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# Consequences of Heteroatomic C-6 Substitution on Rates of the Oxyanionic Cope Rearrangement. The Remarkable Accelerating Effect of Sulfide Groups

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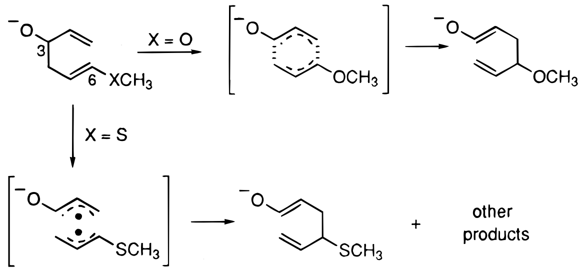
[3,3] Sigmatropic rearrangements have established themselves to be entirely reliable for the stereocontrolled synthesis of a wide array of organic molecules.[2] The discovery that oxy-Cope rearrangements are highly accelerated if mediated by their potassium alkoxides[3] has broadly extended the adaptation of this process to the preparation of structurally intricate end products.[4] The weakening of the adjoining $\sigma$ bonds that materializes in the anionic variant[5] allows many of the structural reorganizations to operate at or below 0 °C, particularly in the presence of 18-crown-6. These conditions are notably conducive to safeguarding the integrity of delicately substituted reactants. In light of these developments, it is rather surprising that the search for additional substituent effects has been quite limited.[5a,6−8] A recent discovery in one of our laboratories provided an indication that a thiophenyl substituent at C-6 promotes remarkable *added* acceleration to an anionic oxy-Cope rearrangement while an alkoxy group at the same site proved to be somewhat decelerating.[8] Subsequent investigation of these contrasting phenomena by hybrid density functional theory revealed further that the oxygen series continues to adhere to a transition state featuring concerted bond reorganization.[9] When sulfide groups reside at either C-4 or C-6, however, acceleration is induced and a stepwise pathway is now favored. This divergent behavior stems from the stabilizing effect provided uniquely by divalent sulfur, a factor that promotes adoption of the homolytic reaction channel.

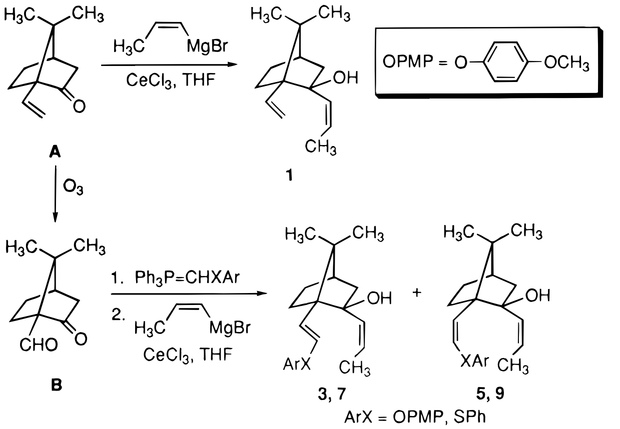
The computational results involved B3LYP/6-31+G* optimizations of transition states for the parent anionic oxy-Cope rearrangement and methoxy or thiomethoxy substituted analogues. The computations predict that a 6-methoxy substituent in a 3-oxido-1,5-hexadiene slows the rearrangement by increasing the activation energy from 8.3 kcal/mol in the parent system to 12.0 kcal/mol. When the 6-substituent is $SCH_3$, the $E_{act}$ decreases to 5−6 kcal/mol and early asynchronous chair transition states make their appearance. Bond cleavage is clearly stimulated, such that a concerted process is not now preferred[9] (Scheme 1).

**Scheme 1**



In the present communication, we report the details of a kinetic investigation designed to quantify the differing effects alluded to above. Our results establish that (1) a C-6 *p*-methoxyphenoxy substituent has little consequence on rate relative to a hydrogen atom similarly positioned, (2) the modulation by OPMP varies from very slightly accelerative for the trans isomer to modestly decelerative in the cis example, (3) both geometric isomers in the phenylthio series rearrange approximately $10^3$ faster than the other three examples, and (4) both of the SPh carbinols deliver the respective product anticipated for a concerted electronic reorganization.

For the present purposes, the camphor-derived ketone **A** was selected as the fundamental carbon framework because of its ready availability[10] and our previous demonstration that appropriate *exo*-norbornanols such as **1** derived therefrom undergo [3,3] sigmatropic rearrangement exclusively via an endo-chair transition state to generate a single bicyclic ketone stereospecifically.[11] Carbinols **3**, **5**, **7**, and **9** were obtained by chemoselective homologation of **B**[12] with the appropiate Wittig reagent,[8,13] followed by cerium trichloride-mediated[14] 1,2-addition of (*Z*)-1-propenylmagnesium bromide[15] to the resulting ketones.



A quantity of the carbinol in dry THF adequate to give a 5% solution was rigorously deoxygenated with $N_2$, cooled to the

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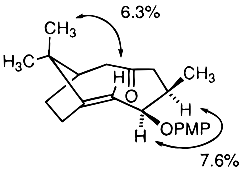
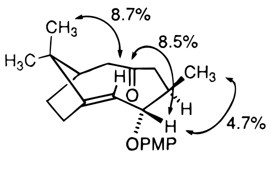
relevant temperature, and treated via insulated cannula with 3 equiv of thermostated potassium hexamethyldisilazide solution (0.5 M in toluene) to achieve conditions pseudo-first order in the alkoxide. Rates were followed by $^1$H NMR analysis at 300 MHz of quenched ($NH_4Cl$ in $H_2O$) aliquots removed periodically from the reaction mixtures. Weighted least-squares analysis showed good linearity to be followed in all cases.

The structures of the lone bicyclic ketones generated from each reactant were deduced by NOE methods. In keeping with expected adoption of an endo-chair transition state,[11] the C-4 methyl group was easily determined to be invariably $\beta$-oriented. Stereochemical transmission to C-3 is intrinsically linked to the (*E*)- or (*Z*)-geometry of the bridgehead olefin and was indeed found to be $\beta$ for **4** and **8**, and $\alpha$ for **6** and **10**. As shown in **C** and **D**, the configuration of the bridgehead double bond was equally self-evident.



**C**



**D**

A *p*-methoxyphenoxy group at C-6 exerts no impact on the rate of oxyanionic Cope rearrangement relative to hydrogen when the starting geometry is trans (Table 1). The cis isomer **5** undergoes [3,3] sigmatropy 20 times more slowly than **3**, a likely consequence of the increased steric congestion encountered during mutual approach of the two trigonal centers about to engage in bonding. For **7** and **9**, the rate differential (2.9) is less. This feature correlates well with the increased length of C−S bonds and the associated dropoff in nonbonded steric compression.

$$\textit{trans}\text{-O}/\textit{cis}\text{-O} = k_3/k_5 = 20$$

$$\textit{trans}\text{-S}/\textit{cis}\text{-S} = k_7/k_9 = 2.9$$

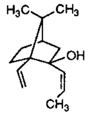
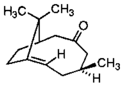
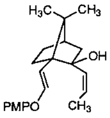
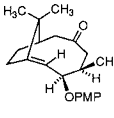
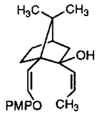
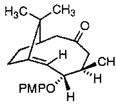
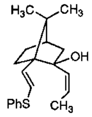
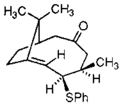
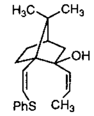
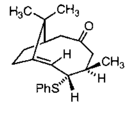
$$\textit{trans}\text{-S}/\textit{trans}\text{-O} = k_7/k_3 = 6{,}620$$

$$\textit{cis}\text{-S}/\textit{cis}\text{-O} = k_9/k_5 = 15{,}700$$

The experimental kinetic data quantify the earlier qualitative results with structurally more complex reactants,[8] and conform as well to the intrinsic reaction coordinate calculations.[9] The computed heterolytic bond dissociation energy of the methylthio model reagent was found to be 12.1 kcal/mol lower than the homolytic bond DE. For the methoxy counterpart, the homolytic BDE was lower than that of the heterolytic option by 4.1 kcal/mol. These are telltale markers of the preferred adoption of heterolytic and concerted rearrangement trajectories, respectively.

Particularly striking are the notable accelerations exhibited by **7** and **9** relative to their oxygen counterparts. The rate enhancements of 6620 in the trans series and 15700 in the cis series are best explained in terms of strong electronic stabilization by sulfur of the rearrangement transition states. Stepwise homolytic cleavage recombination[9] is a real possibility. Should preliminary cleavage of the norbornyl bond occur, the resulting allyl radical fragments are recognized to be maintained in close proximity such that the same thermodynamically favored rearrangement product is formed as in the concerted alternative. Both **7** and **9** advance very rapidly to product at −78 °C *in the absence of 18-crown-6.* When a molar equivalent of this ionophore is present, these rearrangements are complete within 5 min at this temperature. The large magnitude of these rate enhancements makes C-6 substitution by a sulfide group a very attractive feature of synthetic design, particularly in light of the ease with which sulfur-containing groups can be chemically modified or reductively excised as needed. The latent potential for making one reaction channel operative to the exclusion of another in direct intramolecular competition by means of this tactic holds particular fascination.

**Table 1.** Rate and Product Data for the Oxy-Copy Rearrangement of the Potassium Alkoxides of the Parent 1-Vinyl-2-(*E*-1-propenyl)-7,7-dimethyl-*exo*-norbornan-2-ol (**1**) and Heterosubstituted Congeners Thereof

| carbinol | | product | *k*, sec$^{-1}$ (*t*) | relative rate | $t_{1/2}$, h |
|---|---|---|---|---|---|
|  **1** | $\xrightarrow[\text{THF}]{\text{KHMDS}}$ |  **2** | 2.25 (±0.18) x 10$^{-5}$ (-30 °C) | 1 | 8.6 |
|  **3** | $\xrightarrow[\text{THF}]{\text{KHMDS}}$ |  **4** | 3.20 (±0.25) x 10$^{-5}$ (-30 °C) | 1.4 | 6.0 |
| | | | 1.13 (±0.25) x 10$^{-4}$ (-10 °C) | | |
| | | | 7.66 (±0.42) x 10$^{-4}$ (+10 °C) | | |
| | | | 1.16 x 10$^{-7}$ (-78 °C)$^{a,b}$ | 0.52$^{a}$ | 1600 |
|  **5** | $\xrightarrow[\text{THF}]{\text{KHMDS}}$ |  **6** | 1.68 (±0.41) x 10$^{-6}$ (-30 °C) | 0.075 | 114.5 |
| | | | 3.58 (±0.42) x 10$^{-6}$ (-10 °C) | | |
| | | | 2.15 (±0.16) x 10$^{-5}$ (+10 °C) | | |
| | | | 1.66 x 10$^{-8}$ (-78 °C)$^{a,c}$ | 0.075$^{a}$ | 11,600 |
|  **7** | $\xrightarrow[\text{THF}]{\text{KHMDS}}$ |  **8** | 7.68 (±0.24) x 10$^{-4}$ (-78 °C) | 3,450 | 0.25 |
|  **9** | $\xrightarrow[\text{THF}]{\text{KHMDS}}$ |  **10** | 2.61 (±0.42) x 10$^{-4}$ (-78 °C) | 1,175 | 0.74 |

[a] Extrapolated values. [b] An Arrhenius plot gives $\Delta H^{\ddagger} = 10.2$ kcal/mol and $\Delta S^{\ddagger} = 36$ cal/(mol K). [c] An Arrhenius plot gives $\Delta H^{\ddagger} = 8.1$ kcal/mol and $\Delta S^{\ddagger} = -51$ cal/(mol K).

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