Sir:

Over the years [3,3]sigmatropic rearrangements have held the attention of physical organic chemists and have proven to be an exceptionally powerful class of reactions in stereoselective synthesis. Cope rearrangements of 1,5-hexadienes have constituted a historical focal point in establishing precedent for related thermal processes. The oxy-Cope rearrangement (eq 1) has been one such well-studied [3,3]sigmatropic variant.

\[
\text{HO-} + \text{M}^+ + \text{R}^- \rightarrow [\text{HO-} + \text{R}^-] \rightarrow \text{OM}^+ + \text{H}^+ 
\]

Herein we wish to report our observations on the exceptionally facile rearrangement of 1,5-hexadiene alkoxides (eq 2). This simple modification on oxy-Cope substrates results in observed rate accelerations of \(10^{10}\) to \(10^{12}\) and affords enolates which may be further employed in synthesis.

The systems chosen for study were the dienols 1a and 1b, which were prepared via regioselective addition of vinylmagnesium bromide to the requisite ketones. The basis for selecting these substrates rested, in part, upon the kinetic and product data which were available on these systems. As it was suspected that the nature of the metal ion might play a significant role in the rate of rearrangement, counterion effects were tested in the rearrangement of diene alkoxide 2a in refluxing (66°) anhydrous tetrahydrofuran (THF). Although alkoxides 2a, M = Li, MgBr, showed no evidence of rearrangement under these conditions over a 24-hr period, the sodium alkoxide, 2a, M = Na, rearranged to the enolates 3a with a half-life \(t_{1/2}\) of 1.4 min. This strong counterion-controlled rate dependence for selecting these substrates rested, in part, upon the kinetic and product data which were available on these systems. As an example, only a 1.27-fold rate acceleration was observed for the sodium-specific 15-crown-5 to 2a (M = Na) at 66° (THF) and that essentially no rate acceleration was observed for 2a (M = Na) in hexamethylphosphoric triamide (HMPT) at 10°.

The strong counterion dependence in the rearrangement suggested that further acceleration might be achieved by the addition of cationophores. A study of the rate of rearrangement of 2a (M = K) in THF at 0° as a function of added 18-crown-6 is illustrated in Figure 1. In runs containing between 1 and 3 equiv of crown, a limiting 180-fold additional rate acceleration was observed. The same 180-fold rate acceleration was attained in the rearrangement of 2a (M = K) in hexamethylphosphoric triamide (HMPT) at 10°. These observations indicate that ion pair dissociation results in maximal rate acceleration and that the rate dependence upon solvent dielectric is negligible. A fortuitous consequence of this study is that rearrangement rates can be employed as a sensitive probe for metal-alkoxide association in various media. As an example, only a 1.27-fold rate acceleration was obtained upon the addition of the sodium-specific 15-crown-5 to 2a (M = Na) at 66° (THF) and that essentially no rate acceleration was observed for 2a (M = Na) in HMPT at 10°. It thus appears that ion pair dissociation is not being achieved under the above conditions.

First-order rate constants for thermal rearrangement of dienol 1a, 2a (M = K), and 2a (M = Na) with 1.1 equiv of 18-crown-6 determined at four temperatures afforded linear Arrhenius plots and the activation parameters shown in Table 1. From these data the magnitude of the rate acceleration for alcohol vs. alkoxide can be assessed. At 25° the rate acceleration of 1a vs. 2a (M = K) with 1.1 equiv of crown (entries A and C) is \(10^{12}\). The corresponding rate acceleration of 1b vs. 2b (M = K) at 40° in the absence of crown is \(10^{12}\) and at 0° in the presence of crown, \(10^{17}\).

There have been isolated examples of exceptionally facile Cope rearrangements; however, in the absence of comparative kinetic data between catalyzed and uncatalyzed rearrangements, the magnitudes of catalytic acceleration cannot be assessed. In the present study rate enhancements in the range of \(10^{10}\) to \(10^{12}\) are truly startling when compared to other catalyzed thermal processes such as the Diels–Alder reaction which shows \(10^2\) rate acceleration with Lewis acid catalysis.

The large substituent-promoted rate enhancements encountered in this study raise questions as to the mechanism of the rearrangement. Observations that bear on this point but which do not rigorously exclude the possibility of intervening diradicals or carbanions have been made. Under...
conditions which 2a (M = K) rearranges within minutes (66°, THF) the diene 7 shows no rearrangement even after heating for 24 hr.

![Diagram](image)

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

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

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:

Sterespecific reduction of pyruvate to D- or L-lactate by the reduced pyridine nucleotide, NADH, is catalyzed by a D- or L-lactate dehydrogenase, respectively. A stereospecific mechanism of biochemical coenzyme-substrate interaction.

Ethyl benzoylformate in acetonitrile is not reduced by 1 equiv 18-crown-6 (a) J. A. Berson and M. Jones, Jr., J. Am. Chem. Soc., 84, 5017 (1964); (b) ibid., 86, 5019 (1964); (c) J. A. Berson and E. J. Walsh, ibid., 90, 4729 (1968); (d) ibid., 86, 4730 (1968); (e) ibid., 86, 4732 (1968).

6. For stimulating discussions during the course of this research, we wish to report mild and stereoselective nonenzymatic reduction of esters of pyruvic acid and benzoic acid 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.

6-K+ binding, ref 9a.
7. 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 percent rearrangement.

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