yields.[69] No other products were observed. Similarly, durene and mesitylene were cleanly mercurated to single products, 2,3,5,6-tetramethylphenylmercury(II) trifluoroacetate and 2,4,6-trimethylphenylmercury(II) trifluoroacetate.[70]

The thermal reactions of thallium(III) trifluoroacetate with tri-*tert*-butylbenzene and trineopentylbenzene were carried out in trifluoroacetic acid in the presence of lithium trifluoroacetate as follows. A 1-mL aliquot of 0.03 M $Tl(O_2CCF_3)_3$ was added to a 2-mL aliquot containing tri-*tert*-butylbenzene and lithium trifluoroacetate such that the final concentrations were 0.01 M $Tl(O_2CCF_3)_3$, 0.01 M tri-*tert*-butylbenzene, and 0.05 M lithium trifluoroacetate. The solution was allowed to react overnight at 25 °C in the dark. It was quenched with 2 mL of 1.0 M potassium iodide. Tridecane was added as an internal standard. Iodo-di-*tert*-butylbenzene was obtained in ~10% judging from its mass spectrum: *m/z* (%) 316 (30), 302 (12), 301 (72), 159 (30), 143 (11), 131 (17), 129 (34), 128 (28), 127 (27), 120 (14), 117 (18), 116 (11), 115 (42), 91 (27), 77 (14), 63 (12), 57 (100). The latter was identical with the product derived from 1,3-di-*tert*-butylbenzene. Two minor products (~5-10%) with GC retention times similar to that of di-*tert*-butylbenzene were observed but not identified. The balance of the tri-*tert*-butylbenzene was recovered intact. No GC/MS corresponding to iodotri-*tert*-butylbenzene was detected.

In a similar procedure, 1,3,5-trineopentylbenzene[71] afforded ~20% of iodotrineopentylbenzene as judged by GC/MS analysis: *m/z* (%) 414 (4), 358 (4), 302 (14), 246 (24), 129 (5), 128 (7), 119 (10), 117 (6), 115 (7), 91 (5), 71 (7), 58 (5), 57 (100). The residue was accounted for as unreacted 1,3,5-trineopentylbenzene.

**Isolation of Single Crystals for X-ray Crystallographic Analysis.** Single crystals of the EDA complex of hexamethylbenzene-mercury(II) trifluoroacetate, 2,4,6-trineopentylphenylmercury(II) trifluoroacetate, and 1,3,5-trineopentylbenzene were obtained by the controlled removal of the solvent. Into a flask with two chambers (connected by a transfer tube with a fine frit) was introduced a concentrated solution of the components. The system was frozen and the contents (in one chamber) were degassed by repeated freeze-pump-thaw cycles. The flask was warmed to room temperature, and only the empty chamber was cooled to 0 °C. The rate of solvent transfer was controlled at ~1.0 mL $h^{-1}$. The details of the crystal structure of hexamethylbenzene-mercury(II) trifluoroacetate have been described earlier.[31] The details of the crystal structure of 2,4,6-trineopentylphenylmercury(II) trifluoroacetate and 1,3,5-trineopentylbenzene illustrated in Figures 10 and 15 are included in the supplementary material.

**Acknowledgment.** We thank S. Fukuzumi for helpful suggestions, J. C. Huffman for the crystal structures in Figures 10 and 15, and the National Science Foundation and Robert A. Welch Foundation for financial support.

**Registry No.** $[(CH_3)_6C_6Hg(O_2CCF_3)_2]$, 77001-38-8; $[(CH_3)_5C_6H-Hg(O_2CCF_3)_2]$, 103621-77-8; $[1,2,4,5-(CH_3)_4C_6H_2Hg(O_2CCF_3)_2]$, 78717-21-2; $[1,2,3,5-(CH_3)_4C_6H_2Hg(O_2CCF_3)_2]$, 103621-78-9; $[1,2,3,4-(CH_3)_4C_6H_2Hg(O_2CCF_3)_2]$, 78717-15-4; $[1,2,3-(CH_3)_3C_6H_3-Hg(O_2CCF_3)_2]$, 103621-79-0; $[1,2,4-(CH_3)_3C_6H_3Hg(O_2CCF_3)_2]$, 103621-80-3; $[1,3,5-(CH_3)_3C_6H_3Hg(O_2CCF_3)_2]$, 78717-11-0; $[1,2-(C-H_3)_2C_6H_4Hg(O_2CCF_3)_2]$, 78716-61-7; $[H_3CC_6H_5Hg(O_2CCF_3)_2]$, 78716-26-4; $[C_6H_6Hg(O_2CCF_3)_2]$, 78716-15-1; $[(CH_3)_6C_6Tl(O_2CCF_3)_3]$, 92397-33-6; $[(C_2H_5)_6C_6Tl(O_2CCF_3)_3]$, 92397-34-7; $[(CH_3)_5C_6HTl(O_2-CCF_3)_3]$, 92397-35-8; $[1,2,3,4-(CH_3)_4C_6H_2Tl(O_2CCF_3)_3]$, 92397-36-9; $[1,2,3,5-(CH_3)_4C_6H_2Tl(O_2CCF_3)_3]$, 92397-37-0; $[1,2,4,5-(CH_3)_4C_6H_2-Tl(O_2CCF_3)_3]$, 92397-38-1; $[1,2,3-(CH_3)_3C_6H_3Tl(O_2CCF_3)_3]$, 92397-39-2; $[1,2,4-(CH_3)_3C_6H_3Tl(O_2CCF_3)_3]$, 92397-40-5; $[1,3,5-(CH_3)_3C_6-H_3Tl(O_2CCF_3)_3]$, 92397-41-6; $[1,2-(CH_3)_2C_6H_4Tl(O_2CCF_3)_3]$, 92397-42-7; $[1,3-(CH_3)_2C_6H_4Tl(O_2CCF_3)_3]$, 92397-43-8; $[1,4-(CH_3)_2C_6H_4-Tl(O_2CCF_3)_3]$, 92420-19-4; $[t-C_4H_9C_6H_5Tl(O_2CCF_3)_3]$, 92397-44-9; $[i-C_3H_7C_6H_5Tl(O_2CCF_3)_3]$, 92397-45-0; $[C_2H_5C_6H_5Tl(O_2CCF_3)_3]$, 92397-46-1; $[H_3CC_6H_5Tl(O_2CCF_3)_3]$, 92397-47-2; $[C_6H_6Tl(O_2CCF_3)_3]$, 92397-48-3; $1,3,5-(CH_3)_3C_6H_3$, 108-67-8; $1,2,4-(CH_3)_3C_6H_3$, 95-63-6; $1,2,3-(CH_3)_3C_6H_3$, 526-73-8; $1,2,3,4-(CH_3)_4C_6H_2$, 488-23-3; $1,2,3,5-(CH_3)_4C_6H_2$, 527-53-7; $1,2,4,5-(CH_3)_4C_6H_5$, 95-93-2; $(CH_3)_5C_6H$, 700-12-9; $1,3-(CH_3)_2C_6H_4$, 108-38-3; $1,4-(CH_3)_2C_6H_4$, 106-42-3; $1,2-(CH_3)_2C_6H_4$, 95-47-6; $t-C_4H_9C_6H_5$, 98-06-6; $i-C_3H_7C_6H_5$, 98-82-8; $C_2H_5C_6H_5$, 100-41-4; $CH_3C_6H_5$, 108-88-3; $C_6H_6$, 71-43-2; $ClC_6H_5$, 108-90-7; D, 16873-17-9; $F_3CCO_2H\cdot{}^1/_2Hg^{II}$, 13257-51-7; $F_3CCO_2H\cdot{}^1/_3Tl^{III}$, 23586-53-0; $((CH_3)_3CCH_2)_3C_6H_3$, 21411-39-2; $((CH_3)_3CC-H_2)_3C_6H_2HgO_2CCF_3$, 103621-81-4.

**Supplementary Material Available:** Data collection, processing parameters and positional parameters for X-ray crystallography of 2,4,6-trineopentylphenylmercury(II) trifluoroacetate and 1,3,5-trineopentylbenzene (6 pages). Ordering information is given on any current masthead page.

(69) See ref 38b and compare ref 13 and 14.
(70) For earlier studies of mercuration, see: Smith, L. I.; Taylor, F. L. *J. Am. Chem. Soc.* **1935**, *57*, 2370.
(71) Martinson, P.; Marton, J. *Acta Chem. Scand.* **1968**, *22*, 2382; **1969**, *23*, 751.

# Asymmetric Oxidoreductions Catalyzed by Alcohol Dehydrogenase in Organic Solvents[1]

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**Abstract:** A methodology is developed for the use of alcohol dehydrogenase (and other $NAD^+/NADH$-dependent enzymes) as catalysts in organic solvents. The enzyme and the cofactor are deposited onto the surface of glass beads which are then suspended in a water-immiscible organic solvent containing the substrate. Both NADH and $NAD^+$ are efficiently regenerated in such a system with alcohol dehydrogenase-catalyzed oxidation of ethanol and reduction of isobutyraldehyde, respectively; cofactor turnover numbers of $10^5$ to greater than $10^6$ have been obtained. With use of asymmetric oxidoreductions catalyzed by horse liver alcohol dehydrogenase in isopropyl ether, optically active (ee of 95 to 100%) alcohols and ketones have been prepared on a 1 to 10 mmol scale.

The use of alcohol dehydrogenases (ADH) for preparative production of optically active alcohols and ketones has received much attention[2] due to the importance of asymmetric carbonyl/alcohol oxidoreductions in organic chemistry[3]. Despite some impressive successes,[4] this synthetic strategy still has serious practical drawbacks such as operational instability of most ADH[2b] and their cofactor NADH,[5] insolubility of most of their substrates in water which necessitates work in emulsions or suspensions, product inhibition of the enzyme,[4c] and lability of some substrates and products of ADH in aqueous solutions.[6]

We have recently employed enzymes for preparative transformations in organic solvents instead of water.[7] Although this

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(1) This paper is dedicated to the memory of Professor Nathan O. Kaplan who passed away on April 15 of this year. Dr. Kaplan, a pioneer in many areas of biochemistry, made a number of pivotal and insightful contributions to dehydrogenase enzymology.
(2) (a) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119-130. (b) Jones, J. B.; Beck, J. F. In *Applications of Biochemical Systems in Organic Chemistry*; Jones, J. B., Sih, C. J., Perlman, D., Eds., Wiley: New York, 1976; Part 1, pp 107-401. (c) May, S. W.; Padgette, S. R. *Bio/Technology* **1983**, *1*, 677-686. (d) Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617-638. (e) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351-3403.

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approach might eliminate the aforementioned shortcomings in the ADH catalysis, its applicability seemed doubtful because both enzymes and nicotinamide adenine dinucleotide (and most other) cofactors are insoluble in nearly all organic solvents, and effective interactions between two insoluble species appeared impossible. In the present study we have elaborated on a straightforward and general method for utilization of cofactor-requiring enzymes in organic media, which also affords cofactor regeneration. This method has been used for preparation of optically active compounds catalyzed by horse liver ADH.

## Results and Discussion

In order to achieve an interaction between the enzyme and the cofactor in organic media, we have decided to turn a liability of the system into an advantage: if ADH and $NAD^+/NADH$ cannot react with each other when suspended in organic solvents individually, then, by the same token, they should not disaggregate when suspended together in such a milieu. Therefore, if a mixture of the enzyme and the cofactor is preformed in water, dehydrated, and placed in an organic solvent, then the biocatalyst should remain intact. To eliminate diffusional limitations in such a system,[8] the biocatalyst was deposited on the surface of glass beads.[9] Horse liver ADH (20 mg) was dissolved in 0.5 mL of 20 mM Tris·HCl buffer (pH 7.0) containing 1 μg (1.4 nmoles) of NADH. The solution was added to 1 g of glass powder, and the slurry was gently mixed, spread on a watch glass, and left to dry at room temperature with occasional mixing until visibly dry (freely flowing) beads were obtained. The biocatalyst prepared in this fashion was then used for the reduction of 2-methylvaleraldehyde (**1**): the beads covered by the enzyme and cofactor were added to 10 mL of ethyl acetate, presaturated with the buffer containing 2.5 mmol of **1** and 10 mmol of ethanol (to enzymatically regenerate the NADH oxidized in the reaction). Then 20 μL of the aqueous buffer were added to secure the necessary mobility of the cofactor with respect to ADH,[10] and the suspension was vigorously shaken at 25 °C; periodically, aliquots were withdrawn and assayed by gas chromatography. After 7 days, more than three-quarters of **1** was reduced to the alcohol corresponding to a turnover number for NADH of greater than 1 000 000. The biocatalyst had reasonable operational stability—after six consecutive reuses[11] over a period of 3 weeks

**Scheme I**

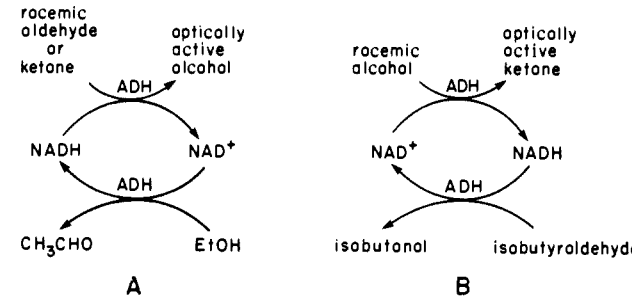


**Table I.** Asymmetric Oxidoreductions Catalyzed by Horse Liver Alcohol Dehydrogenase (Scheme I) in Isopropyl Ether

| substrate | product | ee of the product, % |
|---|---|---|
| (±)-2-phenylpropionaldehyde[a] | (−)-2-phenylpropanol[a] | 95[b] |
| (±)-2-chlorocyclohexanone[c] | (+)-*trans*-2-chlorocyclohexanol[c] | 98[d] |
| (±)-*trans*-3-methylcyclohexanol[e] | (−)-3-methylcyclohexanone[e] | 100[f] |
| (±)-*cis*-2-methylcyclopentanol[g] | (+)-2-methylcyclopentanone[g] | 96[h] |

[a] 200 mL of isopropyl ether (presaturated with aqueous buffer (20 mM Tris·HCl, pH 7.0)) containing 8.05 g (60 mmol) of (±)-2-phenylpropionaldehyde and 1 M ethanol were supplemented with 8 g of glass beads, coated with horse liver ADH and NADH (as described in the text), and 0.5% of the buffer. The suspension was shaken at 25 °C and 250 rpm for 113 h when the degree of conversion reached 15.3%. Then the biocatalyst was removed by decantation, the solvent evaporated in a rotary evaporator, and the remainder dissolved in $CH_2Cl_2$ and separated on a silica gel column. As a result, 0.5 g (3.7 mmol, 41% yield) of (−)-2-phenylpropanol (97% pure by GC) were obtained. [b] Due to a controversy in the literature concerning $[\alpha]^{25}_D$ for 2-phenylpropanol (Cohen, J. B.; Marshall, J.; Woodman, H. E. *J. Chem. Soc.* **1915**, 887–902. Eliel, E. L.; Freeman, J. P. *J. Am. Chem. Soc.* **1952**, *74*, 923–927. Roger, R.; Neilson, D. G. *J. Chem. Soc.* **1960**, 627–629. Watson, M. B.; Youngson, G. W. *J. Chem. Soc.* **1972**, 1597–1958.), we determined the enantiomeric excess by NMR. Both $^{19}F$ (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549) and $^1H$ (Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519) NMR following formation of the MTPA esters gave the same ee value. [c] The procedure was similar to that described in footnote *a* except that 2.1 g (16 mmol) of (±)-2-chlorocyclohexanone were dissolved in 250 mL of the solvent containing 0.5 M ethanol and then 16 g of glass beads coated with the enzyme and NADH were added. The reaction was stopped after 120 h when it reached 8.3% conversion. Following isolation, 0.13 g (1 mmol, 75% yield) of (+)-*trans*-2-chlorocyclohexanol (the trans configuration was proven by using the base-catalyzed epoxidation reaction: Bergkvist, T. *Svensk. Kem. Tidskr.* **1947**, *59*, 224–226) (100% pure by GC) were obtained. [d] Determined by both $^{19}F$ and $^1H$ NMR as mentioned in footnote *b*. [e] The experimental protocol was similar to that described in footnote *a* except that 4.5 g (40 mmol) of (±)-*trans*-3-methylcyclohexanol were dissolved in 400 mL of the solvent containing 0.1 M isobutyraldehyde and then 40 g of glass beads coated with ADH and $NAD^+$ were added. The reaction was stopped after 61 h when it reached 28% conversion. We obtained 0.7 g (6.2 mmol, 56% yield) of (*S*)-(−)-3-methylcyclohexanone (100% pure by GC). [f] Determined by comparing its $[\alpha]^{25}_D$ −11.5° (*c* 1.37, hexane/ether (8:3)) with that of the authentic sample of the (*R*)-(+) isomer purchased from Aldrich ($[\alpha]^{25}_D$ +11.4° (*c* 1.37, the same hexane/ether mixture)). [g] The experimental conditions were similar to those described in footnote *e* except that 2.7 g (27 mmol) of (±)-*cis*-2-methylcyclopentanol were dissolved in 270 mL of the solvent and 27 g of glass beads were added. The reaction was stopped after 47 h (20% conversion). We obtained 0.3 g (3 mmol, 55% yield) of (*S*)-(+)-2-methylcyclohexanone (95% pure by GC). [h] Determined by comparing its $[\alpha]^{25}_D$ +112.5° (*c* 0.95, chloroform) with the literature value of +117.5° (Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532–540).

(3) (a) Eliel, E.; Otsuka, S., Eds. *Asymmetric Reactions and Processes*; American Chemical Society: Washington, D. C., 1982. (b) Mosher, H. S.; Morrison, J. D. *Science* **1983**, *221*, 1013–1019.

(4) For most recent examples, see: (a) Lok, K. P.; Jakovak, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521–2526. (b) Wong, C.-H.; Drueckhammer, D. G. *Bio/Technology* **1985**, *3*, 649–651. (c) Lee, L. G.; Whitesides, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 6999–7008. (d) Wong, C.-H.; Drueckhammer, D. G.; Sweers, H. M. *Ibid.* **1985**, *107*, 4028–4031. (e) Keinan, E.; Hafeli, E. K.; Seth, K. K.; Lamed, R. *Ibid.* **1986**, *108*, 162–169.

(5) (a) Wong, C. -H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1981**, *103*, 4890–4899. (b) Walt, D. R.; Findeis, M. A.; Rios-Mercadillo, V. M.; Auge, J.; Whitesides, G. M. *Ibid.* **1984**, *106*, 234–239.

(6) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474–3480.

(7) (a) Kirchner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072–7076. (b) Cesti, P.; Zaks, A.; Klibanov, A. M. *Appl. Biochem. Biotechnol.* **1985**, *11*, 401–407. (c) Kazandjian, R. Z.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 5448–5450.

(8) Klibanov, A. M. *CHEMTECH* **1986**, *16*, 354–359.

(9) As described previously for polyphenol oxidase.[7c]

(10) Although an addition of 0.5% (v/v) water exceeds the solubility in the solvent, in the presence of glass powder the aqueous droplets are immediately adsorbed by the glass beads. If no water was added, the biocatalyst was found to be completely inactive. A possible explanation for that fact is that when glass beads adsorb some water from the solvent (which was presaturated with the aqueous buffer) the latter begins to strip the "essential" water[8] from the enzyme, thereby inactivating it. The dependence of the rate of ADH-catalyzed reduction of **1** in ethyl acetate on the amount of water added was bell-shaped with a broad maximum between 0.5 and 1.5% (v/v). We have established that the cofactor can freely enter and exit the active center of the enzyme: when 25 nmol of ADH and 7 μmol of NADH were used to reduce **1** (2.5 mmol) in 10 mL of ethyl acetate (no ethanol added for cofactor regeneration), μmol of 2-methyl-1-pentanol were obtained (if the cofactor could not leave the active center of the enzyme, then the amount of the product would not exceed that of ADH, i.e., 25 nmol). No appreciable amount of the biocatalyst existed in the form of a microemulsion in the solvent detached from glass beads. This follows from an experiment in which the ADH/NADH-bearing glass beads were removed from ethyl acetate by decantation; afterwards, virtually no reduction of **1** was observed in the supernatant.

it still exhibited more than a one-third of the initial activity.

Other organic solvents, including isopropyl ether, butyl acetate, and chloroform (all presaturated with the aqueous Tris buffer, pH 7), were also suitable as the reaction medium for the ADH catalysis. It should be stressed that both the enzyme and NADH were insoluble in all of these solvents and therefore were trapped in the hydration layer on the surface of the glass beads. In the systems described, which represented a suspension of ADH and NADH (codeposited onto glass beads) in a monophasic organic solvent,[10] the water content was crucial—if no aqueous buffer was added to the water-saturated solvent or if the latter was not presaturated with water, then no enzymatic activity was expressed.

We then employed ADH/NADH in organic solvents for preparative, stereospecific reduction of carbonyl compounds (Scheme IA). The aforedescribed experimental design was scaled up (using isopropyl ether as a solvent) and used for asymmetric enzymatic reduction of 2-phenylpropionaldehyde and 2-chlorocyclohexanone. As the first two entries in Table I indicate, millimolar quantities of the corresponding alcohols of high optical purity were obtained.

The direction of the ADH-catalyzed production of optically active compounds in organic solvents can be reversed if the system is appropriately modified. Using the approach depicted in Scheme IB (isobutyraldehyde is employed for the enzymatic regeneration of $NAD^+$), racemic *trans*-3-methylcyclohexanol and *cis*-2-methylcyclopentanol were preparatively converted to the corresponding *S* ketones of 100% and 96% ee, respectively (Table I).

The experimental strategy developed herein should be applicable to the use of other $NAD^+$/NADH-dependent dehydrogenases in organic solvents—either alone or coupled with horse liver ADH for cofactor regeneration. Some of the advantages of conducting enzymatic oxidoreductions in organic solvents vs. water are a much greater solubility (and, e.g., in the case of 2-chlorocyclohexanone, stability) of substrates, significantly higher cofactor turnover numbers,[12] the ease of enzyme immobilization and reuse (a major bottleneck in preparative transformations catalyzed by ADH[4e]), and product recovery.

## Experimental Section

Horse liver alcohol dehydrogenase (EC 1.1.1.1) was purchased from Sigma Chemical Co. as a crystalline powder with a specific activity of 1.5 units/mg of protein. Glass beads (nonporous), 75-150 μm in diameter, were also purchased from Sigma. All chemicals used in this work were obtained commercially and were of the highest purity available.

Enzymatic oxidoreductions in organic solvents were carried out as described in the text and footnotes to Table I (no reactions were detected when ADH was omitted from the system). The time courses of all reactions studied were followed by gas chromatography: periodically, 1-μL aliquots of the liquid phase were withdrawn and analyzed with use of a 5 m capillary column with 530 μm fused silica gel (Hewlett-Packard) ($N_2$ carrier gas, 30 mL/min, detector and injector port temperature 250 °C). In the case of the last two entries in Table I, precolumn derivatization with acetic anhydride[13] was employed to improve the GC separation between the alcohol and the ketone. All yields quoted in footnotes to Table I are calculated on the transformed material only.

(11) After each run, the biocatalyst-bearing glass beads were separated from solution by decantation and added to the next fresh substrate solution (an addition of 0.5% aqueous buffer was unnecessary in all but the first runs, presumably because the glass beads were already "saturated" with water).

(12) Compared to the same compounds converted in water by the enzyme, e.g., see: Lemiere, G. L.; Lepoivre, J. A.; Alderweirdeldt, F. C. *Tetrahedron Lett.* **1985**, *26*, 4527-4528. This may be due to a high effective concentration of the cofactor in the microenvironment of the enzyme in organic solvents.

(13) Watts, R. B.; Kekwick, R. G. D. *J. Chromatogr.* **1974**, *88*, 15-24.

(14) This work was financially supported by W. R. Grace & Co. We are grateful to Dr. Michel Therisod for helpful discussions.

# Electron-Transfer Reactions of Bicyclo[4.2.1]nonatrienes: Formation of a Bishomoheptafulvene Radical Cation

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**Abstract:** The radical cation ($3^{\bullet+}$) of 9-methylenebicyclo[4.2.1]nona-2,4,7-triene undergoes rapid intramolecular cyclization to generate an isomeric radical cation ($15^{\bullet+}$) derived from a tetracyclic structure. In contrast, the hydrocarbon **15** suffers

$3^{\bullet+}$ $15^{\bullet+}$

retrocyclization to regenerate **3**. The comparative stability of $15^{\bullet+}$ is ascribed to its bishomoaromatic character. Four radical cations of less unsaturated model compounds support the assigned structure.

The concepts of both bicycloaromaticity[1,2] and homoaromaticity[3] have been proposed in order to account for the enhanced stability of molecules possessing interacting, nonplanar π-systems. Homoaromaticity encompasses systems where a cyclic array of $(4n + 2)\pi$ electrons is interrupted by an aliphatic fragment, whereas bicycloaromaticity deals with π-systems of diverse topologies (e.g., spirocyclic, longicyclic, etc.). Homoaromaticity has been documented particularly well in carbonium ion chemistry, whereas bicycloaromaticity has been demonstrated less frequently. Yet, neither effect has been documented in radical cation chemistry. Indeed, it has been shown only very recently that the radical cations derived from barbaralane and several derivatives adopt a 5π-electron bishomoaromatic structure.[4] The only other ex-

(1) Goldstein, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 6357-6359.
(2) Goldstein, M. J.; Hoffman, R. *J. Am. Chem. Soc.* **1971**, *93*, 6193-6203.
(3) Winstein, S. *J. Am. Chem. Soc.* **1959**, *81*, 6524-6525.

0002-7863/86/1508-6734$01.50/0 