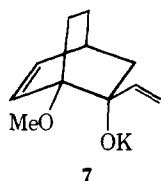


Figure 1. Effect of 18-crown-6 on the rate of rearrangement of **2a** (M = K) in THF at 0°C.

conditions which **2a** (M = K) rearranges within minutes (66°, THF) the diene **7** shows no rearrangement even after heating for 24 hr.



Both the increased yields and lower reaction temperatures encountered in these anionic oxy-Cope processes imply that these modifications should significantly improve the synthetic utility of these and related molecular rearrangements. The full scope of these modified sigmatropic processes will be reported in due course.

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References and Notes

- (1) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968); W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963).
- (2) (a) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 4389 (1965); (b) W. von E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971); (c) M. J. S. Dewar and L. E. Wade, *J. Am. Chem. Soc.*, **95**, 290 (1973); (d) M. J. Goldstein and M. R. DeCamp, *ibid.*, **96**, 7356 (1974); (e) H. J. Hansen and H. Schmid, *Tetrahedron*, **30**, 1959 (1974).
- (3) (a) D. J. Faulkner and M. R. Peterson, *J. Am. Chem. Soc.*, **95**, 553 (1973); (b) H. O. House, J. Lubinkowski, and J. J. Good, *J. Org. Chem.*, **40**, 86 (1975); (c) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5897 (1972); (d) R. C. Cookson and N. R. Rogers, *J. Chem. Soc., Chem. Commun.*, 248 (1972); (e) D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 137 (1972); (f) W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4779 (1972).
- (4) (a) J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86**, 5017 (1964); (b) *ibid.*, **86**, 5019 (1964); (c) J. A. Berson and E. J. Walsh, Jr., *ibid.*, **90**, 4729 (1968); (d) *ibid.*, **90**, 4730 (1968); (e) *ibid.*, **90**, 4732 (1968).
- (5) (a) A. Viola and L. A. Levasseur, *J. Am. Chem. Soc.*, **87**, 1150 (1965); (b) A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, V. Nayak, and P. J. Kocienski, *ibid.*, **89**, 3462 (1967); (c) A. Viola and J. H. MacMillan, *ibid.*, **92**, 2404 (1970); (d) A. Viola and E. J. Iorio, *J. Org. Chem.*, **35**, 856 (1970); (e) A. Viola, A. J. Padilla, D. M. Lennox, A. Hecht, and R. J. Provert, *J. Chem. Soc., Chem. Commun.*, 491 (1974).
- (6) (a) R. W. Thies, *J. Am. Chem. Soc.*, **94**, 7074 (1972); (b) R. W. Thies, M. T. Wills, A. W. Chin, L. E. Schick, and E. S. Walton, *ibid.*, **95**, 5281 (1973); (c) R. W. Thies and J. E. Billigmeier, *ibid.*, **96**, 200 (1974).
- (7) The various metal salts of **1** were prepared in THF from the following bases: CH₂=CHMgBr, LiH, NaH, KH. In all uses the metal alkoxides **2** were soluble in THF. All rearrangements were carried out under either an argon or nitrogen atmosphere and were followed by GLPC using octadecane as an internal standard.
- (8) Satisfactory spectra and elemental analyses were obtained on all compounds reported herein.
- (9) (a) J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974); (b) C. J. Pederson and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).
- (10) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).
- (11) 15-Crown-5 binding efficiency to Na⁺ should be greater than 18-crown-6-K⁺ binding, ref 9a.
- (12) It is significant to note that **2b** (M = K) had been prepared by Berson, ref 4c, but the conditions under which it was generated would have resulted in a few per cent rearrangement.
- (13) R. Breslow and J. M. Hoffman, Jr., *J. Am. Chem. Soc.*, **94**, 2111 (1972); P. Yates and P. Eaton, *Tetrahedron Lett.*, **11**, 5 (1960); R. C. Cookson, J. Hudec, and R. O. Williams, *ibid.*, **22**, 29 (1960).
- (14) T. Inukai and T. Kojima, *J. Org. Chem.*, **32**, 872 (1967).
- (15) Camille and Henry Dreyfus Teacher-Scholar Recipient (1971-1976).

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Reduction by a Model of NAD(P)H. Effect of Metal Ion and Stereochemistry on the Reduction of α -Keto Esters by 1,4-Dihydronicotinamide Derivatives

Sir:

Stereospecific reduction of pyruvate to D- or L-lactate by the reduced pyridine nucleotide, NADH, is catalyzed by a D- or L-lactate dehydrogenase, respectively.¹⁻³ To help understand the mechanism of biochemical processes,⁴ we have constructed and studied a model system⁵ whose reduction proceeds stereoselectively under mild conditions and which, therefore, may also be used in organic syntheses.

In this communication, we wish to report mild and stereoselective nonenzymatic reduction of esters of pyruvic acid⁶ and benzoylformic acid^{6,7} in the presence of magnesium perchlorate or zinc perchlorate and a 1,4-dihydronicotinamide derivative, a model of NAD(P)H. Stereoselective reduction by a model of NAD(P)H has not previously been reported. The reaction may be valuable in determining the mechanism of biochemical coenzyme-substrate interaction.

Ethyl benzoylformate in acetonitrile is not reduced by 1-benzyl-1,4-dihydronicotinamide (BNAH) alone at room temperature in the dark.⁸ In the presence of an equimolar amount of magnesium perchlorate, however, ethyl benzoylformate was converted into racemic ethyl mandelate quantitatively. A mixture of 1 mmol each of ethyl benzoylformate, BNAH, and magnesium perchlorate in 15 ml of acetonitrile was allowed to react for 17 hr at room temperature; 5 ml of water was then added. The mixture was concentrated in vacuo and the residual oil was column-chromatographed on silica gel and eluted with benzene or ethanol. Recovered ethyl benzoylformate, ethyl mandelate, and 1-benzyl-3-carbamoylpyridinium perchlorate (BNA⁺ClO₄⁻) were identified from their spectra which were compared with those of authentic samples. The reaction was not affected by hydroquinone (0.5 mmol). Under the same reac-

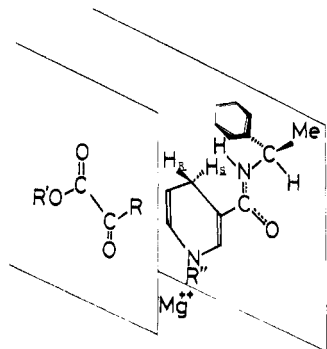


Figure 1. Schematic representation for stereochemical interpretation of the reaction.

pro-*R* hydrogen from the pro-*S* counterpart in NAD(P)H and its analog.²⁵ The stereochemistry of the reactions with the enantiomers of **1** as well as the effect of the prochirality of the C₄ hydrogens are currently under investigation in these laboratories.

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References and Notes

- (1) J. Everse and N. O. Kaplan, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **37**, 61 (1973).
- (2) R. Bentley, "Molecular Asymmetry in Biology", Vol. 2, Academic Press, New York, N.Y., 1970, p 50.
- (3) B. L. Vallee and W. E. C. Wacker, *J. Am. Chem. Soc.*, **78**, 1771 (1956).
- (4) (a) H. R. Mahler and H. E. Cordes, "Biological Chemistry", Harper and Row, New York, N.Y., 1966, Chapters 8 and 15; (b) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley-Interscience, New York, N.Y., 1971, p 539; (c) Chapter 1 in ref. 2.
- (5) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanism", Vol. 2, W. A. Benjamin, New York, N.Y., 1966, p 301; (b) H. Sund, H. Diekmann, and K. Wallenfels, *Adv. Enzymol. Relat. Subj. Biochem.*, **26**, 115 (1964).
- (6) For model reduction of α -keto acids, see (a) R. H. Abeles and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 5459 (1958); (b) K. Wallenfels and D. Hofmann, *Tetrahedron Lett.*, 10 (1959).
- (7) For the enzymatic reduction of benzoylformic acid, see G. D. Hegeman, *J. Bacteriol.*, **91**, 1140, 1155, 1161 (1966).
- (8) The effect of irradiation will be reported elsewhere.
- (9) The apparent primary kinetic-isotope effect is calculated to be 3, which is comparable to reported values; see (a) J. J. Steffens and D. M. Chipman, *J. Am. Chem. Soc.*, **93**, 6694 (1971); (b) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *ibid.*, **79**, 712 (1957).
- (10) E. Wassmer and P. Guye, *Chem. Zentralbl.*, 1419 (1903).
- (11) Control experiments showed that isolation and purification of the active product do not affect the rotation.
- (12) (a) D. J. Creighton and D. S. Sigman, *J. Am. Chem. Soc.*, **93**, 6314 (1971); (b) S. Shinkai and T. C. Bruice, *Biochemistry*, **12**, 1750 (1973).
- (13) The absorption maximum of BNAH in acetonitrile shifts from 347 nm (without metal ion) to 360 nm (with Mg²⁺) or to 362 (with Zn²⁺). Added ethyl benzoylformate did not change positions and intensities of absorption maxima.
- (14) (a) J. P. Klinman, *J. Biol. Chem.*, **247**, 7977 (1972); (b) M. F. Dunn and J. S. Hutchison, *Biochemistry*, **12**, 4882 (1973); (c) D. E. Drum and B. L. Vallee, *ibid.*, **9**, 4078 (1970); (d) J. H. Wang, *Science*, **161**, 328 (1968).
- (15) M. J. Adams, M. Buehner, K. Chandrasekhar, G. C. Ford, M. L. Hackert, A. Lijias, M. G. Rossmann, I. E. Smiley, W. S. Allison, J. Everse, N. O. Kaplan, and S. S. Traylor, *Proc. Nat. Acad. Sci. U.S.A.*, **70**, 1968 (1973).
- (16) The stereochemistry was followed by NMR spectroscopy of the menthyl ester because it was found that solvolysis of the menthyl ester is accompanied by change in optical activity of the acid part.
- (17) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, Chapters 2 and 5.
- (18) This generalization has been proved to be valid in the reduction of achiral benzoylformate with lithium aluminum hydride modified by chiral compounds¹⁹ or magnesium alkoxides.²⁰
- (19) A. Horeau, H. B. Kagan, and J. P. Vignerson, *Bull. Soc. Chim. Fr.*, 3794 (1968).
- (20) G. Vavon and A. Antonini, *C. R. Acad. Sci.*, **230**, 1870 (1950) and **232**, 1120 (1951).
- (21) It may be reasonable to assume that larger carboalkoxy group in α -keto esters points against the amide in 1.^{4c}
- (22) (a) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828, 5851 (1952); (b) Chapter 1 in ref 17.
- (23) It is proposed that the carbonyl-oxygen axis of a substrate points toward the pyridine-ring nitrogen of NADH; p 36 of ref 2. For a lactate dehydrogenase, however, the dihedral angle between two planes is not necessarily zero; (a) J. Everse, R. E. Barnett, C. J. R. Thorne, and N. O. Kaplan, *Arch. Biochem. Biophys.*, **134**, 444 (1971); (b) J. Everse, E. C.

- Zoll, L. Kahan, and N. O. Kaplan, *Bioorg. Chem.*, **1**, 207 (1971); (c) ref 15.
- (24) For an X-ray crystal structure study of BNAH, see I. L. Karle, *Acta Crystallogr.*, **14**, 497 (1961).
- (25) N. J. Oppenheimer, L. J. Arnold, and N. O. Kaplan, *Proc. Nat. Acad. Sci. U.S.A.*, **68**, 3200 (1971).
- (26) In the partial fulfillment of requirement of the Master of Science degree, Tokai University (1973-1974).

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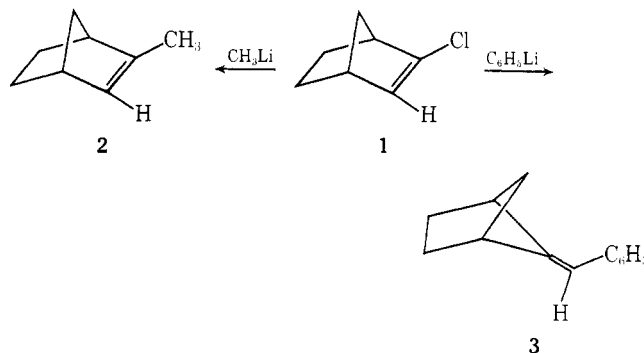
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Norbornyne¹

Sir:

The reaction of organolithium reagents with cyclic vinyl halides has been much discussed as a route to strained cycloalkynes.^{2,3} Thus, it was of interest that the reactions of methyllithium and phenyllithium with 2-chlorobicyclo[2.2.1]heptene (**1**) gave 2-methylbicyclo[2.2.1]heptene (**2**)⁴ and 5-benzalicyclo[2.1.1]hexane (**3**)⁵ in 73 and 62% yields, respectively. Even more surprising was the observation that optically active **1** gave optically active **2** with retention of stereochemistry.⁶ These observations, in particu-



lar those associated with the formation of **2**, rule out the intermediacy of a symmetrical intermediate in the reaction of **1** with certain organolithium reagents. The failure of **1** to react with methyllithium to form a cycloalkyne can be rationalized in terms of the large amount of strain which would occur if a triple bond were to be incorporated into the bicyclo[2.2.1]heptyl skeleton. This rationalization would appear to be justified by the difficulty observed in the generation of cyclopentyne from a variety of precursors.² With this background in mind, we wish to report that the reaction of **1** with *n*-butyllithium takes yet a different mechanistic pathway, which is best explained by the intermediacy of bicyclo[2.2.1]heptyne (norbornyne).

Treatment of a solution of **1** with 4-5 equiv of *n*-butyllithium in tetrahydrofuran⁷ at 25° for 2 hr, followed by quenching with water, gave 80% of a 1:1.6 mixture of 3-*n*-butyltricyclo[2.2.1.0^{2,6}]heptane (**4**) and 2-*n*-butylbicyclo[2.2.1]heptene (**5**). In order to elucidate the mechanistic pathway from **1** to **4** and **5**, three sets of labeling experiments were carried out. In the first of these studies, the reaction mixture was quenched with deuterium oxide instead of with water. This gave an 88% yield of a 1:1.6 mixture of **4** (no deuterium incorporation) and **5**. Both mass