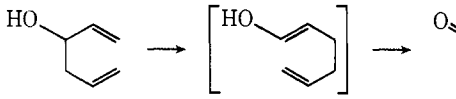
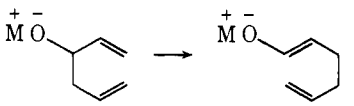
[3,3]Sigmatropic Rearrangements of 1,5-Diene Alkoxides. The Powerful Accelerating Effects of the Alkoxide Substituent

Sir:

Over the years [3,3]sigmatropic rearrangements[1] have held the attention of physical organic chemists[2] and have proven to be an exceptionally powerful class of reactions in stereoselective synthesis.[3] 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.[4-6]



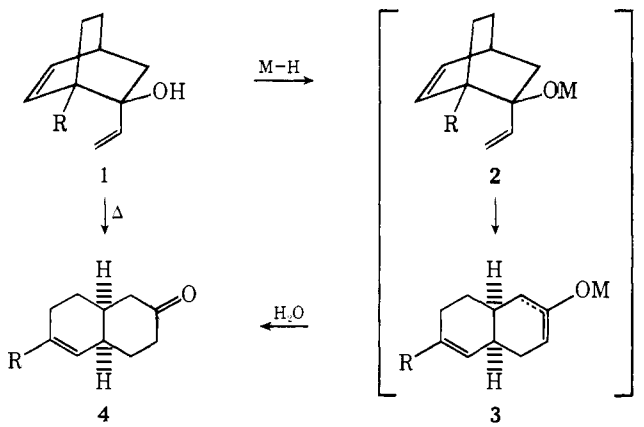
(1)



(2)

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}–10^{17} and affords enolates which may be further employed in synthesis.*

The systems chosen for study were the dienols **1a**[4a] and **1b**[3e] 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.[3e,4a] 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).[7] 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



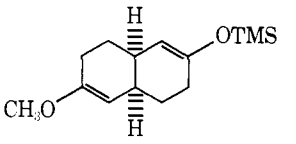
a, R = OCH_3; b, R = H

1.2 hr. The potassium alkoxide, **2a** (M = K), on the other hand, underwent rearrangement within several minutes at 66° and, upon quenching the enolate mixture with water, the methoxy ketone **4a** was obtained in ≥98% yield. Employing the activation parameters from Table I (entry B), the calculated half-life for this rearrangement at 66° is 1.4 min. This strong counterion-controlled rate dependence has, no doubt, been responsible for concealing this interesting substituent-related acceleration of diene-alkoxide rearrangements. Preliminary experiments suggest that facile enolate equilibration occurs under the conditions of the rearrangement. For example, addition of 1 equiv of **1a** to 1.1 equiv of potassium hydride in THF at 25° followed by stirring for 20 hr resulted in a mixture of enolates **3a** which was trapped by the addition of chlorotrimethylsilane to give the silyl enol ethers **5** and **6** in a ratio of 90:10, respectively.[8]

Table I. Activation Parameters for Oxy-Cope Rearrangement

Substrate	E_a (kcal/mol)	Log A (sec^{-1})	Temp range, °K	Entry
1a	35.9 ± 1.8	12.6 ± 0.6	448–488	A
2a (M = K)	19.4 ± 0.7	10.3 ± 0.4	283–328	B
2a (M = K)[a]	18.2 ± 0.1	11.5 ± 0.1	253–278	C
1b[b]	41.8 ± 0.4	12.5 ± 0.2		D

[a] Kinetic runs carried out in the presence of 1.1 equiv of 18-crown-6. [b] Values determined by J. A. Berson and E. J. Walsh, Jr., ref 4d.



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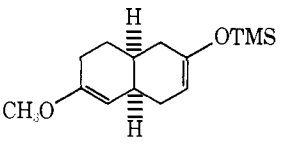

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The strong counterion dependence in the **2a** → **3a** rearrangement suggested that further acceleration might be achieved by the addition of ionophores.[9] A study of the rate of rearrangement of **2a** (M = K) in THF at 0° as a function of added 18-crown-6[10] 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 attained upon the addition of the sodium-specific 15-crown-5[9a] to **2a** (M = Na) at 66° (THF)[11] 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 = K) with 1.1 equiv of 18-crown-6 determined at four temperatures afforded linear Arrhenius plots and the activation parameters shown in Table I. 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}.[12]

There have been isolated examples of exceptionally facile Cope rearrangements;[13] 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}–10^{17} are truly startling when compared to other catalyzed thermal processes such as the Diels-Alder reaction which shows 10^5 rate acceleration with Lewis acid catalysis.[14]

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

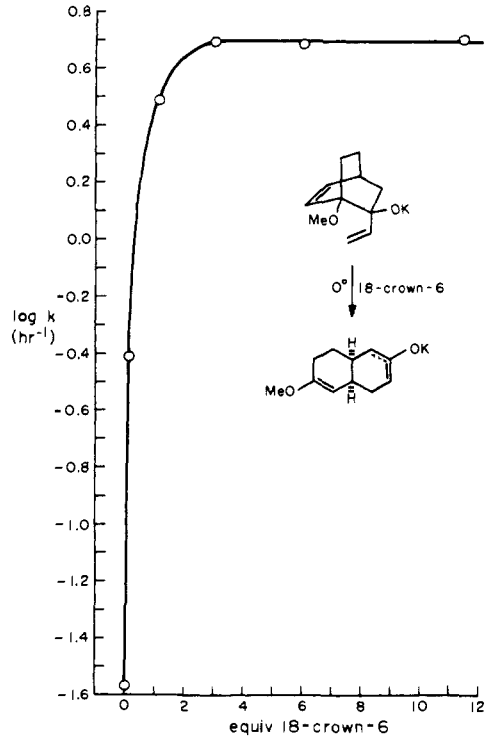
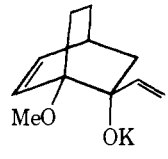


Figure 1. Effect of 18-crown-6 on the rate of rearrangement of **2a** (M = K) in THF at 0°.

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



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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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(7) The various metal salts of **1** were prepared in THF from the following bases: CH_2=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.
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(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.
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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 system[5] 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 acid[6] 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 ($BNA^+ClO_4^-$) 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-