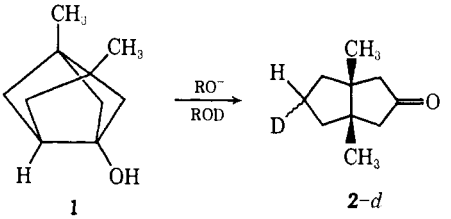
Stereochemistry of Electrophilic Attack in the Base-Catalyzed Cleavage of 3,7-Dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol

Sir:

Recently we reported the synthesis of 3,7-dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol (**1**) by reaction of 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione with zinc and hydrochloric acid in acetic anhydride.[1] When treated with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, **1** undergoes rapid cleavage to 1,5-dimethylbicyclo[3.3.0]octan-1-one (**2**). Since **1** is stable under these conditions in the absence of base, this appears to be an example of what Cram terms[2] an SEi reaction with carbon as the leaving group. Cram finds in acyclic systems that the stereochemistry of this reaction depends on the solvent.[2] Retention of configuration predominates in solvents of low dielectric constant like *tert*-butyl alcohol, while inversion is the major course in solvents which have high dielectric constants and are good proton donors like ethylene glycol.

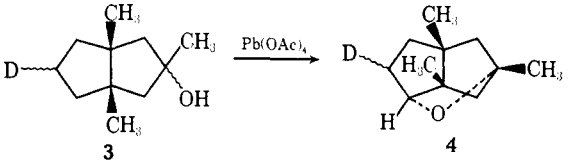
The solvent dependence of the stereochemistry of electrophilic attack at carbon has also been studied in the base-catalyzed cleavage of cyclopropanols. Nickon found that nortricyclanol undergoes base-catalyzed reketonization to norbornanone with 90% net inversion, independent of solvent.[3] However, Wharton has argued that this is due to a special feature of the rigid skeleton of this system and not to a special feature of cyclopropanols in general, for he found that *exo*-7-hydroxy-1,6-dimethylbicyclo[4.1.0]heptane behaves like the systems studied by Cram in cleaving to the corresponding cyclohexanecarboxaldehyde with nearly quantitative retention of configuration in *tert*-butyl alcohol and 40% net inversion in ethylene glycol.[4] Nevertheless, the endo alcohol, also studied by Wharton and Bair, seems anomalous in giving 20% retention of configuration in ethylene glycol.

In the hope of clarifying some of the effects important in controlling the stereochemistry in such ring-opening reactions, we examined the stereochemistry of the base-catalyzed conversion of **1** to **2**. The reactions were carried out in $(CH_3)_3COD$[5] at 70° and $(CH_2OD)_2$[6] at 175° using the corresponding potassium alcoholates as base. Under these conditions the reactions were complete in 5 hr, and the sole product was ketone **2-*d***.



1 **2-*d***

In order to facilitate analysis of the stereochemistry of the deuterium in **2-*d***, the protons α to the carbonyl, which had been partially exchanged for deuterium during the reaction, were reexchanged by refluxing **2-*d*** in methanol in the presence of sodium methoxide. After 4 hr the mass spectrum of **2-*d*** was unchanged and showed that the molecule contained one nonexchangeable deuterium atom. To establish the stereochemical disposition of the deuterium, it was desirable to functionalize **2** stereospecifically at C-6.[7] To this end, **2-*d*** was converted by reaction with methyllithium to a 1:1 mixture of epimeric alcohols **3** which was oxidized with lead tetraacetate in benzene to give the expected[8] cyclic ether **4** in 60% yield, after chromatography.[9]



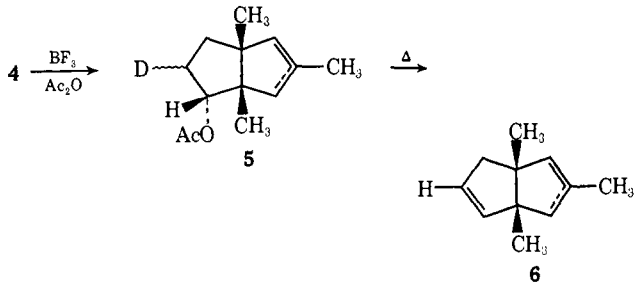
3 **4**

In the nmr spectrum of the undeuterated ether the methine proton appeared as a doublet with $J = 4$ Hz. Models show that this splitting must be due to the exo proton at C-7, since the dihedral angle between the endo C–H and methine C–H bonds is ~90°; so, according to the Karplus relationship,[11] the coupling constant between these protons should be close to zero. The methine proton of **4** also showed this same nmr signal in the material obtained from the cleavage reaction run in either $(CH_3)_3COD$ or $(CH_2OD)_2$. This implies that the deuterium must be incorporated predominantly in the endo position, irrespective of the solvent.

To make this result more quantitative the ether **4** was treated with boron trifluoride in acetic anhydride.[12] The methyl group at C-3 ensured that the ether opened in only one direction so as to give the more stable carbonium ion, and the endo acetate **5** was obtained as a mixture of two double bond isomers. No attempt was made to separate these; the mixture was pyrolyzed at 550° in a flow system and a mixture of the two isomeric bicyclooctadienes **6** was isolated. Mass spectral analysis showed that within experimental error **6** contained no deuterium. Since acetate pyrolysis results in cis elimination,[13] the deuterium must have been >98% endo.

The stereospecificity of the base-catalyzed cleavage of **1** to give **2** with >98% retention of configuration in both *tert*-butyl alcohol and ethylene glycol is all the

(1) W. T. Borden and T. Ravindranathan, presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 29, 1971.
(2) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 137–158.
(3) A. Nickon, J. L. Lambert, S. J., R. O. Williams, and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **88**, 3354 (1966).
(4) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **31**, 2480 (1966).
(5) A. T. Young and R. D. Guthrie, *ibid.*, **35**, 853 (1970).
(6) D. J. Cram and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 2178 (1961).
(7) A reaction that functionalized at C-7 would be subject to a large primary isotope effect, which, unless the reaction proceeded in quantitative yield, could introduce an uncertainty as to the exact distribution of deuterium between the exo and endo positions before reaction.
(8) This reaction usually proceeds to give tetrahydrofuran derivatives. A review is given in M. Mihailovic and Z. Cekovic, *Synthesis*, **2**, 209 (1970). That the reaction had indeed taken this course and had not led instead to the symmetrical C-7 ether was assured by the fact that **4** displayed two singlets from the nonequivalent methyl groups and by the appearance of the methine proton in the nmr (see text).
(9) This good yield of ether **4** starting with the 1:1 mixture of alcohols suggests that the exo alcohol epimerizes to the endo from which the ether is formed. Such epimerizations during $Pb(OAc)_4$ oxidation of alcohols have been observed in other systems.[10]
(10) K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).
(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(12) A. C. Cope, M. Gorden, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, **87**, 3119 (1965).
(13) E. E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 149.



more remarkable since it is exactly the opposite of the result found by Nickon in the opening of nortricyclanol.[3] The two systems differ, of course, in that the carbanionic center and ketone leaving group probably cannot escape interaction in the bicyclo[2.2.1] ring system, while during the cleavage of **1** to **2** they must move apart a considerable distance. Both systems demonstrate, however, that in SEi reactions in which the carbon leaving group remains in the same molecule as the carbanion, structural effects can be far more important than solvent effects in determining the stereochemical course of reaction.[14]

Although the enforced proximity of carbanion and ketone in the nortricyclanol opening might be expected[2] to produce inversion, the structural features responsible for the observed retention of configuration in the cleavage of **1** are less obvious. One possibility is that the cage structure of **1** excludes solvent from part of one face of the developing carbanion. Protonation of the carbanion from the backside to give inversion would then generate an ion pair separated by a cavity of low dielectric constant and would be energetically less favorable than protonation from the same side as the departing carbonyl group, a process leading to retention.[15] Experiments to test this and other[16] hypotheses are in progress.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(14) For another example in a less rigid system, see T. D. Hoffmann and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 1009 (1969).

(15) A similar explanation based on inefficient solvation of the cation on the endo face of the bicyclic system studied by Wharton[4] could rationalize why the endo alcohol, in contrast to the exo, gives predominant retention in ethylene glycol.

(16) A referee has suggested that in the cleavage of **1** "the geometry is such that the departing carbonyl group moves away from the carbanion but cannot escape completely; it does, however, distinguish between polar and nonpolar sides of the fixed (nonrotatable) carbanion, the polar side probably aggregating more available solvent and certainly lowering the energy of activation of protonation." Although it may well be that protonation occurs from a solvent molecule bound to a cation coordinated at the carbonyl[14] or aggregated by the carbonyl itself, it is not clear how this explanation would be applied to other systems[4] in which only one isomer gives an anomalous amount of retention.

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A Model of the Methylmalonyl Isomerase Reaction

Sir:

Several years ago, a mechanism was proposed[1] for the vitamin B_{12} catalyzed methylmalonyl isomerase reaction which involves ionic cleavage of an organocobalt intermediate and subsequent rearrangement of the resulting carbanion. This mechanism is supported by the statistical partitioning of deuterium between substrate and product,[2] but there has been no organic analog of the reaction. Now that a method for ionic cleavage of the carbon–cobalt bond has been found,[3] we have been able to show the rearrangement of an organocobalt compound comparable to the methylmalonyl isomerase reaction.[4] A solution of 0.52 mmol of 1-carbethoxy-2-oxocyclopentylmethyl(pyridinato)bis(dimethylglyoximato)cobalt(III) (I) (*Anal.* Calcd: C, 49.16; H, 6.00; N, 13.03. Found: C, 49.11; H, 5.98; N, 13.20) prepared by the method of Schrauzer and Windgassen[5] from ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate[6] in 10 ml of dimethylformamide and 10 ml of absolute alcohol at 50° was allowed to react with 4.6 mmol of 1,4-butanedithiol for 48 hr. Product isolation was accomplished by dilution with water, extraction with petroleum ether, and washing with 2% aqueous KOH, 1 *N* HCl, and finally water. Gas chromatograms of this mixture were compared to those of known esters on four analytical columns with different stationary phases (SE-30, Carbowax 20M, LAC-446, and DEGS). On each column, peaks corresponding to 5% of the unrearranged ester, ethyl 2-oxo-1-methylcyclopentanecarboxylate (II),[7] 0.3% of the rearranged ester, ethyl 3-oxocyclohexanecarboxylate (III),[8] and none of the other possible rearranged ester, ethyl 2-oxocyclopentaneacetate (IV)[9] were obtained. Using gas chromatography followed by mass spectrometry, mass spectrograms of components of the reaction mixture were found to be identical with those of authentic II and III. (Peaks with *m/e* greater than 102 were: II, 170 (m^+), 142, 125, 115, 114, 113; III, 170 (m^+), 142, 128, 127, 125, 124, 114, 113.) The reaction sequence in Scheme I appears reasonable. In a similar reaction of cobaloxime I in ethanol, smaller yields were observed and in dimethylformamide only a trace of the rearranged product, III, was observed. The low yield of rearranged ester may result from the addition of 1,4-butanedithiol to a ketene intermediate. In methanol, neither ethyl nor methyl 3-oxocyclohexanecarboxylate was observed.

A solution of the cobaloxime, I, in ethanol containing 10% of toluene was exposed to sunlight for 6 hr. This photolysis gave 0.2% of unrearranged ester, II, but no (<0.01%) rearranged products, III and IV, by gas chromatographic analysis.

These results support an ionic but not a radical mechanism for the methylmalonyl isomerase reaction. Attempts to show similar rearrangements in acyclic sys-

(1) L. L. Ingraham, *Ann. N. Y. Acad. Sci.*, **112**, 713 (1963).

(2) W. W. Miller and J. H. Richards, *J. Amer. Chem. Soc.*, **91** 1498 (1969).

(3) J. W. Sibert and G. N. Schrauzer, *ibid.*, **92**, 1421 (1970); G. N. Schrauzer and J. W. Sibert, *ibid.*, **92**, 3509 (1970).

(4) This study shows that a carbanion intermediate will account for the rearrangement regardless of the method of generation.

(5) G. N. Schrauzer and R. J. Windgassen, *J. Amer. Chem. Soc.*, **88**, 3738 (1966).

(6) R. Mayer and E. Alder, *Chem. Ber.*, 1866 (1955).

(7) Ya. I. Denisenko and A. D. Naber, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 35 (1945).

(8) (a) W. A. Perkin, Jr., and G. Tattersall, *J. Chem. Soc.*, **91**, 480 (1907); (b) the corresponding acid was prepared following the procedures of R. Grewe, A. Heinke, and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956).

(9) R. Granger, P. F. G. Nau, and J. Nau, *Bull. Soc. Chim. Fr.*, 1807 (1959).