Table I. CASSCF Energetics Relative to *trans*-1,5-Hexadiene at 523 K (kcal/mol)

transition state	ΔE	ΔH^a	$\Delta S^{a,b}$	ΔG^a
chair	40.7	37.7	−9.0	42.0
boat	47.3	43.6	−6.2	46.8

[a] See ref 12. [b] In cal/(mol·deg).

even that of two allyl radicals by 8.6 kcal/mol. Therefore, passage of molecules through the C_{2h} biradicaloid geometry does not contribute to the Cope rearrangement.

The present results indicate that both the chair and boat Cope rearrangements are not only concerted (proceeding without formation of an intermediate) but also synchronous (with bond forming and breaking occurring simultaneously in the transition states of lower energy). Our results contrast with those from a recent AM1 study,[10] which found a biradicaloid transition state with small R (1.66 Å) to be lower in energy than an "aromatic" transition state with larger R (1.98–1.99 Å). Our results also disagree with the inference, drawn from recent ab initio calculations,[11] that "There is every reason to believe that the biradicaloid structure is in fact lower in energy" than an aromatic transition state with a large R.

As shown in Table I, the energy of the chair transition state is 40.7 kcal/mol, above the CAS-optimized C_i geometry for 1,5-hexadiene. After correction for vibrational energy differences, an enthalpy of activation of 37.7 kcal/mol is obtained,[12] which is in reasonable agreement with the experimental value of 33.5 kcal/mol.[13] Although the calculated enthalpy of activation for the chair Cope is a little too high, the calculated difference of 5.9 kcal/mol between the enthalpies of the two transition states is nearly 50% too low, compared to the difference of 11.1 kcal/mol that has been obtained experimentally.[14,15]

The value of R (2.316 Å) in the boat is 0.23 Å longer than that in the chair, and the pyramidalization angles at C2 and C5 are smaller in the boat. Electron correlation enhances the larger value of R in the boat, since Hartree–Fock (HF) optimization of the two transition states gives a diference in R that is only half as large as that found by CASSCF. AM1 calculations give virtually no difference in R between the two transition states.[6]

A "looser" transition state for the boat Cope rearrangement implies lower frequency vibrations, which is consistent with the experimental fact that the entropy of the boat transition state is considerably larger than that of the chair.[14,15] However, the CASSCF second derivatives give the vibrational entropy of the boat at 523 K as only 2.6 eu larger than that of the chair. The 0.2 eu rotational entropy difference brings the total difference in calculated entropies to 2.8 eu. This is considerably smaller than the experimental difference of 11 eu between the two transition states, but the calculated entropy of activation for the chair[12] is in reasonable agreement with the experimental value of −13.8 eu.[13]

The differences between both the enthalpies and the entropies of the two transition states appear to be underestimated by our CASSCF calculations. A possible explanation is that the variational transition state that maximizes the *free* energy of activation for the boat Cope rearrangement occurs at a looser geometry, which has a higher enthalpy and entropy than the saddle point that we have located on the CASSCF *potential* energy surface.[16,17] A similar proposal has recently been made by Dewar and Jie[10] based on their AM1 calculations.

Acknowledgment. Numerical calculations were carried out at the Computer Center of the Institute for Molecular Science. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for partial support of this research.

(10) Dewar, M. J. S.; Jie, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1451.
(11) Dewar, M. J. S.; Healy, E. F. *Chem. Phys. Lett.* **1987**, *141*, 521.
(12) Although CASSCF frequencies for the transition states were used, for 1,5-hexadiene HF frequencies were employed. This results in magnitudes for ΔH, ΔS, and ΔG that we estimate are too small by 1–1.5 kcal/mol, 2–3 eu, and 2–3 kcal/mol, respectively. However, the boat–chair differences in these quantites are not affected by this inconsistency.
(13) Doering, W. von E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299.
(14) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7147.
(15) See also: Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156.
(16) First suggested by one of us (W.T.B.) at the Joint U.S.–Japan Meeting on Computational Chemistry, Bloomington, Indiana, 1985.
(17) For reviews of variational transition-state theory see: Truhlar, D. G.; Garrett, B. C. *Acc. Chem. Res.* **1980** *13*, 440. Hase, W. L. *Ibid.* **1983**, *16*, 258.

Anti-Cram Selective Reduction of Acyclic Ketones via Electron-Transfer-Initiated Processes

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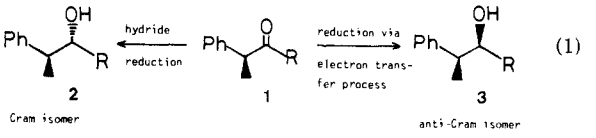
It is well-recognized that hydride reduction (e.g., $LiAlH_4$) of acyclic ketones (**1**) produces the Cram isomer (**2**) predominantly.[1] We report that the reduction via electron-transfer-initiated processes gives the anti-Cram isomer (**3**) preferentially (eq 1). This surprising finding provides a conceptual advance in the area of stereocontrol of acyclic systems.[2] The results are summarized in Table I.



(1)

Birch reduction (entries 3, 4, 9, 10, 19), Bouvault–Blanc reduction (entries 5, 11, 13, 16, 20), and samarium iodide reduction[3] (entries 6, 14, 17) always produced the anti-Cram isomers predominantly, though the selectivity itself was variable and remained at a low level. Needless to say, $LiAlH_4$ reduction gave the Cram isomers preferentially (entries 1, 7, 12, 15, 18). L-Selectride produced the Cram isomers exclusively (entries 2, 8). It was confirmed that epimerization of the product alcohols did not take place during Birch conditions and work-up procedures.

There has been a controversy on the mechanism of metal–ammonia reductions of cyclic aliphatic ketones:[4] Barton's dianion mechanism,[5] House's mechanism,[6] Rautenstrauch's mechanism[7a]

(1) (a) Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1987; p 105. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (c) Zioudrou, C.; M-Mavridis, I.; Chrysochou, P.; Karabatsos, G. J. *Tetrahedron* **1978**, *34*, 3181. (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.
(2) For example: (a) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (b) Heathcock, C. H.; Filippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. Lodge, E. P.; Heathcock, C. H. *Ibid.* **1987**, *109*, 2819. Lodge, E. P.; Heathcock, C. H. *Ibid.* **1987**, *109*, 3353. Mori, I.; Bartlett, P. A.; Heathcock, C. H. *Ibid.* **1987**, *109*, 7199. (c) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Matz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108.
(3) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693; (b) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175. The reduction via the original procedure was quite sluggish, so we employed a modified method (SmI_2–THF in the presence of excess H_2O). See also: Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187. However, the reduction still proceeded slowly and resulted in low yield.
(4) A number of the stereochemical studies on cyclic ketones have been done: Caine, D. *Org. React.* **1976**, *23*, 1. Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351. Also ref 8. To our knowledge, however, there is no report on acyclic ketones.
(5) Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3045.
(6) House, H. O. *Modern Synthetic Reactions*, 2nd ed.: W. A. Benjamin: New York, 1972; pp 152–158.
(7) (a) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Burger, U. *Helv. Chim. Acta* **1981**, *64*, 2109. (b) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1986**, 1558.

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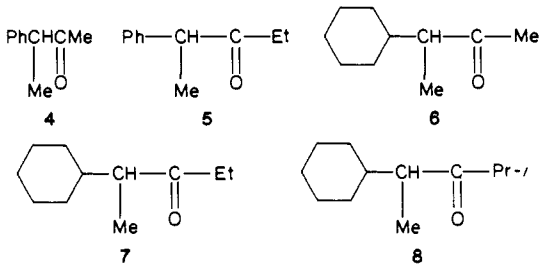
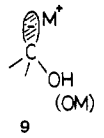
Table I. Diastereodivergent Reduction of Ketones



entry	ketone	reducing agents	Cram:anti-Cram[b]	total isolated yield, %
1	4	$LiAlH_4$	74:26	97
2	4	L-Selectride	>99:<1	80
3	4	$Li-NH_3$	24:76	94
4	4	$Li-NH_3-NH_4^+$	28:72	94
5	4	Na-EtOH	42:58	99
6	4	SmI_2	38:62	41 (27)[c]
7	5	$LiAlH_4$	77:23	74
8	5	L-Selectride	>99:<1	80
9	5	$Li-NH_3$	31:69	69
10	5	$Li-NH_3-NH_4^+$	16:84	70
11	5	Na-EtOH	43:57	98
12	6	$LiAlH_4$	58:42	92
13	6	Na-EtOH	48:52	99
14	6	SmI_2	36:64	28 (53)[c]
15	7	$LiAlH_4$	68:32	99
16	7	Na-EtOH	48:52	92
17	7	SmI_2	42:58	88 (50)[c]
18	8	$LiAlH_4$	81:19	99
19	8	$Li-NH_3$	45:55	99
20	8	Na-EtOH	43:57	99

[a] Reduction with $LiAlH_4$ was conducted in ether at 0 °C. Birch reduction was carried out in liquid NH_3 at −78 °C. The aromatic ring was reduced to the cyclohexadiene ring (entries 3 and 4). When it was partially reduced (entries 9 and 10, cyclohexadiene + aromatic derivatives), the mixture was completely reduced to cyclohexane ring with H_2/Rh–C and compared with the products derived from **7**. Bouvault–Blanc reduction was conducted in EtOH under reflux. Samarium iodide reduction was carried out in THF–H_2O according to Kagan's procedure[3]. [b] The ratio was determined by a capillary GLC (PEG, 25 m) or by 270-MHz ^1H NMR. The structures were determined unambiguously by comparison with authentic samples, prepared by the literature procedure.[9a] [c] 41 (27); the ketone was recovered in 73% yield and the alcohol was obtained in (27 × 0.41) % yield. The reason for low material balance is not clear, but other products such as pinacol, hydrocarbon, and iodide were not detected.

(hydrogen-transfer mechanism), and Huffman's mechanism.[8] However, the stereochemical outcome of reduction is normally determined by the protonation step of the intermediate carbanion (**9**),[5,6,8] except the hydrogen-transfer mechanism[7] in which it is



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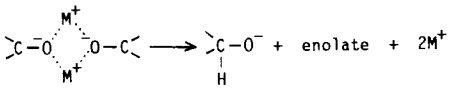
determined by the hydrogen abstraction within the ketyl dimer (**10**).[7] The latter process is favorable in the absence of an added



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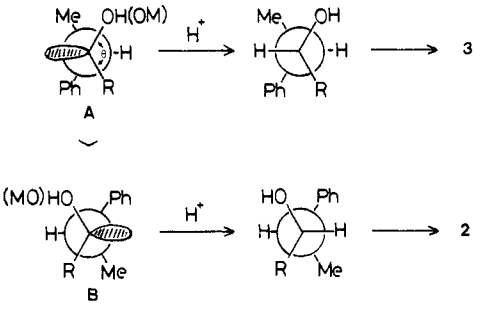
proton donor and may be accompanied by dimerization. Formation of pinacol derivatives was not observed. The stereoselectivity of the reduction with Na–EtOH exhibited essentially the same tendency as that of the reduction via $Li-NH_3$. Further, the reduction via $Li-NH_3-NH_4Cl$[7b] gave similar anti-Cram selectivity as the reduction with $Li-NH_3$. Therefore, the anti-Cram selectivity is presumably a reflection of the protonation to **9**. This is further confirmed by the SmI_2 reduction, in which the protonation to **9** is a stereodetermining step.[3b]

Preference of the anti-Cram selectivity is accounted for by the relative stability of the conformation of carbanion intermediates (A, B, ...).[4] It is easily understood that A is more stable than B for steric reason; it is reasonable to assume that the protonation



takes place with retention of configuration. Consequently, formation of **3** is preferred to that of **2**. Variation of the anti-Cram selectivity among the three reducing methods may reflect the extent of pyramidalization of the intermediate carbanion.[4]

If the bulkiness is in the order of OH(OM) > R > the minus charge, proton attacks from the left side of A. When the angle θ becomes 180°, in other words when the geometry becomes very close to that of the parent ketone, a hydride in the case of ketone or a proton in the case of a carbanion comes from the right side. Therefore, a dichotomy that hydride reduction and electron transfer induced reduction have the opposite stereochemistry is often but not always observed. The present findings usher in a new phase in the area of acyclic stereoselection.[9] The extent of preference of anti-Cram isomer can be used to prove whether the reduction proceeds through electron-transfer-initiated process or through hydride attack.

(8) Huffman, J. W. *Acc. Chem. Res.* **1983**, *16*, 199.

(9) For the acyclic stereoselection via an electron-transfer process in the reaction of organometallic compounds (C–M) with electrophiles, see: (a) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1985**, *107*, 6411. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *Ibid.* **1988**, *110*, 617. (c) Electrochemical reductions were carried out with **4**, but the ratio of **2**:**3** was 1:1.