Table VI. Mean Bond Lengths in **7**, **11**, **13**, and **20**

| | **7** | **11** | **13** | **20** |
|---|---|---|---|---|
| arom C—C | 1.39 (1) | 1.37 (2) | 1.39 (1) | 1.39 (2) |
| C(arom)—$C_{sp^3}$ | 1.55 (1) | 1.52 (2) | 1.50 (1) | 1.52 (2) |
| $C_{sp^3}$—$C_{sp^3}$ | 1.52 (2) | 1.30 (3) | 1.48 (2) | 1.51 (2) |
| $C_{sp^3}$—$C_{sp^2}$ | 1.49 (1) | 1.50 (2) | 1.44 (1) | 1.50 (2) |
| C(arom)—O | 1.41 (1) | 1.42 (1) | 1.38 (1) | 1.40 (1) |
| $C_{s}p_{3}$—O | 1.46 (1) | 1.45 (1) | 1.42 (1)[a] | 1.40 (1) |
| $C_{sp^2}$=O | 1.19 (1) | 1.21 (2) | 1.16 (1)[a] | 1.19 (1) |
| $C_{sp^2}$—O | 1.31 (1) | 1.30 (2) | 1.29 (2)[a] | |

[a] Bond lengths of disorder component A not included in the calculations.

**Tetraadamantyl Ketone 23–KSCN Complex.** Mp > 283 °C (dec) (from acetonitrile; $^1$H NMR ($CDCl_3$) $\delta$ 1.19, 1.38–2.29, 3.27, 4.13, 4.69, 7.11; IR (KBr) 1695, 1705, 2045 cm$^{-1}$. Anal. Calcd for $C_{92}H_{120}O_8$·KSCN·$CH_3CN$: C, 76.52; H, 8.25; N, 1.88; S, 2.15; K, 2.62. Found: C, 76.00; H, 8.12; N, 1.67; S, 1.89; K, 3.73.

**Tetraethyl Ester 7–NaSCN Complex.** Mp 181–184 °C (from methanol); $^1$H NMR ($CDCl_3$) $\delta$ 1.17, 1.38, 3.31, 3.85–4.64, 7.06; IR (KBr) 1735, 2050 cm$^{-1}$. Anal. Calcd for $C_{60}H_{80}O_{12}$. NaSCN: C, 68.24; H, 7.45; N, 1.30; S. 2.99; Na, 2.14. Found: 68.13; H, 7.21; N, 1.55; S, 2.94; Na, 1.94.

**Tetraethyl Ester 7–$NaBF_4$ Complex.** Mp 216–220 °C (from methanol); $^1$H NMR ($CDCl_3$) $\delta$ 1.15, 1.36, 3.33, 3.89–4.54, 7.06; IR (KBr) 1740 cm$^{-1}$. Anal. Calcd for $C_{60}H_{80}O_{12}$·$NaBF_4$: C, 65.37; H, 7.26; B, 0.98; F, 6.89; Na, 2.09. Found: C, 65.74; H, 7.36; B, 0.98; F, 6.42; Na, 1.80.

**X-ray Crystal Structure Analysis of 7, 11, 13, and 20.** For the four structures, cell parameters and crystal orientation matrices were obtained by a least-squares refinement of the setting angles of 25 reflections (6° < $\theta$ < 15°) measured on a Enraf-Nonius CAD4 diffractometer using graphite monochromatized Mo K$\alpha$ radiation. None of the crystals diffracted well. For each compound, data were corrected for Lorentz and polarization effects; absorption corrections were not considered necessary. There was no evidence in each case for crystal decay in the X-ray beam. For **7**, the crystals are triclinic; space group $P\bar{1}$ was assumed and was confirmed by the analysis. Systematic absences for **11** and **13** allowed the space group to be *C*2/*c* or *Cc*; in each case, the former was assumed and was confirmed by the analysis. For **20**, the orthorhombic space group *Pbcn* is determined uniquely by the systematic absences.

The structures were solved with the aid of MULTAN 82[48] and were refined by full-matrix least-squares calculations using SHELX[49] or SDP-PLUS.[50] For **7**, one of the *tert*-butyl groups was disordered over two sites, and a partially occupied site with a water of solvation was also found. No allowance was made for hydrogen atoms. In **11** and **13**, fewer than half of the measured data had $I > 3\sigma(I)$ (because the molecules are so loosely held in the crystal lattice). One of the side chains was equally disordered over two sites. The hexamer molecule **11** lies about a crystallographic symmetry; a partially occupied acetone of solvation (disordered about an inversion center) was also found in the asymmetric unit. For **11** and **20**, hydrogen atoms were positioned on geometric ground (C-H, 0.95 Å) and included as riding atoms in the structure factor calculations. Details of the cell data, data collection, and refinement are in Table V. For the refinements, weights were derived from the counting statistics, and scattering factors were from the *International Tables for X-ray Crystallography*.[51] Difference maps computed at the conclusion of the refinements (shift/error < 0.1) were devoid of chemically sensible features. Mean dimensions are summarized in Table VI. Tables of final fractional coordinates, thermal parameters, molecular dimensions, and structure factor listings for **7**, **11**, **13**, and **20** are available as supplementary material. The drawings of the molecules (Figures 3–7) were prepared with the aid of ORTEP.[52]

**Acknowledgment.** We thank the Irish Department of Education and UCC for postgraduate studentships (to M.D. and E.M.S.). We thank Loctite (Ireland) Ltd. for a research studentship (to E.M.C.). We are indebted to the NSERC Canada for the award of an operating grant (to G.F.) and a Visiting Professorship (to B.K.).

**Supplementary Material Available:** Tables of fractional coordinates, thermal parameters, and molecular dimensions of **7**, **11**, **13**, and **20** (58 pages); tables of calculated and observed structure factors (85 pages). Ordering information is given on any current masthead page.

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(48) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.: Woolfson, M. M. MULTAN-82. University of York, England, and Louvain, Belgium, 1982.

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(50) Frenz, B.; Associates Inc. SPD-Plus. College Station, TX, and Enraf-Nonius, Delft, Holland, 1983.

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(52) Johnson, C. K. ORTEP II. Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN 1976.

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# Dimeric Products and Hydrogen Transfer in the Dissolving Metal Reduction of Camphor[1]

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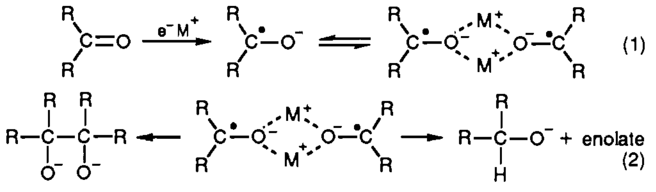
*Contribution from the Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-1905.* *Received April 24, 1989*

**Abstract:** The hydrogen-transfer step in the dissolving metal reduction of ketones in the absence of an added proton donor has been investigated by carrying out the reduction of (+)- and (±)-3-*exo*- and -3-*endo*-deuteriocamphor (**5** and **6**). Reduction to the epimeric alcohols (**3** and **4**) proceeds principally by transfer of an *exo*-hydrogen, with negligible transfer of an *endo*-hydrogen. Enolate formation from camphor using strong, sterically hindered bases gives significant amounts of product arising by removal of an *endo*-hydrogen in contrast to results obtained using hydroxide. A detailed study of the dimeric reduction products from (+)- and (±)-camphor (**1**) indicated that not only were pinacol mixtures formed but a product (**12**) was obtained, which apparently arises from coupling of a ketyl with ketone, followed by $\beta$-cleavage of an alkoxyl radical. On the basis of these and other data, a new mechanism for the reduction of ketones by dissolving metals is suggested. The key step in this mechanism is hydrogen transfer from a ketone to a ketyl to afford an $\alpha$-keto radical and an alkoxide.

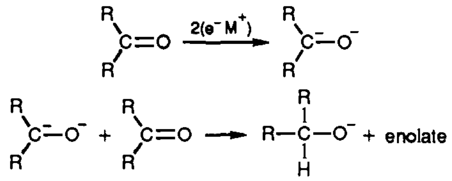
The reduction of ketones by dissolving metals, in particular, alkali metals in ammonia or alcohols, is a common synthetic procedure for the conversion of ketones to secondary alcohols. In early work on conformational analysis Barton suggested that these

0002-7863/89/1511-8691$01.50/0

**Scheme I**



**Scheme II**



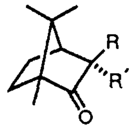
reductions were under thermodynamic control and would invariably afford the more stable of a pair of epimeric alcohols.[2] Subsequently, however, it was observed that under certain conditions (+)-camphor and some 12-ketosteroids gave the less stable alcohol on reduction with metals in ammonia or alcohol.[3]

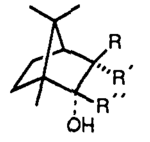
As a consequence of these apparently anomalous results a contining series of investigations of these reactions has been carried out, which has resulted in at least a partial understanding of their mechanism.[4] Although certain aspects remain unclear, it is generally recognized that there are two related but distinctly different reaction paths, one of which is operative in metal–alcohol and metal–ammonia–proton donor systems. The other path, which frequently affords product mixtures different from those obtained in the presence of proton donors, prevails in reductions carried out in liquid ammonia or ethereal solvents in the absence of an added proton donor.[4] At this point, it appears to be generally accepted that the mechanism of reduction in the presence of proton donors is some variation of that suggested some years ago by House.[4,5]

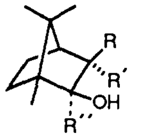
There is, however, some disagreement concerning the course of the reductions in the absence of an added proton donor. We have suggested a mechanism for the reduction of enolizable ketones (Scheme I), which is based primarily on a combination of work from our laboratory,[4a] deuterium-transfer studies carried out by Rautenstrauch,[6] and Hirota's work on ketyls and ketyl aggregates derived from aromatic and nonenolizable aliphatic ketones.[7] An alternative mechanism in which a ketone is reduced by the sequential addition of two electrons to give a vicinal dianion (Scheme II) has also been suggested.[1a,2,4,5,9]

Although the general mechanism presented in Scheme I appeared to accommodate the available experimental data for these reductions, some details remained undefined. In particular, the intervention of ketyl aggregates was based on analogy with structures deduced by Hirota on the basis of ESR and UV spectra of ketyls in ethereal solvents[7] and the observation that 2,2,6,6-tetramethylcyclohexanone with Li–THF or Li–$NH_3$ gave a stable ketyl dimer.[6a]

Reductions of ketones in the absence of proton donors give varying amounts of pinacol, and at least in the case of (+)-camphor (**1**) it had been observed that different ratios of two stereoisomeric pinacols were obtained using Na and Li (K does not normally give pinacols).[6b] It has been assumed that pinacols are formed via the combination of two ketyl units in a reaction that is competitive with hydrogen transfer. The detailed course of pinacol formation impacts upon the overall mechanism of ketone reduction since pinacols are almost certainly formed from the intermediates responsible for ketone reduction.


**1**: R,R′ = H
**2**: R,R′ = D
**5**: R = D, R′ = H
**6**: R = H, R′ = D


**3**: R,R′,R″ = D
**7**: R,R′,R″ = H


**4**: R,R′,R″ = D
**8**: R,R′,R″ = H

In an attempt to gain additional information concerning the structure of the ketyl aggregates assumed to be intermediates, we have undertaken an investigation of the stereochemistry of the hydrogen-transfer step and a detailed reinvestigation of the dimeric reduction products of camphor. Camphor was chosen as the substrate in view of its extensive use in the study of dissolving metal reductions combined with the fact that both enantiomers and the racemic ketone are available commercially.

## Results

It has been established that alkali-metal (Li, Na, K)–$NH_3$ reduction of (+)-3,3-dideuteriocamphor (**2**) in the absence of an added proton donor provides mixtures of 2,3,3-trideuterioborneol (**3**) and trideuterioisoborneol (**4**),[6b] however, the stereochemistry of hydrogen transfer has not been determined. It appeared plausible that the variation of product ratios obtained on reduction of (+)-camphor with various metals[3a,6b] could be explained on the basis of variations in ketyl aggregate structure, and it might be expected that there would be similar differences in the stereochemistry of hydrogen transfer with a metal. A possible, and experimentally feasible, approach to this problem was an investigation of the reduction of 3-*exo*- (**5**) and 3-*endo*-deuteriocamphor (**6**).

Both (+)- and (±)-3-*exo*-deuteriocamphor (**5**) were prepared by a modification of the published method[10] to give material that was exclusively the desired isomer. The (+)- and (±)-endo isomers (**6**) were prepared from 3,3-dideuteriocamphor (**2**)[6b] by treatment with lithium hexamethyldisilazide (LHDS) followed by acidification ($NH_4Cl$ or HOAc) to give material that contained 98% of **6** and 2% of **2**. The stereochemical homogeneity of ketones **5** and **6** was confirmed by $^1H$ and $^2H$ NMR.

Reductions of ketones **5** and **6** were carried out using less than 1 equiv of metal (Li, Na, K) in liquid $NH_3$ at −70 °C both with and without THF as cosolvent, conditions similar to those employed by Rautenstrauch in the reduction of dideuteriocamphor.[6b] For analysis by GC/MS a portion of each reaction mixture was treated with TBDMS–Cl to convert the product alcohols to the TBDMS ethers. For reference, authentic samples of the TBDMS ethers of borneol (**7**), isoborneol (**8**), and all possible combinations of mono-, di-, and trideuterio derivatives of **7** and **8** that could be obtained on reduction of ketones **1**, **2**, **5**, and **6** were prepared. The results of metal–$NH_3$ reductions of **5** and **6** are summarized in Table I.

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[1] Portions of this work have been published as preliminary communications: (a) Huffman, J. W.; Liao, W.-P.; Wallace, R. H. *Tetrahedron Lett.* **1987**, *28*, 3315. (b) Huffman, J. W.; Wallace, R. H.; Pennington, W. T. *Ibid.* **1988**, *29*, 2527.

[2] (a) Barton, D. H. R. *J. Chem. Soc.* **1953**, 1027. (b) Barton, D. H. R.; Cookson, R. C. *Q. Rev., Chem. Soc.* **1956**, *10*, 44.

[3] (a) Ourisson, G.; Rassat, A. *Tetrahedron Lett.* **1960**, 16. (b) Huffman, J. W.; Alabran, D. M.; Bethea, T. W.; Ruggles, A. C. *J. Org. Chem.* **1964**, *29*, 2963.

[4] There have been two recent reviews of these reductions, which present somewhat differing interpretations of the experimental data. (a) Huffman, J. W. *Acc. Chem. Res.* **1983**, *16*, 399. (b) Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351.

[5] House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 152–158.

[6] (a) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1977**, *99*, 6280. (b) Rautenstrauch, V.; Willhalm, B., Thommen, W.; Burger, U. *Helv. Chim. Acta* **1981**, *64*, 2109.

[7] Nakamura, K.; Wong, B. F.; Hirota, N. *J. Am. Chem. Soc.* **1973**, *95*, 6919, and earlier papers in this series.

[8] Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3045.

[9] (a) Rautenstrauch, V. *Tetrahedron* **1988**, *44*, 1613. *He* presents compelling arguments criticizing this mechanism. (b) Song, W. M.; Dewarld, R. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, 269. They have recently reported a kinetic study of the Na–$NH_3$ reduction of di-*tert*-butyl ketone in which the results are interpreted in terms of a dianion mechanism.

[10] Joshi, G. C.; Warnhoff, E. W. *J. Org. Chem.* **1972**, *37*, 2383.

[11] The exception is run 5 in which 12% of the borneol and 8% of the isoborneol were $d_2$ species. These data are the average of three runs.

Table I. Reduction of Deuterium-Labeled Camphor in Ammonia–THF at −70 °C[a]

| | | | products | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | camphor | | | borneol | | | | isoborneol | | | | |
| run | ketone | metal | % | $d_0$ | $d_1$ | % | $d_0$ | $d_1$ | $d_2$ | % | $d_0$ | $d_1$ | $d_2$ | pinacol,[b] % |
| 1 | (+)-**5** | Li | 66 | 11 | 89 | 15 | 13 | 49 | 38 | 5 | 11 | 35 | 54 | 14 |
| 2 | (±)-**5** | | 66 | 21 | 79 | 13 | 5 | 31 | 64 | 4 | 20 | 27 | 53 | 17 |
| 3 | (+)-**5**[c] | | 80 | 15 | 85 | 7 | 13 | 47 | 40 | 3 | 11 | 39 | 50 | 10 |
| 4 | (±)-**5**[c] | | 73 | 10 | 90 | 19 | 7 | 41 | 52 | 4 | 18 | 33 | 49 | 4 |
| 5 | (+)-**6** | | 59 | 3 | 97 | 15 | 3 | 85 | 12 | 5 | 0 | 92 | 8 | 21 |
| 6 | (±)-**6** | | 61 | <5 | >95 | 14 | 9 | 88 | 3 | 3 | 20 | 80 | 0 | 22 |
| 7 | (+)-**6**[c] | | 83 | <5 | >95 | 11 | 10 | 85 | 5 | 2 | 0 | >95 | <5 | 4 |
| 8 | (±)-**6**[c] | | 79 | <5 | >95 | 15 | 9 | 91 | 0 | 2 | 8 | 92 | 0 | 4 |
| 9 | (+)-**5** | Na | 60 | 27 | 73 | 21 | 19 | 45 | 36 | 16 | 14 | 38 | 48 | 3 |
| 10 | (±)-**5** | | 61 | 44 | 56 | 31 | 7 | 37 | 56 | 6 | 19 | 33 | 48 | 2 |
| 11 | (+)-**5**[c] | | 67 | 33 | 67 | 18 | 19 | 47 | 34 | 13 | 21 | 33 | 46 | 2 |
| 12 | (±)-**5**[c] | | 59 | 32 | 68 | 35 | 9 | 43 | 48 | 5 | 21 | 32 | 47 | <1 |
| 13 | (+)-**6** | | 57 | <5 | >95 | 22 | 0 | >95 | <5 | 15 | 0 | >95 | <5 | 6 |
| 14 | (±)-**6** | | 58 | 13 | 87 | 35 | 5 | 95 | 0 | 6 | 10 | 90 | 0 | 1 |
| 15 | (+)-**6**[c] | | 64 | <5 | >95 | 21 | 0 | >95 | <5 | 12 | 0 | >95 | <5 | 3 |
| 16 | (±)-**6**[c] | | 69 | 7 | 93 | 27 | 5 | 95 | 0 | 3 | 0 | >95 | <5 | <1 |
| 17 | (+)-**5** | K | 65 | 60 | 40 | 14 | 11 | 5 | 31 | 21 | 9 | 45 | 46 | <1 |
| 18 | (±)-**5** | | 63 | 80 | 20 | 32 | 8 | 40 | 52 | 5 | 15 | 41 | 44 | <1 |
| 19 | (+)-**5**[c] | | 64 | 38 | 62 | 14 | 21 | 55 | 24 | 22 | 21 | 43 | 36 | <1 |
| 20 | (±)-**5**[c] | | 63 | 52 | 48 | 32 | 5 | 42 | 53 | 5 | 14 | 45 | 40 | <1 |
| 21 | (+)-**6** | | 64 | 13 | 87 | 14 | 0 | >95 | <5 | 22 | 0 | >95 | <5 | <1 |
| 22 | (±)-**6** | | 66 | 31 | 69 | 29 | 6 | 94 | 0 | 5 | 20 | 80 | 0 | <1 |
| 23 | (+)-**6**[c,d] | | 65 | <5 | >95 | 15 | 9 | 86 | 5 | 20 | 0 | >95 | <5 | <1 |
| 24 | (±)-**6**[c,d] | | 59 | 11 | 89 | 36 | 6 | 94 | 0 | 5 | 12 | 88 | 0 | <1 |

[a] All runs were carried out using 0.8 mol of metal under the standard conditions described in the Experimental Section. The product mixtures were analyzed by GLC, and the reported results are the average of at least two runs, unless otherwise noted. The relative amounts of deuterium were dertermined by GC–MS. All runs were reproducible within ±4%. [b] Includes all dimeric products. [c] No THF or other cosolvent. [d] One run.

Examination of the data in Table I reveals a number of trends. First, in virtually all of the reductions of *exo*-deuterio ketone (**5**) there is some net loss of deuterium, which increases with the size of the metal. This loss of label has been noted previously by Rautenstrauch and was attributed to partial enolization of the substrate.[6b] There is virtually no loss of deuterium in the reduction of endo isomer **6** with Li and only a small loss with Na and K.

The most obvious feature of these reactions is that there is negligible transfer of an *endo*-deuterium in reductions of ketone **6** and significant transfer of *exo*-deuterium in reductions of ketone **5**. Also, although the degree of deuterium incorporation in isoborneol is the same, approximately 50% (runs 1–4, 9–12, 17–20) for both (+)- and (±)-**5**, there is significantly more deuterium transfer to borneol in the reduction of (±)-**5** than for (+)-**5**. (Compare runs 1 and 2, 3 and 4, etc.) It was observed qualitatively that in the absence of THF as a cosolvent the reductions were somewhat slower than in its presence, and in the case of the reductions carried out with Li, there was somewhat less pinacol produced (runs 1, 2, 5, 6 versus 3, 4, 7, 8). The product distribution is otherwise essentially identical with those in which THF is present.

The negligible transfer of an *endo*-deuterium is, at least superficially, explicable in terms of a combination of the well-known propensity for exo enolization of bicyclo[2.2.1]heptan-2-ones[12] and a primary deuterium isotope effect, which would further suppress transfer of an *endo*-deuterium. ($k_H/k_D$ for hydrogen transfer in the reduction of 2,2-dimethylcyclohexanone is 2.7.[6a]) Similarly, at least a portion of the apparent inefficient *exo*-deuterium transfer could be explained by competitive transfer of an *endo*-hydrogen in reductions of ketone **4**.[13] Although these rationalizations agree with the experimental data, the agreement could be fortuitious rather than correct. In particular, $k_H/k_D$ for camphor is not necessarily the same as that for 2,2-dimethylcyclohexanone, and there is no assurance that the relative rate of exo versus endo enolate formation of camphor using aqueous hydroxide[12e] is the same as the relative rate of hydrogen transfer in dissolving metal reduction.

Table II. Enolization of Deuterium-Labeled (+)-Camphor by Strong Bases[a]

| | | | camphor | | | | |
|---|---|---|---|---|---|---|---|
| run | ketone | base | $d_0$ | $d_1$ | $k_x/k_n$(obs) | $k_H/k_D$ | $k_x/k_n$ |
| 1 | **5** | LHDS | 24 | 76 | 0.32 | 12.4 | 4.0 |
| 2 | **6** | | 2 | 98 | 49 | | |
| 3[b] | **5** | | 40 | 60 | 0.67 | 2.8 | 1.9 |
| 4[b] | **6** | | 16 | 84 | 5.25 | | |
| 5[c] | **5** | | 23 | 74 | 0.31 | 5.7 | 1.8 |
| 6[c] | **6** | | 9 | 91 | 10 | | |
| 7 | **5** | LITMP | 11 | 85[d] | 0.13 | 4.8 | 0.6 |
| 8 | **6** | | 25 | 75 | 3.0 | | |
| 9 | **5** | LDA | 44 | 50[e] | 0.88 | 2.3 | 1.9 |
| 10 | **6** | | 18 | 81[f] | 4.5 | | |

[a] All runs carried out at least in duplicate with agreemwnt of ±4%. Unless otherwise noted, the experiments were carried out as noted in the Experimental Section. [b] Entire run at 25 °C. [c] Solvent was ether. [d] 4% camphor-$d_2$ was obtained. [e] 6% camphor-$d_2$. [f] 1% camphor-$d_2$.

The isotope effect for hydrogen transfer in the reduction of camphor was determined by reducing an accurately weighed 4:1 mixture of (+)-dideuteriocamphor (**2**) and unlabeled (+)-camphor (**1**) under the standard conditions. For Li at −70 °C, $k_H/k_D$ = 2.6 in good agreement with the data for 2,2-dimethylcyclohexanone.[6a,14]

To better approximate the inherent tendency of *exo*- versus *endo*-hydrogen transfer ($k_x/k_n$), the reaction of ketones **5** and **6** with sterically hindered amide bases at low temperature was investigated. Although this model may not be ideal, the net conversion depicted in eq 2 (Scheme I) in which an enolate is

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(12) (a) Thomas, A. F.; Willhalm, B. *Tetrahedron Lett.* **1965**, 1309. (b) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 701. (c) Werstiuk, N. H.; Banarjee, S. *Can. J. Chem.* **1985**, *63*, 534, and earlier papers in this series. (d) Abad, G. A.; Tindall, S. P.; Tidwell, T. T. *J. Am. Chem. Soc.* **1973**, *95*, 6326. (e) Tidwell, T. T. *J. Am. Chem. Soc.* **1970**, *92*, 1448. (f) Tee, O. S.; Altmann, J. A.; Yates, K. *J. Am. Chem. Soc.* **1974**, *96*, 3141.

(13) The combination of the isotope effect with the reported rate difference for exo vs endo enolization of camphor ($k_x/k_n$ = 21[12e]) indicates that for ketone **5** the ratio of *exo*-deuterium transfer to *endo*-hydrogen transfer should be about 8. For ketone **6** the ratio of *exo*-hydrogen to *endo*-deuterium transfer would be approximately 57.

(14) The value of $K_H/K_D$ was determined by multiplying the ratio of $d_2$ to $d_3$ alcohol by 4. The resulting values are the average of two runs. For Na and K similar values of $K_H/K_D$ were found, but the data were not consistent from run to run nor for both isomeric alcohols, probably due to the scrambling problem noted above.

produced is similar to the conversion of a ketone to its enolate by strong base. The reactions were carried out by treating the substrate ketone with excess base at −78 °C, warming slowly to ambient temperatures to ensure complete enolization, followed by either cooling to −78 °C and quenching with solid $NH_4Cl$ or cooling to 0 °C and treatment with aqueous acetic acid.[15] Both methods of quenching gave identical results. The results of these experiments are summarized in Table II.

The data in Table II indicate that in all cases enolate formation occurs with considerably less exo selectivity than would be expected on the basis of the data obtained using aqueous base.[12e] For LDA deuterium isotope effects of 3.3 and 3.8 at 0 °C have been reported for enolate formation.[16] On the basis of $k_H/k_D = 3.6$, and given $k_x/k_n$ for camphor of **21**,[12e] $k_x/k_n$(obs) with LDA should be approximately 6 for ketone **5**. For ketone **6**, $k_x/k_n$(obs) would be in the range of 75. However, the experimental data (Table II, runs 9 and 10) are 0.88 and 4.5, respectively, for ketones **5** and **6**.

From the data in Table II, it is possible to calculate values for $k_H/k_D$ for enolate formation under the specific conditions employed in the reactions described in Table II.[16] For LDA under these conditions $k_H/k_D = 2.3$, which is in the same range as that reported.[15] This corresponds to an "intrinsic" value of $k_x/k_n$ of 1.9 for enolate formation from camphor with LDA under these reaction conditions. Similar treatment of the data for enolate formation with LHDS and LITMP indicates a range of $k_x/k_n$ from 0.8 to 4.0 with $k_H/k_D$ from 2.3 to 12.4. The value of 12.4 for LHDS at low temperature (runs 1 and 2) decreases to a more normal value of 2.8 at 25 °C (runs 3 and 4) as expected.[17]

These data indicate that enolate formation from **1** by these hindered bases occurs with much attenuated selectivity for removal of the *exo*-hydrogen. In fact, for the most hindered of these bases, LITMP, *endo*-hydrogen abstraction is preferred. A plausible explanation for the reduced tendency of *exo*-hydrogen abstraction by these hindered strong bases is steric interference to exo approach of the base caused by the bridgehead methyl group.[18]

If enolate formation by hindered bases constitutes a reasonable model for the hydrogen-transfer step in the dissolving metal reduction of **1** (eq 2, Scheme I), it follows that significant amounts of *endo*-hydrogen transfer should occur during reduction. This, however, does not occur, indicating that either the model is not appropriate or the mechanism depicted in Scheme I is not correct. One possible variable that could be considered is solvent: the reductions were carried out in $NH_3$–THF, while enolate formation was done in THF. In order to investigate this possible uncertainty, reductions of (+)-**1**, (±)-**1**, and (+)-**2** in THF were carried out.

It has long been known that ketones afford ketyls on treatment with metals in ethereal solvents and alcohols have been obtained in many cases.[4,6,19] However, the only detailed study of alcohol production by this method appears to be Rautenstrauch's investigation of the reduction of 2,2-dimethylcyclohexanone.[19a] In preliminary work, we found that 4-*tert*-butylcyclohexanone was reduced slowly to a mixture of *trans*-4-*tert*-butylcyclohexanol (20%), recovered ketone (21%), and pinacol (59%) on stirring for 12 h with an equimolar amount of K in THF at 25 °C.[20] When a simple ultrasonic cleaner is used,[21] reduction of (+)- or (±)-camphor could be accomplished in 0.5–3 h using alkali metals in THF (K > Na > Li).

**Table III.** Reduction of (+)- and (±)-Camphor by Alkali Metals–THF with Sonication[a]

| run | ketone | metal | **8** (rel %) | **7** (rel %) |
|---|---|---|---|---|
| 1 | (+) | Li | 73 (78) | 27 (22) |
| 2 | (±) | | 76 (80) | 24 (20) |
| 3 | (+) | Na | 68 (63) | 32 (37) |
| 4 | (±) | | 81 (85) | 19 (15) |
| 5 | (+) | K | 42 (40) | 58 (60) |
| 6 | (±) | | 52 (84) | 48 (16) |

[a] All runs are the average of at least two experiments, which were reproducible within ±4%. All runs were carried out at ambient temperature using 0.8 mol of metal as described in the Experimental Section. Significant amounts of dimeric products (10–30%) were obtained with Li and Na. The product mixtures were analyzed by GLC. [b] Figures in parentheses are the relative percentages obtained using the metal in $NH_3$–THF as formed in this work. These data are in agreement with those reported in ref 4a and 6b.

The results of these experiments (Table III) indicate that, with the exception of the reduction of (±)-camphor with K, the results are, within experimental error, the same as those obtained using the corresponding metal in $NH_3$. In order to obtain additional confirmation that the reductions in THF were mechanistically similar to those in $NH_3$, the reduction of deuteriocamphors **2**, **5**, and **6** in THF was investigated. In the course of these relatively slow reactions, specifically labeled ketones **5** and **6** underwent sufficient scrambling of the label that the results were meaningless. However, the results for reduction of **2** described in Table IV are in good agreement with those reported by Rautenstrauch for reductions carried out in $NH_3$, which are included in Table IV.[6b] The extent of deuterium transfer to the product alcohols is nearly identical in both systems with Li and K and qualitatively similar with Na.

In both this work (Tables I and IV) and Rautenstrauch's,[6] reductions of labeled camphor (**2**, **5**, and **6**) gave product alcohols that contain somewhat less deuterium than can be accounted for by the various paths discussed above. A possible reaction that could be responsible for this effect is hydrogen abstraction from solvent by the radical center of a ketyl. A reaction of this type was suggested by Rautenstrauch to account for lower than expected deuterium incorporation in the Li–THF reduction of 2,2-dimethyl-6,6-dideuteriocyclohexanone,[6a] and coupling reactions of ketyls with ethereal solvents at −25 °C and above have been observed.[1a,19a] Hydrogen abstraction by ketyls in liquid $NH_3$ has, however, apparently not been observed.

Although an ideal probe of this reaction path would be to carry out reductions in $ND_3$, this material is exceedingly expensive and as an alternative reductions of (+)-**1** were carried out using Li, Na, and K in $NH_3$–THF-$d_8$. The reductions were carried out under the standard conditions, and the results are presented in Table V.

Reduction with Li under these conditions gave product alcohols containing modest amounts of deuterium indicative of hydrogen transfer from solvent to ketyl. Quite unexpectedly, however, a significant amount of deuterium was incorporated into the recovered (+)-camphor. Although only 7% of the camphor was deuterated, the overall conversion to alcohols was 17%, indicating that approximately 40% of the ketone, which had undergone the hydrogen-transfer reaction to provide the product alcohols, subsequently incorporated deuterium. The extent of deuterium incorporation in the reaction products when Na and K were employed as reducing agents was less than with Li but could still be detected.

It has been found that reduction of (+)-**1** with Na in moist ether or Na–$NH_3$ gave, in addition to a mixture of epimeric alcohols, *endo–endo*-pinacol, **9**.[6b,22–24] A second pinacol, which was assigned

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(15) These conditions were chosen to approximate as closely as possible the conditions of temperature employed in the dissolving metal reductions. However, it was found that the rate of enolization of camphor at −78 °C was exceedingly slow, and conditions were used that permitted enolization to occur at the lowest possible temperature. The data were uniformly reproducible to within ±4%. The reported values of $K_H/k_D$ were calculated using the following relationships: For ketone **5**, $k_x/k$(obs) = $(k_x/k_n)/(k_H/k_D)$, and for ketone **6** $kx/k_N$(obs) = $(k_x/k_n)(k_H/k_D)$. In these expressions $k_x/k_N$ refers to the "intrinsic" ratio of *exo*- vs *endo*-hydrogen abstraction.

(16) (a) Miller, D. J.; Saunders, W. H. *J. Org. Chem.* **1982**, *47*, 5039. (b) Beautelman, H. P.; Xie, L.; Miller, D. J.; Saunders, W. H. *Ibid.* **1988**, *53*, 2396. (c) Beautelman, H. P.; Xie, L.; Saunders, W. H. *Ibid.* **1989**, *54*, 1703.

(17) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row: New York, 1981, pp 207–208.

(18) The authors thank Dr. Eugene C. Ashby for helpful discussions concerning this portion of the work.

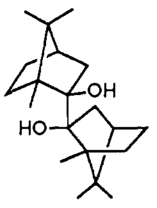
(19) (a) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1976**, *98*, 5035. (b) Reference 5, pp 166–172.

(20) Liao, W.-P. M.S. Thesis, Clemson University, 1984.

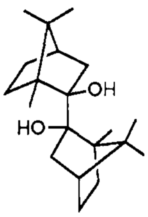
(21) Lindely, J.; Mason, T. J. *Chem. Soc. Rev.* **1987**, *16*, 275.

(22) Beckmann, E. *Liebigs Ann. Chem.* **1896**, *292*, 1.

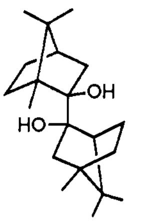
exo–endo structure **10** was obtained by Li–$NH_3$ reduction.[6b,24,25]



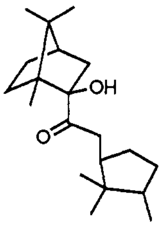
**9**



**10**



**11**



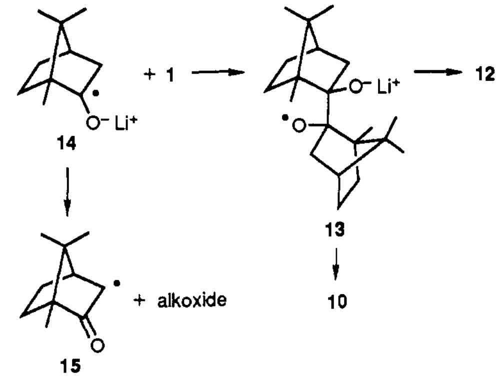
**12**

Bimolecular reduction of ketones is generally considered to proceed by radical coupling of two ketyl units,[19b] and a similar mechanism has been invoked to explain pinacol formation in the metal–$NH_3$ reduction of ketones.[4a,6b] Since ketyls are implicated in the reduction of ketones to alcohols by dissolving metals as well as in the formation of pinacols, the mechanisms of these reactions must be closely related and a detailed investigation into the factors governing pinacol formation should afford additional insight into the overall course of the reductions.

While this investigation was in progress Pradhan reported a study of pinacol formation using (+)- and (±)-**1** as substrates, in which some criteria were found for the selective formation of **9** and **10**.[24] There was also described a rather remarkable enantioselective effect in the reduction of (±)-**1** in which *only* racemic pinacols **9** and **10** were obtained. It was reported that neither *meso*-pinacol **11** nor the diastereomer of **10** was formed.[26] Repetititon of the reduction of (+)-**1** gave results that were qualitatively similar to those reported. However, in $NH_3$ neither pinacol **9** nor **10** was obtained exclusively; invariably approximately 10% of the other pinacol was present.[1b] In the runs carried out using Li–THF under Pradhan's conditions (stirring)[24] or with sonication, small amounts (4%) of another bimolecular reduction product were obtained in addition to 20% of pinacol **9**. This material was identified as hydroxy ketone **12** on the basis of spectroscopic data, and the structure was confirmed by crystallography.[1b,28] In some experiments, not necessarily restricted to those specifically designed to investigate pinacol formation, in which (+)-camphor was reduced with Li–$NH_3$–THF, small amounts of ketone **12** could be detected. A series of experiments was carried out using Li–$NH_3$–THF in order to ascertain more specifically the conditions that lead to the formation of **12** and if possible to optimize the yield of this unusual reduction product. These runs were carried out by adding a standard solution of (+)-**1** in THF to a solution of Li–$NH_3$ via a syringe pump and varying the time of addition. The results are summarized in Table VI.

The data in Table VI show that the formation of ketone **12** is optimized by addition of the substrate at a moderate rate to the Li–$NH_3$ solution and that formation of this dimeric reduction product apparently occurs at the expense of pinacol. The conditions employed in the reactions described in Table VI are similar to those for the preparation of symmetrical pinacol **9**; however, in Pradhan's work,[24] the Li concentration is much greater (0.5 vs 0.1 mg/atom per mL) than those used in the preparation of **12**. Also, the pinacol produced in conjunction with **12** is *exo–endo*-pinacol **10** (Table VI). On a somewhat larger scale (see the Experimental Section), it was possible to prepare ketone **12** in 59% yield by a modification of the procedure used in the experiments described in Table VI.

Scheme III



In contrast to the published data[24] reduction of (±)-camphor with either Li–THF or Li–$NH_3$ gave not only racemic pinacols **9** and/or **10** plus **12** but significant amounts of *meso-endo–endo*-pinacol (**11**), the structure of which was confirmed by X-ray crystallography.[1b,28] As shown in Table VII conditions that afford predominantly pinacol **9** from (+)-camphor provided approximately 1:1 mixtures of (±)-**9** and **11**. Conditions under which (+)-camphor provides unsymmetrical pinacol **10** gave mixtures of **11** and (±)-**10** when carried out on the racemate. Reductions of (±)-**1** also provide amounts of racemic ketone **12** comparable to those obtained from (+)-**1**.

In none of these experiments and in agreement with Pradhan's observations[24] was there any detectable amount of the diastereomers of **10** or **12**, which would result from reaction of (+)- and (−)-camphor units. In contrast, racemic pinacol **9** is accompanied by the diastereomer (**11**) resulting from heterochiral coupling. To confirm that (±)-**10** and (±)-**12** were, in fact, the racemates, racemic mixtures of these isomers were prepared. This was accomplished by preparing **10** and **12** from (−)-camphor, mixing these enantiomers with the corresponding material prepared from (+)-camphor and comparing the mixtures with the products from reduction of (±)-camphor.

## Discussion

At the time this work was initiated, the mechanism outlined in Scheme I appeared to accommodate the available data for reductions of saturated aliphatic ketones by alkali metals–$NH_3$ in the absence of an added proton donor. However, the results reported above are very difficult to rationalize in terms of this mechanism.

In particular, it is not possible to explain formation of hydroxy ketone **12** by a simple combination of two ketyls. The most plausible route to this compound is β-cleavage of alkoxyl radical **13** (Scheme III), which leads after hydrogen atom abstraction, presumably from solvent, to **12**.[29] Electron transfer to **13** leads by protonation during workup to pinacol **10**. The exo–endo geometry assigned to **13** is based on the observation that (±)-**1** provides, apparently exclusively, (±)-**10** and (±)-**12**. This rationale combined with the fact that **10** is the principal pinacol that accompanied **12** (Table VI) suggests this route to **10**. Also, increased yields of **12** invariably result in decreased yields of **10** (Table VI), implying that **10** and **12** arise from a common intermediate.

Alkoxyl radical **13** would arise from reaction of ketyl **14** with a molecule of **1**. Although the addition of a ketyl to a ketonic carbonyl group is a known reaction,[30] this appears to be the first example in a metal–$NH_3$ reduction. This path is consistent with the observation that pinacol **10** and ketone **12** are formed under conditions in which the overall concentration of $Li^+ (e(NH_3)_x)^-$ is low. This optimal concentration should be achieved by a low overall concentration of solvated electrons, which may be effected

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[23] Huckel, W.; Maier, M.; Jordan, E.; Seeger, W. *Liebigs Ann. Chem.* **1958**, *616*, 46.

[24] Pradhan, S. K.; Thakker, K. R.; McPhail, A. T. *Tetrahedron Lett.* **1987**, *28*, 1813.

[25] Murphy, W. S.; Sullivan, D. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, *999*.

[26] These results imply a lack of coupling of (+)-camphor units with their (−)- counterparts.

[27] The dimeric products were isolated as described in the Experimental Section. It was found that $^{13}C$ NMR was the best way to distinguish between the various isomers.

[28] ORTEP structure is presented in ref 1b. For information regarding the crystallographic data, see ref 1 and 6 in ref 1b.

[29] (a) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593. (b) Nickon, A.; Iwadare, T.; McGuire, F. J.; Umezawa, B. *J. Am. Chem. Soc.* **1970**, *92*, 1688. (c) Gray, P.; Williams, A. *Chem. Rev.* **1959**, *59*, 239.

[30] Clerici, A.; Porta, O. *J. Org. Chem.* **1987**, *52*, 5099, and earlier papers in this series.

**Table IV.** Reduction of (+)-3,3-Dideuteriocamphor (**1**) by Alkali Metals in THF with Sonication and by Metals in $NH_3$[a]

| | camphor | | | | borneol | | | | | isoborneol | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| metal–solvent | % | $d_0$ | $d_1$ | $d_2$ | % | $d_0$ | $d_1$ | $d_2$ | $d_3$ | % | $d_0$ | $d_1$ | $d_2$ | $d_3$ |
| Li–THF | 88 | 0 | 27 | 73 | 9 | 5 | 3 | 26 | 66 | 3 | 0 | 0 | 24 | 76 |
| Li–$NH_3$–THF | 62 | 0 | 31 | 69 | 28 | 0 | 0 | 28 | 72 | 10 | 0 | 0 | 25 | 75 |
| Na–THF | 78 | 6 | 46 | 48 | 14 | 1 | 2 | 20 | 77 | 8 | 0 | 0 | 18 | 82 |
| Na–$NH_3$–THF | 56 | 0 | 37 | 63 | 25 | 0 | 5 | 37 | 58 | 19 | 0 | 4 | 31 | 65 |
| K–THF | 73 | 9 | 43 | 48 | 9 | 2 | 4 | 30 | 64 | 18 | 0 | 3 | 25 | 72 |
| K–$NH_3$–THF | 84 | 0 | 25 | 75 | 6 | 0 | 0 | 22 | 78 | 10 | 0 | 0 | 15 | 85 |

[a] The runs were carried out as described in Table III and the products analyzed as described in Table I. The data in $NH_3$ are those reported in ref 6b, Table I, run 1.

**Table V.** Reduction of (+)-Camphor in $NH_3$–THF-$d_8$ at −70 °C[a]

| | camphor | | | isoborneol | | | borneol | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| metal | % | $d_0$ | $d_1$ | % | $d_0$ | $d_1$ | % | $d_0$ | $d_1$ | pinacol,[b] % |
| Li | 76 | 93 | 7 | 4 | 93 | 7 | 13 | 92 | 8 | 7 |
| Na | 71 | >95 | <5 | 10 | >95 | <5 | 18 | >95 | <5 | <1 |
| K | 6k | >95 | <5 | 20 | >95 | <5 | 15 | >95 | <5 | <1 |

[a] Carried out as described in *a*, Table I. [b] Includes all dimeric products.

**Table VI.** Addition of (+)-Camphor in THF to Li–$NH_3$[a]

| time of addition | camphor, % | isoborneol, % | borneol, % | pinacol,[b] % | **12** |
|---|---|---|---|---|---|
| <5 s | 46 | 8 | 25 | 21 | <1 |
| 1 min | 47 | 3 | 12 | 14 | 24 |
| 2 min | 43 | 4 | 17 | 12 | 24 |
| 4 min | 42 | 4 | 17 | 9 | 28 |
| 5 min | 65 | 2 | 10 | 3 | 20 |
| 7 min | 56 | 5 | 16 | 18 | 5 |
| 10 min | 58 | 6 | 20 | 16 | <1 |
| 15 min | 67 | 6 | 18 | 9 | <1 |

[a] A solution of 1.3 mmol of (+)-**1** in 1 mL of THF was added via syringe pump, to a solution of 1 mg/atom of Li in 10 mL of $NH_3$. Products isolated as described in the Experimental Section and relative percentages of products determined as described in *a*, Table I. [b] Structure not determined in every run. In all cases in which it was determined, it was **10**.

**Table VII.** Reduction of (±)-Camphor

| | procedure[a] | | |
|---|---|---|---|
| product | ketone into Li–$NH_3$ | Li into ketone–$NH_3$–THF | Li–THF with sonication |
| **1** | 31 | 40 | 48 |
| **8** | 6 | 6 | 4 |
| **7** | 32 | 36 | 18 |
| **11** | 12 | 7 | 13 |
| **10** | tr | 11 | tr |
| **9** | 19 | tr | 17 |

[a] Li–$NH_3$ reductions carried out as described in ref 24. Li–THF reduction as described in the Experimental Section. [b] Traces of this isomer could be detected.

by adding small pieces of Li to a solution of the ketone in $NH_3$–THF[6b,24,25] or by addition of a THF solution of ketone at a controlled rate to a solution of Li–$NH_3$ (Table VI). In the latter case the course of these very fast reactions would be governed by local concentration and mixing effects.[9a,31]

Pinacol **9** is formed from (+)-**1** under either heterogeneous conditions or by addition of the ketone to a relatively concentrated solution of Li–$NH_3$.[22,24] However, under these conditions (±)-**1** gives approximately equal amounts of (±)-**9** and *meso*-pinacol **11** (Table VII). These are conditions that would favor rapid formation of high concentrations of ketyl, either in $NH_3$ solution or on the metal surface in ethereal solvents. The result would be conditions that favor pinacol formation by the accepted mechanism of radical coupling.[4a,18b] It might be expected that in the reduction of (±)-**1** such a process would lead to both (±)- and *meso*-pinacols as is observed.

Interpretation of the data incorporated in Tables I and III–V leads to a number of conclusions regarding the mechanism of these reactions. The most obvious of which is that the overalll course is the same in THF as in $NH_3$ (Tables III and IV), indicating that the mechanism is similar in both solvents, as noted by Rautenstrauch.[6a]

The data in Table I indicate that in reduction of (+)- or (±)-**1** to mixtures of alcohols **7** and **8** *endo*-hydrogen transfer is disfavored (5% or less except in run 6). Transfer of an *exo*-hydrogen occurs but with (+)-**1** never exceeds 54%, although (±)-**1** is converted to (±)-**8** with significantly greater *exo*-hydrogen transfer. *Exo*-hydrogen transfer to produce alcohol **7** is, within experimental error, the same with (+)- and (±)-**1**.

The mechanism for reduction depicted in Scheme I (eq 2) leads to enolate formation by abstraction of an α-hydrogen from a ketyl by the bulky radical center of a second ketyl. As discussed above (Table II) abstraction of a proton from (+)-**1** by bulky strong bases shows relatively little selectivity for exo versus endo proton abstraction. Both these processes represent the net reaction of geometrically similar substrates (ketone and ketyl) with a bulky reagent to form the same enolate. Although the analogy may not be quantitatively correct, similar steric factors should be operative in both processes and they should be qualitatively similar. This suggests that eq 2 in Scheme I does not correctly represent the exclusive path by which hydrogen transfer occurs.

The presence of deuterated camphor (presumably **5**) in the product mixtures in reductions carried out with metals (particularly Li) in $NH_3$ in THF-$d_8$ is also incompatible with the mechanism presented in Scheme I. The most obvious route to deuterated camphor is via an α-keto radical (**15**; Scheme III) derived from **1** by hydrogen abstraction. This process has been observed by ESR in the reaction of aliphatic ketyls with the parent ketone at low temperature (<−100 °C)[32] and certainly should be operable in metal–$NH_3$ or THF systems. The preference for *exo*-hydrogen transfer is also consistent with a radical intermediate. It has been noted that bicyclo[2.2.1]heptyl radicals are pyramidal with the substituent skewed toward endo geometry.[33]

The enhanced deuterium transfer from (±)-**5** in the formation of borneol (Table I; runs 2, 4, 10, 12, 18, 28) is probably related

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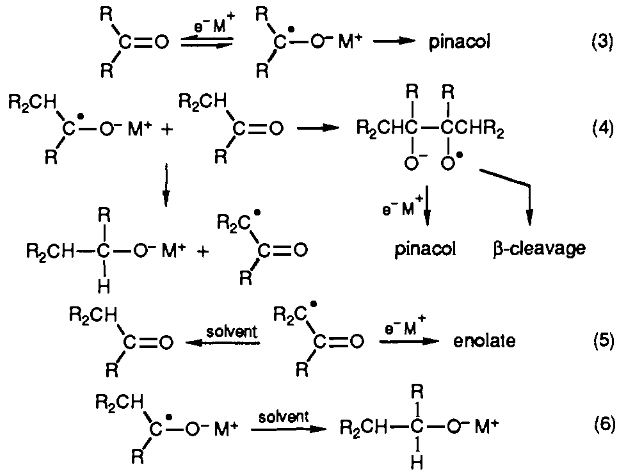
(31) (a) Meijs, G. F.; Bunnett, J. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 4899. (b) Bourne, J. R.; Ravindranath, K.; Thomas, S. *J. Org. Chem.* **1988**, *53*, 5166.

(32) (a) Bennett, J. E.; Mile, B.; Thomas, A. *J. Chem. Soc. A* **1968**, *298*. (b) Sevilla, M. D.; Swarts, S.; Rearden, R.; Morehouse, K. M.; Vartanian, T. *J. Phys. Chem.* **1981**, *46*, 993.

(33) (a) Kuwamura, T.; Koyama, T.; Yonezawa, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 3220. (b) Fujimoto, H.; Fukui, K. *Tetrahedron Lett* **1966**, 5551. (c) Kleinfelter, D. C.; Dye, T. E.; Mallory, J. E.; Trent, E. S. *J. Org. Chem.* **1967**, *32*, 1734. They describe the Li–$NH_3$ reduction of *exo*- and *endo*-3-phenylbicyclo[2.2.1]heptan-2-one. The endo epimer is reduced normally; however, the *exo*-phenyl isomer undergoes reduction of the aromatic ring. (d) Luche, J. L.; Allvenu, C.; Petrier, C.; DuPuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373. They provide evidence for α-keto radical intermediates in the conjugate addition of alkyl groups to conjugated enones.

**Scheme IV**



to the increased **7**/**8** ratio found in the reduction of (±)-**1** with Na or K–$NH_3$ relative to the behavior of (+)-**1** (Table I).[3a,4a] (This effect has been explained in terms as different reactions rates of diastereomeric species.[34])

On the basis of these data, we suggest an alternative mechanism (Scheme IV) for the reduction of ketones by dissolving metals in the absence of an added proton donor. This mechanism is based on the reaction path described in Scheme III, which requires the simultaneous existence of ketyl and ketone. Mechanistically this may be accomplished via an equilibrium between ketyl and ketone as depicted in eq 3, Scheme IV. The position of this equilibrium is difficult to predict due to a dearth of knowledge concerning the reduction potentials of ketones in liquid $NH_3$.[35] Apparently, the only equilibrium constant that has been determined for the reaction of an organic substrate with $e^-(NH_3)_x$ is biphenyl for which $K_{eq} \simeq 10^5$ with a rate of $8 \times 10^{10}$ $M^{-1}$ $s^{-1}$ (diffusion controlled) for the forward reaction and approximately $10^6$ $M^{-1}$ $s^{-1}$ for the regeneration of the substrate.[36] The reduction potentials of **1** and biphenyl are –2.75[37] and –2.70 V,[38] respectively, in aqueous media, indicating that the equilibrium shown in eq 3 would be effectively irreversible.

A more plausible explanation involves micromixing effects such that local concentrations of $e^-(NH_3)_x$ become depleted, permitting the simultaneous existence of ketyl and ketone.[31] The rate of the reaction of acetone with $e^-(NH_3)_x$ to give the ketyl has been found to be $9 \times 10^7$ $M^{-1}$ $s^{-1}$ using pulse radiolysis,[39] and the rate of reaction of other ketones should be about the same magnitude. This gives $t_{1/2}$ of ca. $10^{-5}$–$10^{-6}$ s for the reaction of a ketone with $e^-(NH_3)_x$, which is well within the range where micromixing effects are important.[31b] In this instance $K_{eq}$ for ketone $\rightleftharpoons$ ketyl becomes unimportant.

This step must be fast relative to subsequent steps because the ketyl must possess a sufficient lifetime to undergo cation exhange with an added metal salt.[25] The relative rates of dimerization of the ketyl and all other reactions are then competitive in rate with subtle variations in the rates of each as a function of a variety of factors, such as the metal cation or mode of addition of reagents.

Equation 4 is a generalized summary of the reactions described in detail for **1** in Scheme III, and eq 5 and 6 depict reduction of the $\alpha$-keto radical to enolate and hydrogen abstraction from solvent by keto radicals and ketyls. While there is experimental evidence that THF serves as a hydrogen atom donor (Table V), it is possible that $NH_3$ fulfills the same role.[40] These hydrogen-transfer reactions may account for a significant amount of the net loss of deuterium label in the reactions described in Table I. The possibility of a mechanism similar to that outlined in Scheme III was mentioned by Rautenstrauch in his study of reductions of 2,2-dimethylcyclohexanone.[6a]

The mechanism outlined in Scheme IV appears to agree with the available experimental data for the dissolving metal reduction of ketones; however, there is still insufficient evidence to clearly define the factors that govern the stereochemical course of these reactions. It is also entirely possible that the path outlined in Scheme I and that described in Scheme IV both play important roles in these reductions. There is, however, no doubt that these reactions are mechanistically very complex and that the overall product distribution can be profoundly affected by subtle changes in conditions, which will cause rather unpredictable variations in product distributions.

## Experimental Section

Infrared spectra are reported in reciprocal centimeters ($cm^{-1}$), measured as neat films between NaCl plates, as pellets, or as solutions in $CCl_4$ using Nicolet 5DX or Perkin-Elmer Model 1310 spectrometers. All $^1H$ and $^{13}C$ spectra were obtained on a JEOL FX-90Q (90-MHz) NMR spectrometer, IBM Instruments NR200-AR (200-MHz) NMR spectrometer, or a Hitachi Perkin-Elmer R-24 (60-MHz) NMR spectrometer using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million ($\delta$) relative to tetramethylsilane. The center signal of $CDCl_3$ (77.0 ppm) was used as the internal standard for $^{13}C$ chemical shifts. $^2H$ NMR spectra were obtained using chloroform as the solvent, and the chemical shifts are reported in parts per million upfield relative to $CDCl_3$ GC/MS analyses were performed on a Hewlett-Packard 5985 gas chromatograph/mass spectrometer at 70 eV. Columns used were 1.0 m × 2.0 mm 2% OV-101 on 100–200-mesh Chromosorb WHP and 2.0 m × 2.0 mm 10% Carbowax 20M on 80–100-mesh Chromosorb WHP. Gas chromatographic analyses were performed on a Perkin-Elmer Sigma 3B Dual FID chromatograph with a Sigma 15 data station. Columns used included a 6 ft × 0.125 in. 10% Carbowax 20M on 80–100-mesh Chromosorb WHP a 6 ft × 0.125 in. SE-30 on 80–100-mesh Chromosorb W, and a 30 m × 0.53 mm × 1.0 $\mu$m film thickness Supelcowax 10 WCOT fused-silica column.

Tetrahydrofuran (THF) and ethyl ether were distilled from sodium–benzophenone ketyl. 2,2,6,6-Tetramethylpiperidine, dichloromethane, diisopropylamine, dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride. 1,4-Dioxane was distilled from lithium aluminum hydride. Commercially available (Aldrich) solutions of *n*-butyllithium in hexane and lithium hexamethyldisilazide (LHDS) in THF were titrated with 1,3-diphenyl-2-propanone tosylhydrazone as indicator, prior to use.

Alkali metals Li, Na, and K were cut under mineral oil, washed free of mineral oil in hexanes (stored over sodium wire), and weighed in a tared vial of mineral oil. The metals were washed again in hexanes before being used in the reactions.

A Bransonic Model B-2200R was used as the sonicator for those reactions in which ultrasound was employed.

**3-*exo*-Deuteriocamphor** (**5**). 3-*exo*-Deuteriocamphor was prepared by the following modification of the method of Joshi and Warnhoff:[10] A solution of 5.0 g (33 mmol) of (+)- or (±)-camphor (**1**) in 125 mL of THF under $N_2$ was treated with 22 mL (44 mmol) of 2 M *n*-butyllithium at 25 °C. After stirring for 30 min, the solution was transferred via cannula to a solution of 2.8 mL of perdeuterioacetic acid and 2.5 mL of deuterium oxide. After stirring for 1 h, the mixture was poured into brine and extracted with ether. After drying with $Na_2SO_4$ and evaporation of the solvent, a semisolid was obtained, which. on sublimation [100 °C (3 mmHg)], gave 4.0 g (79%) of pure **5** (100% $d_1$). $^2H$ NMR: $\delta$ –4.99. MS ($m/z$): 153 (34), 110 (36), 108 (410), 95 (100), 82 (76), 69 (54), 55 (31), 41 (42).

**3,3-Dideuteriocamphor** (**2**). 3,3-Dideuteriocamphor (**2**) was prepared by the following modification of Rautenstrauch's method:[6a] To a stirred solution of 30 mL of dioxane and 50 mL of $D_2O$ under a $N_2$ atmosphere was added 1.0 g of Na metal in small pieces. After the Na had reacted, 6.0 g (39 mmol) of camphor (+ or ±) was added and the resulting

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(34) Rautenstrauch, V. *Helv. Chim. Acta* **1982**, *65*, 402.

(35) We presented a very crude estimate of $K_{eq} = 3 \times 10^2$ for **1** $\rightleftharpoons$ **14** based on reduction potentials in aqueous media and noted the relationship between reduction potentials and $K_{eq}$.[1a]

(36) Farhataziz; Parkey, L. M. *J. Phys. Chem.* **1976**, *80*, 122.

(37) Hamon, D. P. G.; Richards, K. R. *Aust. J. Chem.* **1983**, *36*, 109. Other aliphatic ketones are in the same range.

(38) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; pp 8–77.

(39) (a) Parkey, L. M.; Farhataziz. *Int. J. Radiat. Phys. Chem.*, *Chem. Abst.* **1976**, *85*, 54550C. (b) Schindewolf, U.; Wünschel, P. *Can. J. Chem.* **1977**, *55*, 2159. This reaction rate is well within the range at which local concentration effects (micromixing) become important.[31]

(40) One unsuccessful attempt to detect $NH_2$ radicals in these reductions has been described,[25] which employed a test for the presence of hydrazine. Formation of hydrazine requires a sufficient lifetime for $NH_2$ in the presence of $e^-(NH_3)_x$ to permit dimerization, which seems unlikely.

two-phase solution was stirred at 50 °C for 168 h and cooled to ambient temperature. Brine and ether were added, and the aqueous layer was drawn off and extracted with three portions of ether. The combined organic extracts were washed with brine and dried over $Na_2SO_4$, and the solvent was removed to give a viscous oil. Removal of the residual dioxane under high vacuum gave a semisolid, which was sublimed [100 °C (3 mmHg)] to give 5.3 g (88%) of pure **2** (100% $d_2$). $^2H$ NMR: $\delta$ −4.99, −5.49. MS (*m/z*): 154 (35), 111 (22), 108 (39), 95 (100), 83 (93), 69 (60), 55 (31).

**3-*endo*-Deuteriocamphor (6).** A solution of 4.0 g (26 mmol) of **2** in 25 mL of THF was cooled to −78 °C, and 80 mL (80 mmol) of 1 M LHDS in THF was added. The resulting solution was allowed to warm to room temperature over a period of 3 h and cooled to −78 °C, and 20 g of $NH_4Cl$ was added. The reaction was warmed to room temperature over 2 h, diluted with brine, and extracted with three portions of ether. The combined ether extracts were dried with $Na_2SO_4$, and the solvent was removed to give a semisolid, which on sublimation gave 3.0 g (76%) of **6** (98% $d_1$, 2% $d_0$). $^2H$ NMR: $\delta$ −5.49. MS (*m/z*): 153 (29), 110 (26), 108 (26), 95 (100), 82 (58), 69 (55), 55 (20).

**Purification of (+)- or (±)-Camphor.** Commercially available (+)- or (±)-**1** contained approximately 5% of a mixture of **7** and **8**. Purification was effected by Jones oxidation in the usual manner. This procedure provided camphor, which was completely homogeneous (NMR–GLC–IR).

***tert*-Butyldimethylsilyl Ethers of 7 and 8.** A solution of 0.50 g (3 mmol) of alcohol **7** or **8**, 0.555 g (8 mmol) of imidazole, and 0.60 g (4 mmol) of *tert*-butyldimethylsilyl chloride in 2.5 mL of DMF was stirred at 50 °C for 36 h. The solution was cooled to ambient temperature, and brine and ether were added. The reaction mixture was extracted with three portions of ether, the combined ether extracts were washed with brine and dried over $Na_2SO_4$, and the solvent was evaporated to give the TBDMS ethers of **7** and **8** in greater than 95% yield. Derivative of **8**. $^1H$ NMR: $\delta$ 0.02 (s, 6 H), 0.81 (s, 3 H), 0.83 (s, 3 H), 0.88 (s, 9 H), 1.02 (s, 3 H), 1.08–1.81 (m, 7 H), 3.51 (m, 1 H). MS (*m/z*): 268 (0.2), 211 (23), 135 (4), 117 (5), 101 (6), 95 (5), 75 (100), 73 (11), 67 (4), 41 (4). Derivative of **7**. $^1H$ NMR: $\delta$ 0.02 (s, 6 H), 0.79 (s, 3 H), 0.86 (s, 6 H), 0.91 (s, 9 H), 0.97 (s, 3 H), 0.86 (s, 6 H), 0.91 (s, 9 H), 0.97–2.36 (m, 7 H), 2.92 (m, 1 H). MS (*m/z*): 268 (0.5), 211 (72), 135 (8), 117 (6), 101 (8), 95 (9), 75 (100), 73 (114), 67 (5), 41 (5).

**Metal–Ammonia Reduction of 1.** A solution of 0.152 g (1 mmol) of (+)- or (±)-**1**, **-2**, **-5**, or **-6** in 1 mL of THF was cooled to −70 °C, and 10 mL of dry $NH_3$ was distilled into the reaction. To this solution was added 0.8 mmol of the appropriate metal (Li, Na, K). When the metal had completely reacted, as evidenced by the disappearance of any blue color, 1.0 g of $NH_4Cl$ was added. The reaction was allowed to warm to room temperature, and after the $NH_3$ had evaporated, brine and ether were added. The aqueous layer was drawn off and extracted with three portions of ether. The combined ether extracts were washed with brine and dried over $Na_2SO_4$, and the solvent was removed.

The procedure for the reductions carried out in the absence of cosolvent was the same, but with the omission of THF. An aliquot of each of the crude reaction mixtures was converted to the TBDMS ethers, using the procedure outlined above, and subjected to analysis by GC/MS.

**Enolizations of Deuteriocamphors 5 and 6.** To a solution of 0.153 g (1 mmol) of **5** or **6** in 1 mL of THF cooled to −78 °C was added 3.0 mmol of the desired base (LDA, LDHS, or lithium 2,2,6,6-tetramethylpiperidide (LITMP)) in THF or ether. The resulting solution was slowly warmed to room temperature and cooled to −78 °C, and 0.76 g of $NH_4Cl$ was added. Alternatively, the reaction was quenched at 0 °C with 2 mL of 1/1 acetic acid, water, or 1/1 perdeuterioacetic acid and $D_2O$. The resulting solutions were warmed to room temperature, diluted with brine, and extracted with three portions of ether. After drying with $Na_2SO_4$, the solvent was removed to give a semisolid, which was subjected to analysis by GC/MS.

**Reduction of Camphor in THF.** To a solution of 0.1549 g (1 mmol) of (+)- or (±)-**1**, **-2**, **-5**, or **-6** in 10 mL of THF was added 0.8 mmol of the appropriate metal. The reaction mixtures were stirred at ambient temperatures or sonicated until the metal completely disappeared. The time required varied according to the alkali metal used. With sonication Li usually required approximately 2 h, Na, 1 h, and K, 30 min. With stirring the reactions were significantly slower. Brine and ether were added, and the products were isolated with ether. After drying over $Na_2SO_4$, the solvent was removed and the product mixtures were analyzed in the same manner as those obtained from the metal–$NH_3$ reductions described above.

**Isolation of Camphor Pinacols.** The crude product mixtures from the appropriate reactions were subjected to Kugelrohr distillation, and the mixtures of dimeric products were isolated from the high-boiling fraction as described by Rautenstrauch.[6b] The pure products were obtained by crystallization or medium-pressure liquid chromatography (MPLC). The properties of the dimeric products are summarized below:

**Pinacol 10. (A) From (+)- or (−)-1.** Mp: 113 °C (lit.[6b,25] mp 113–114 °C). $^1H$ NMR: $\delta$ 0.82 (s, 3 H), 0.95 (s, 3 H), 1.00 (s, 3 H), 1.02 (s, 3 H), 1.09 (s, 6 H), 1.09–2.11 (m, 13 H), 2.63 (m, 1 H). $^{13}C$ NMR: $\delta$ 13.07, 13.51, 21.09, 22.06, 23.42, 23.64, 26.29, 26.51, 29.98, 33.17, 43.03, 43.31, 44.93, 50.02, 50.51, 55.06, 57.71, 84.85, 85.02. MS (CI) (*m/z*): 3.07 (1.5) 289 (100), 271 (25), 203 (61), 179 (86), 165 (32), 153 (66), 137 (11), 109 (12).

(B) **From (±)-Camphor.** Mp: 112–114 °C, undepressed on admixture with an equimolar mixture of **10** prepared from equal parts (+)- and (−)-camphor. The spectral properties, including solution IR, were identical with those of the optically active materials.

**Pinacol 9.** From (+)- or (−)-camphor, crystals from petroleum ether. MP 157 °C (lit.[22-24] mp 157 °C). $^1H$ NMR: $\delta$ 0.81 (s, 6 H), 1.04 (s, 6 H), 1.07 (s, 6 H), 1.20–1.98 (m, 14 H). $^{13}C$ NMR: $\delta$ 13.57, 20.77, 21.53, 26.78, 28.51, 42.55, 44.98, 49.86, 55.66, 89.73. MS (CI) (*m/z*): 307 (1.1), 289 (100), 271 (18), 203 (42), 179 (99), 165 (44), 153 (51), 109 (9).

**Pinacol 11.** Mp 119–121 °C. Crystals suitable for X-ray structure determination were grown from pentane at 0 °C.[28] $^1H$ NMR: $\delta$ 0.83 (s, 6 H), 1.05 (s, 6 H), 1.11 (s, 6 H), 1.23–2.20 (m, 14 H), 1.58 (s, 1 H), 2.75 (s, 1 H). $^{13}C$ NMR: $\delta$ 13.73, 21.58, 22.71, 27.54, 29.27, 43.68, 43.96, 51.59, 53.87, 88.76. MS (CI) (*m/z*): 307 (1), 289 (84), 271 (14), 205 (3.5), 179 (100), 165 (11), 153 (32), 137 (10), 109 (7).

***endo*-2-[1-Oxo-2-(2,2,3-trimethylcyclopentyl)ethyl]-*exo*-2-hydroxycamphane (12).** To a solution of 0.13 g (19 mmol) of Li in 130 mL of liquid $NH_3$ was added 3.7 g (24 mmol) of **1** in 13 mL of THF at a rate of 6.5 mL/min using a syringe pump. When the blue disappeared, the addition of **1** was stopped. The reaction was allowed to warm to room temperature, and after evaporation of the ammonia, brine and ether were added. The reaction mixture was extracted with three portions of ether, the combined ether extracts were washed with brine and dried with $Na_2SO_4$, and the solvents were removed. The dimeric products were isolated by bulb to bulb distillation as described above, and the fraction containing the dimeric products was subjected to chromatography on MPLC (98/2 hexane–ethyl acetate) to give 2.0 g (59%) of pure **12**. Crystals suitable for X-ray structure determination were grown from pentane–ether (5/1) at 0 °C.[28] Mp 77–79 °C. IR ($CCl_4$): 1707, 1696 cm$^{-1}$. $^1H$ NMR: $\delta$ 0.81 (s, 3 H), 0.84 (s, 6 H), 0.87 (d, $J$ = 7.47 Hz, 3 H), 0.94 (s, 3 H), 1.11 (s, 3 H), 1.16–2.67 (m, 15 H), 2.81 (s, 1 H). $^{13}C$ NMR: $\delta$ 10.37, 16.47, 20.30, 20.71, 23.41, 24.24, 26.65, 29.31, 30.05, 31.28, 40.67, 41.20, 41.92, 43.36, 45.01, 50.15, 52.45, 87.06, 214.42. MS: *m/z* 306 (8), 153 (100), 135 (8), 109 (10), 95 (16), 69 (18).