W. H.; Burke, J. A., III; Wilson, S. R. *Ibid.* **1989**, *111*, 9222-9223.

(11) Note that for **1-2a** vs **3-4a** (unoxygenated erythro vs threo), α decreases, whereas for **1-2b** vs **3-4b** (methylenedioxy erythro vs threo), α increases.

(12) For a study of the separation of enantiomeric and diastereomeric di- and tripeptides that also showed primary dependence only on the absolute configuration of the stereocenter nearest the chiral binding sites, see: Pirkle, W. H.; Alessi, D. M.; Hyun, M. H.; Pochapsky, T. C. *J. Chromatogr.* **1987**, *398*, 203-209.

On the Hydroxide Ion as a One-Electron Reductant in Organic Chemistry

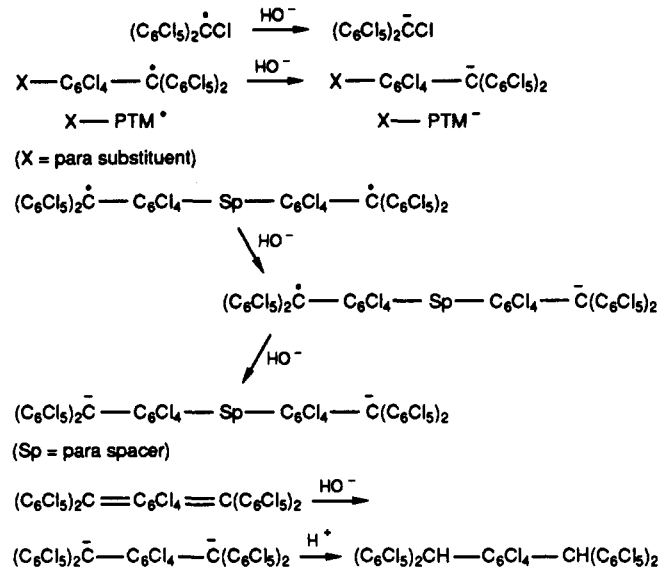
Manuel Ballester* and Isabel Pascual

Departamento de Materiales Orgánicos Halogenados, Centro de Investigación y Desarrollo (CSIC), Jordi Girona 18-24, 08034 Barcelona, Spain

Received March 12, 1990

In 1967 it was announced[1a,2] that in certain polar solvents hydroxide ion converts perchlorotriphenylmethyl radical (PTM•), the paradigm of an "inert free radical",[1,3-5] rapidly and quantitatively into perchlorotriphenylmethyl anion (PTM⁻). This is a simple, clear-cut, unambiguous example of one-electron donation to radical PTM•, i.e., a genuine single-electron transfer (SET).

Scheme I



In recent years, strong evidence supporting HO^- as a one-electron donor in other areas of organic chemistry has been reported.[6-9] ESR spectroscopy has shown the involvement of radical-anions in the Cannizzaro reaction of substituted benzaldehydes with NaOH in THF/HMPT.[10] However, evidence for the formation of extremely reactive HO• radical remains either ambiguous or circumstantial. A review on general and fundamental aspects of HO^- as one-electron reducing agent in displacement, addition, and single-electron transfer reactions has recently been published.[11]

It is quite surprising that for a species so familiar as the HO^- so little experimental evidence on its reductive character had been reported, this being due to various factors: (1) The vast majority of reactions with HO^- were, and still are, carried out in water or protic solvents because of insolubility of the alkali-metal hydroxides in other organic solvents. In water and in aqueous solvents, HO^- is highly stabilized by hydration (about 100 kcal/mol),[12] and therefore its reactivity in simple SET processes is either very low or practically nonexistent. (2) The overwhelming majority of potential organic SET acceptors cannot provide a drive (positive redox potential) to offset the HO^- hydration free energy. (3) The complexity of the mechanisms going from substrate to product often masks the nature of the processes involved. (4) The awkwardness of alternative (to ionic) radical mechanisms proposed. (5) The low thermodynamic stability and chemical reactivity of the relevant reaction intermediates and products. (6) The lack of appropriate experimental techniques, such as advanced ESR spectrometry.

Nevertheless, polar solvents, such as DMSO, HMPT, and THF, in which alkali-metal hydroxides are at least somewhat soluble, particularly in the presence of water, diminish dramatically the HO^- solvation,[13] and so they may

(1) Ballester, M. *Pure Appl. Chem.* **1967**, *15*, 123-151 (review); (a) p 142.

(2) Ballester, M. *Proc. OAR Res. Appls. Conf., USAF, Washington D.C.* **1967**, *1*, 237-248.

(3) Ballester, M.; Olivella, S. In *Polychloroaromatic Compounds*; Suschitzky, H., Ed.; Plenum Press: New York, 1974; pp 4-196 (review); (a) p 126; (b) p 154; (c) p 129.

(4) Ballester, M. *Acc. Chem. Res.* **1985**, 380 (review).

(5) Ballester, M. *Adv. Phys. Org. Chem.* **1989**, *25*, 267-445 (review); (a) p 394; (b) p 375; (c) p 431, 436; (d) pp 328-332; (e) p 351.

(6) Endo, T.; Miyazawa, T.; Shiihashi, S.; Okawara, M. *J. Am. Chem. Soc.* **1984**, *106*, 3877.

(7) Arai, S.; Kato, S.; Hida, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1458.

(8) Umemoto, K. *Chem. Lett.* **1985**, 1415.

(9) Umemoto, K.; Okamura, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3047.

(10) Ashby, E. C.; Coleman, D. T. III; Gamasa, M. P. *Tetrahedron Lett.* **1983**, *24*, 851.

(11) Sawyer, D. T.; Roberts, J. L., Jr. *Acc. Chem. Res.* **1988**, *21*, 469.

(12) Pearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109.

0022-3263/91/1956-0841$02.50/0