By analogy with the term anticodon we suggest calling this the *antipharmacophore* (shorted by convenience to *antiphore*). Thus Figure 3 is (low resolution) maps of estimates of the distribution of XH groups in the antiphores of molecules binding the appropriate groups such as ketones, epoxides, ethers, and esters. If we assume that the geometry of the receptor–ligand interaction is optimized when the ligand is bound to the most biologically active ligand, then we can suggest that the highest contour levels in the maps in Figures 4 and 5 represent the preferred directions of hydrogen bonding from the biological receptor (as hydrogen-bond donor) to the ligand.

Conclusion

For most common oxygen-containing functional groups there are hundreds of reported structures on file (CCDF). It is straightforward to compare their hydrogen-bonding patterns, both in terms of frequency and in terms of distance and angular distribution, as shown for selected examples in Figure 6. Beside giving a useful, practical addition to our understanding of the geometry of ligand–macromolecule binding, they provide maps of lone pair density that can be compared with those produced by X-ray crystallography (at high resolution using, for example, X–N maps) or by ab initio calculations. As more of the types of maps illustrated in this article become available, further variations in the stereochemical specificity of binding of differing functional groups should be quantifiable.

Acknowledgment. We thank Drs. H. L. Carrell, Philip Coppens, and Richard E. Rosenfield, Jr. for helpful discussions. Diagrams were drawn with the computer programs VIEW,[48] DOCK,[49] GENAT,[29] and GENMAP.[29] This work was supported by Grants BC-242 from the American Cancer Society and CA-10925, CA-22780, CA-06927, and RR-05539 from the National Institutes of Health and by an appropriation from the Commonwealth of Pennsylvania.

Registry No. I, 75-21-8; VI, 3189-43-3; cyclohexanone, 108-94-1; oxygen, 7782-44-7.

Supplementary Material Available: Tables of references to the structures that contain the O···H–X interactions described in this article (46 pages). Ordering information is given on any current masthead page.

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The Anionic Oxy-Cope Rearrangement: Structural Effects in the Gas Phase and in Solution

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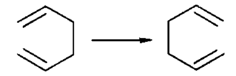
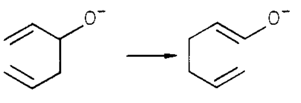
Abstract: The Cope rearrangement of 1,5-dienes with an anionic oxygen on C-3 has been shown to proceed in the gas phase, using ICR spectrometry, for the case where the precursor is a tertiary alcohol. The secondary alcohol, if it reacts at all, is slower than the ICR time scale. A similar rate difference is observed in THF or Me_2SO solvents. The rate variation is ascribed to an intrinsic structural effect, not to differential ion pairing or solvation effects.

The Cope rearrangement (eq 1) has been shown to have a half-life on a geological time scale at room temperature.[2] If an anionic substituent is present on C-3, however, the rearrangement is accelerated by a factor of 10^{10}–10^{17},[3] so as to proceed in a few minutes to hours. As a result, this reaction has been widely used in synthetic transformations[4] and is the basis for the remarkable acceleration probed by various methods.[5] Reactions of this type can be analyzed in terms of the bond-breaking or bond-making extremes, as detailed in Figure 1, in order to shed further light on the mechanism. In the case of the anionic oxy-Cope rearrangement, simple inspection reveals no reason to expect special acceleration for the bond-making pathway, since a β-alkoxide functionality should not have any specific interaction with the radical site. Goddard and co-workers have examined the thermochemistry of the bond-breaking pathway BB_1 using molecular orbital calculations and have stated that the alkoxide functionality should reduce the C–C bond strength considerably in such species.[5] The calculated decrease of the C–H bond strength in $H–CH_2O^-$ relative to $H–CH_2OH$ of 16.5 kcal/mol was found to be comparable to the ca. 18-kcal/mol reduction in the energy of activation experimentally observed for reaction 2.[3,4f]


(1)


(2)

There is another possible bond-breaking pathway that must be considered, BB_2 in Figure 1, where the electron resides on the allyl moiety rather than the enone. The electron affinity (EA) of the allyl radical in the gas phase is known to be 12.7 kcal/mol.[6] While no experimental value for the EA of acrolein is available, its radical anion is bound,[7a] but undoubtedly less so than for cinnamaldehyde with EA = 19 kcal/mol.[7b] This bracketed value of 10 ± 10 kcal/mol is consistent with the anion not being observed in various

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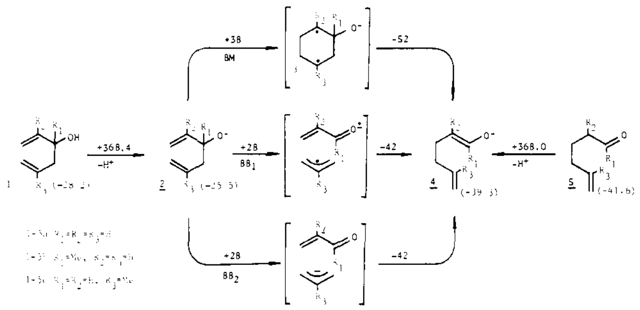

Figure 1. The bond-breaking (BB) and bond-making (BM) extremes for the anionic oxy-Cope rearrangement. Enthalpies are in kcal/mol for **1–4b**.

gas phase ion chemistry studies.[8] We thus expect pathway BB_2 to be comparable in energy to BB_1 in the gas phase.

Examination of the cases in the literature where this reaction is used also reveals a facet that does not appear to have been commented on by other workers: while reaction 2 is the form that is commonly drawn, there is no evidence that the molecule shown undergoes this reaction.[9] The majority of cases involve tertiary alkoxides,[3,4] and for the few cases where secondary systems are mentioned, there are usually groups present on the potential allyl anion fragment, such as thiophenoxy or vinyl, that should appreciably stabilize it.[2a,c,f] In such studies, it appears that secondary and tertiary systems give similar yields. Yields are not necessarily a reflection of the rate ratios, however. For the few cases where stabilizing groups are not present, the analogous secondary and tertiary alkoxides do not seem to have been studied under comparable conditions. It can be argued that a faster rate for tertiary alkoxides is due to the increased steric hindrance around the anionic site, since it is known that decreased ion pairing and solvation at that location result in a rate increase.[3] In order to determine the prevalence of the secondary/tertiary effect, and whether it is mediated by solvation, we have examined alkoxides **2a** and **2b** under comparable conditions in solution, and in the absence of solvent in the gas phase, using ion cyclotron resonance (ICR) spectrometry.

Experimental

The gas-phase ion chemistry was conducted with use of the Indiana University ion cyclotron resonance (ICR) spectrometer, which has been previously described.[10] Much of the work done for this investigation has utilized the recently implemented computer control system for the ICR spectrometer, involving a Data General MicroNova computer driving a Rockland Systems frequency synthesizer. The irradiating frequency is swept over the range of interest under "rapid scan"[11] or "intermediate passage"[12] conditions, so that the ringing of the signal due to ion power loss dies away before the next mass is encountered. This allows the signal intensity to be used as a measure of ion abundance directly, without deconvolution techniques. The data from repetitive sweeps are collected with a 30-kHz A/D converter and accumulated in memory for averaging, then plotted on vaious graphics output devices. The cell is of the cubic type,[13] with a newly designed differential preamplifier for improved performance. All reactions mentioned were confirmed by double resonance, and most experiments were conducted with the ion gauge off to reduce reactions due to pyrolytic species.[14] Acidity measurements were performed by using the standard techniques.[15]

Table I. Solution-Phase Rate Constants for the Anionic Oxy-Cope Rearrangement

anion	$k(\mathrm{THF})^a$	$k(\mathrm{Me_2SO})^a$
2a	2.5×10^{-6}	$<1.0 \times 10^{-6}$
2b	7.0×10^{-4}	5.0×10^{-4}

[a] s^{-1}, 25 °C, 0.1 M, K^+ counterion, see Experimental section.

Alcohols **1a–c** were prepared by addition of allyl Grignard reagent to the appropriate enone.[16] The NMR and mass spectra were consistent with the expected structures. The nitrite esters were prepared in situ.[17] Other compounds were obtained commercially, and all were purified by preparative gas chromatography or distillation before use and then subjected to several freeze–pump–thaw cycles on the foreline of the ICR spectrometer to remove volatile impurities.

The solution-phase rate constants were obtained by two methods. For tetrahydrofuran (THF) as the solvent, the alcohol was added to a threefold excess of potassium hydride in THF at room temperature, to make a 0.1 M solution. Aliquots were analyzed every 15 min for **1b**, and every 12 h for **1a**, by gas chromatography[18] with use of a $^1/_4$ in. by 8 ft column of 5% Carbowax 20M on acid washed Chromosorb W. For dimethyl sulfoxide (Me_2SO) as the solvent, the tertiary alcohol was added to a threefold excess of KH in Me_2SO-d_6 in an NMR tube, and the relative heights of the methyl singlets were followed on a Varian T-60 NMR spectrometer. For the secondary system under similar conditions, it was necessary to degas the sample carefully, or the solution would turn purple within 30 min. No formyl hydrogen was observed in the NMR spectrum of the secondary alkoxide, although there was a degradation of the starting material's spectrum and an increase in the protonic content of the Me_2SO signal with a rate constant of ca. 1×10^{-6} s^{-1}, accompanied by the formation of precipitate in the NMR tube. Since the temperature was not carefully controlled and only a few points were used to calculate the rate constants, the values in Table I are probably only good to ±20%.

Results

Reaction of 1×10^{-6} torr of 3-methyl-1,5-hexadiene-3-ol (**1b**) in the ICR spectrometer with MeO^- results in m/z 111^- corresponding to an M − 1 anion. This ion reacts slowly (an efficiency of 0.05 relative to collision rate) under these conditions, giving solely an M + 28 anion. This reaction has been previously noted as typical of enolate anions[19] and involves a Claisen-type condensation of an enolate with the nitrite ester used to generate the primary alkoxide bases:

$$CH_2{=}CHO^- + MeONO \rightarrow O{=}N{-}CH{=}CHO^- + MeOH$$

When either CH_3OD or t-$BuCH_2OD$ are admitted into the vacuum system at a partial pressure of ca. 1×10^{-6} torr, the M − 1 anion of the alcohol **1b** reacts to give up to three deuterium exchanges. The ion intensities decrease for the successive exchanges, such that a fourth exchange could be occurring, but its signal would be buried in base-line noise. This technique has been shown to be diagnositc for the M − 1 anions of acids containing hydrogens comparable in acidity to the one removed to make the M − 1 anion, with no exchange occurring for monofunctional alcohols.[20] For the product enolate **4b** from the rearrangement, four exchanges are possible, as shown in (3). Observing fewer

$$R'CH{=}C(CH_3)O^- \xrightarrow[\text{-MeOH}]{\text{MeOD}} R'CD{=}C(CH_3)O^- \xrightarrow[\text{-MeOH}]{\text{MeOD}} \xrightarrow[\text{-MeOH}]{\text{MeOD}} \xrightarrow[\text{-MeOH}]{\text{MeOD}} R'CD{=}C(CD_3)O^- \quad (3)$$

exchanges than the maximum number is not uncommon in the ICR, however.[21] To verify that these reactions are good diagnostic

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indicators of ion structure in the present case, 2-pentanone was taken as a model compound for **5b**. Under the same reaction conditions as used for the dienol **1b**, the $M - 1$ anion of 2-pentanone forms the $M + 28$ anion with the nitrite ester and undergoes three of the four possible deuterium exchanges with the same deuterated alcohols. We believe these tests to be indicative that **2b** is rapidly rearranging in the ICR spectrometer to the enolate **4b**. Since the rates of appearance of the first deuterium exchange peaks for **2b** and the enolate anion of 2-pentanone were similar, then the deprotonation of **1b** by methoxide and its subsequent rearrangement must have a pseudo-first-order rate constant comparable to that for deprotonation of 2-pentanone by the same base. While carbon acids giving delocalized anions are known to be slower than alcohols in proton transfer in the gas phase,[24] exothermic reactions from both types of acids to alkoxides occur at rates corresponding to reaction efficiencies of 0.1 to 0.5.[24,15] Based on this and the comparable exchange rates, a lower limit of $>10\ \mathrm{s}^{-1}$ can be placed on the rearrangement rate constant for **2b**. When **2b** is generated not by proton removal from **1b** but by thermal electron impact on the nitrite ester of **1b**, an $(M - 1)^-$ ion is observed which does not give an $M + 28$ anion or undergo any deuterium exchange with MeOD.

In contrast to the behavior of the tertiary compound, when **1a** is deprotonated under similar conditions to those for **1b** above, no $M + 28$ ion is seen, no deuterium exchange occurs with MeOD or t-BuCH$_2$OD, and a prominent $(2M - 1)^-$ signal is observed. This last ion is due to a bimolecular clustering mechanism that occurs on the ICR time scale for alcohols and alkoxides of C_5 or greater size, but not for enolates.[23] This chemical reactivity is not consistent with the ion being the rearranged **4a** but rather remaining as the alkoxide for most of the residence time in the spectrometer. When hexen-3-ol ($\Delta H^\circ_{\mathrm{acid}} = 369.0$ kcal/mol vs. benzyl alcohol and 2,2,4-trimethyl-3-pentanol) is used as a model compound for the unrearranged alcohol, the same reactivity pattern is observed as for **1a**. The $(M - 1)^-$ ion of the enol does not give an $M + 28$ ion, or any masses indicative of deuterium exchange, but it does give a large $(2M - 1)^-$ signal in the unquenched mode.[22] No such $(2M - 1)^-$ ion is seen for **1b** or for the model ketone. If pentanal is used as a model for the rearrangement product in place of **1a**, now the $M + 28$ anion, a single deuterium exchange with t-BuCH$_2$OD, and no $(2M - 1)^-$ signal are observed. These results are consistent with the secondary alkoxide undergoing little or no rearrangement on the ICR time scale. We thus place an upper limit on its rearrangement rate constant of $<0.1\ \mathrm{s}^{-1}$. Similarly, **1c**, when deprotonated by methoxide, behaves like **1a**, showing no evidence for rearrangement by any of the tests employed here.

To compare the rates of rearrangement of **1a** and **1b** under identical conditions in solution, rate constants were obtained for rearrangement of the potassium salts, 0.1 M in THF or Me$_2$SO solvent at 25 °C. The values are given in Table I. The tertiary/secondary rate constant rate is ca. 280 in THF, consistent with the >100 ratio observed in the gas phase. In Me$_2$SO solvent, only a lower limit to the rearrangement rate constant ratio of ca. 10^3 could be obtained, due to decomposition. There does not appear to be a large effect of solvent polarity on the tertiary rate constant, similar to other systems in the literature.[3,4]

Discussion

Any analysis of the rearrangement in the gas phase must include some estimate of the potential surface. In the solution phase, activation energies can be obtained from the rate constants, but the thermochemistry of intermediates other than the highest energy state is not easily available since solvation is not amenable to calculations. In the gas phase, however, we can obtain a reasonable estimate of the reaction surface from the thermochemical parameters of the species involved. Heats of formation for closed-shell anions are available from gas-phase acidities.[15] The acidity of **1a** is taken as that of hexen-3-ol, as noted in the Results section, since aliphatic alcohol acidities should not be greatly affected by unsaturation three carbons away. The acidity of the corresponding tertiary alcohol was not measured, but on the basis of the relative acidities of a number of secondary and tertiary alcohols,[15,25] **1b** is estimated to be 0.8 kcal/mol more acidic than **1a**. For the present work, the ΔH_f° values for several of the neutral species are estimated from group additivity methods.[26] This provides the data in Table II for the various pathways in Figure 1. As mentioned above, an exact electron affinity (EA) and therefore heat of formation is not known for either acrolein or 2-butenone radical anion. MNDO semiempirical calculations[27] indicate that the electron in these two species is bound by 12 and 10 kcal/mol, respectively, for the geometry-optimized radical anions, i.e., the adiabatic electron affinity, in reasonable agreement with the bracketing experimental data. The vertical electron affinities for the neutral enones are smaller, 1 to 2 kcal/mol. The added electron for the optimized anions lies chiefly on the oxygen and the terminal carbon atoms. Within the uncertainty of these estimations, the pathways BB$_1$ and BB$_2$ are comparable in energy, and no clear mechanistic distinction can be made between them here. Methyl substitution would seem to take BB$_1$ ca. 2 kcal/mol higher in energy than the parent system, in contrast to experiment, but such a small difference is probably within the uncertainty of the MNDO results,[27] and should not be regarded as significant. The trend of electron affinities is the same as for methyl substitution onto a simple carbonyl group, however.[7]

Table II. Thermochemical Parameters of Species on the Rearrangement Reaction Surface

compound	ΔH_f°	compound	$\Delta H_f^{\circ a}$
1a	-18.6^b	**1b**	-28.2^b
2a	$-15.3^{c,d}$	**2b**	$-25.5^{c,e}$
3	$22.6^{c,f}$	**3b**	$12.5^{c,f}$
$CH_2{=}CHCH{=}O$	-17.8^b	$CH_2{=}CHC(Me){=}O$	-28.0^b
$CH_2{=}CHCH_2$	39.4^g		
$CH_2{=}CHCH{=}O^-$	-11.7^h	$CH_2{=}CHC(Me){=}O^-$	-33.4^h
$CH_2{=}CHCH_2$	$30.0^{c,f}$		
4a	$-29.8^{c,j}$	**4b**	$-39.3^{c,k}$
5a	-29.1^b	**5b**	-41.6^b

[a] kcal/mol. [b] Estimated by group additivity methods.[25] [d] $\Delta H_f^\circ(X^-) = \Delta H^\circ_{\mathrm{acid}}(HX) - \Delta H_f^\circ(H^+) + \Delta H_f^\circ(HX)$. [d] On the basis of $\Delta H^\circ_{\mathrm{acid}} = 369.0$ kcal/mol, that of 1-hexen-3-ol. [e] On the basis of estimated $\Delta H^\circ_{\mathrm{acid}} = 368.4$ kcal/mol, see text. [f] On the basis of cyclohexanol $\Delta H^\circ_{\mathrm{acid}} = 371.0$ kcal/mol and two secondary C–H bonds of 95 kcal/mol.[31] [g] Reference 31. [h] MNDO calculations.[26] [i] Reference 15. [j] $\Delta H^\circ_{\mathrm{acid}}$ taken as that of propanal at 365.0 kcal/mol.[15] [k] $\Delta H^\circ_{\mathrm{acid}}$ taken as that of butanone at 368.0 kcal/mol.[15]

Certain further corrections to these estimates are necessary. For the intermediates BB$_1$ and BB$_2$ in Figure 1, this thermochemical method gives the heat of formation for the two species at infinite separation, while in practice the ion–dipole and ion–induced dipole interactions that occur for such species in the collision complex can stabilize them by 8 to 40 kcal/mol.[28] For the complexes here, there is no specific hydrogen bonding interaction due to the lack of donor groups and the delocalized nature of the anion,[28,29] so that the lower limit of ca. 8-kcal/mol stabilization has been used to estimate the ΔH_f° of the complex. Also, the pathways in Figure 1 should be regarded as limiting cases, with the actual reaction intermediate or transition-state structure somewhere between the extremes, though biased in structure

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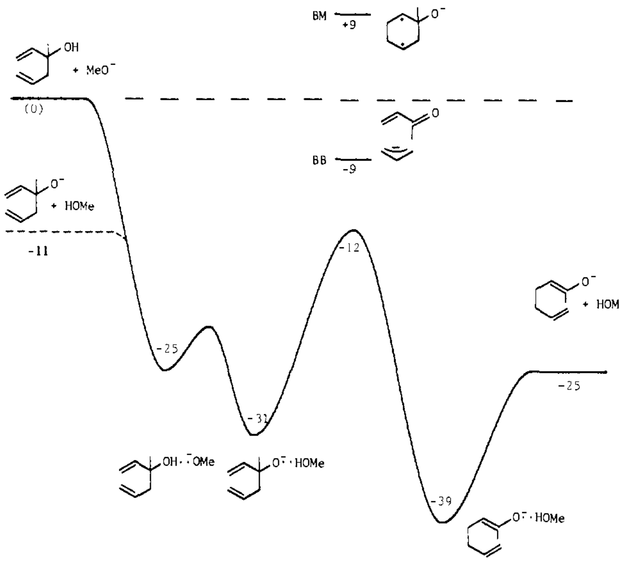
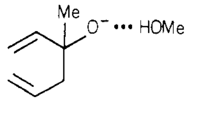


Figure 2. Gas-phase reaction coordinate for deprotonation of **1b** by methoxide and the anionic oxy-Cope rearrangement to the enolate. Enthalpies are in kcal/mol relative to **1b** plus methoxide = 0.

toward the more stable form. Gajewski[30] has applied such an analysis to the Cope rearrangement and has derived eq 4 to fit the literature data for a variety of such reactions. If we substitute

$$\Delta G^{\ddagger} = [\Delta G^{\ddagger}(\mathrm{BB})\cdot\Delta G^{\ddagger}(\mathrm{BM})\cdot 1.5]/\ [\Delta G^{\ddagger}(\mathrm{BB}) + \Delta G^{\ddagger}(\mathrm{BM}) - \Delta G_{\mathrm{rxn}}/1.5] \quad (4)$$

enthalpies for the free energies,[30] this equation predicts that reaction 2 should have a BB-like transition state, ca. 3 kcal/mol more stable than the BB extreme. The derived gas-phase $\Delta H^{\ddagger}$ value of 17 kcal/mol (+28 kcal/mol in Figure 1 − 8 kcal/mol for clustering − 3 kcal/mol from the equation) is remarkably close to the solution-phase $\Delta H^{\ddagger}$ values. While this analysis indicates that the transition state should resemble the BB extreme more than the BM form, nevertheless these are limiting cases and the true transition state should have some BM character. Although a barrier of 17 kcal/mol would imply a relatively fast reaction in solution, this is not necessarily true in the gas phase. On the basis of the precept that any endothermic potential barrier to an ion/molecule reaction slows a reaction to less than the ICR time scale,[24] neither **2a** nor **2b** should undergo rearrangement based on this thermochemical analysis. This assumes, however, that the alkoxides are created without excess energy, while experimentally they are formed by proton transfer from the alcohol to methoxide. If the rearrangement of **2** takes place within the collision complex, after proton transfer but before the methanol departs, then both the exothermicity of the proton transfer and the clustering energy of the two species are available for driving the reaction, as shown in Figure 2. The strength of the hydrogen bond formed between the primary base and the alcohol provides the energy necessary to surmount the barrier to rearrangement, so that the chemically activated reaction can take place in the adiabatic manner above the surface. The well depths in Figure 2 are based on known acidities[15] and the hydrogen-bond strengths of ROH··⁻OR complexes.[29] The top of the rearrangement barrier BB includes the nonspecific cluster energy mentioned above for the two bond-broken components plus another 4-kcal/mol stabilization for the non-specific clustering of the alcohol to the complex.[28] The barrier to rearrangement is thus −13 ± 5 kcal/mol below the adiabatic level in this reaction, so that the reaction should proceed with near-unit efficiency. The lifetimes of such collision complexes should be on the order of microseconds to a millisecond,[23] which are consistent with the observed rearrangement rate constant for **2b** of $>10\ \mathrm{s}^{-1}$. The observation that **2b**, when created by electron impact and not exothermic proton transfer, does not undergo the rearrangement is consistent with this reaction coordinate. Such anions are only a few kcal/mol hot due to their method of formation[31] and as argued above should not have enough energy to surmount the barrier to rearrangement in the gas phase. The deuterium exchange reaction involves clustering of **2** with the MeOD, but on the basis of a analysis like that above, the top of the barrier to rearrangement in this case should be nearly thermoneutral with the colliding species, since it is the exothermicity of the proton-transfer reaction that provides the excess energy in Figure 2. No rearrangement would be expected for such a potential energy surface. Similarly, if the monosolvated ion **6** were created with no excess energy, it should not rearrange. When **1b** is allowed to react with MeO⁻··HOMe, the product of the Riveros reaction of methoxide and methyl formate, no deuterium exchange is observed with MeOD for the products **6** or **7**; the latter is the product of a second exchange of **1b** into **6**. This lack of deuterium incorporation does not denote a lack of rearrangement, however, because when acetone exchanges into the methanol–methoxide ion to give MeOH··⁻OC(Me)=CH$_2$, that product ion does not exchange deuterium with MeOD in the ICR spectrometer, even though the nonsolvated (M − 1)⁻ ion of acetone does. The probe reaction does not appear to be applicable to the monosolvated ions, so no conclusion may be drawn.



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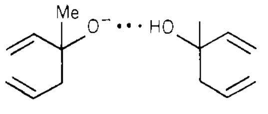

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The estimation methods used here predict essentially the same thermochemical parameters for rearrangement of **1a** and **1b**. The question then arises whether the observed rate difference is due to some true energetic difference too small to be determined by the rough estimations so far or whether the potential energy surfaces for the two actually are the same and the rate difference is due to an entropic factor. The latter is not unreasonable since it may be argued that the solvated complex of **2b** has more degrees of freedom, due to the extra methyl group, than **2a**. Its complex should therefore have a longer lifetime and be more likely to rearrange. The lack of rearrangement for **1c**, with the same number of degrees of freedom as **1b**, but still a secondary alcohol, indicates that complex lifetime is not the critical difference between secondary and tertiary alkoxide reactivity.

The rate difference must therefore be sought in enthalpic terms. It should be noted that the secondary/tertiary reactivity effect can be due to a difference in the height of the barrier to rearrangement of only a few kcal/mol. Such a small change, even when the barrier top is considerably lower than the adiabatic level, can reduce the rate constant for an ion/molecule reaction by two or more orders of magnitude.[24] Two possible reasons for the existence of such a difference can be put forward. The presence of the alcohol molecule in the activated complex should result in an increase in the amount of negative charge localized on the oxygen atom in the intermediates, since that would strengthen the hydrogen bond. This should not only favor BB$_1$ relative to BB$_2$ but, with more electron density on oxygen, the C3 carbon should be more radical-like compared to the planar radical anion. This will result in a larger methyl vs. hydrogen effect on the stability of such a species, with the methyl stabilizing the allyl radical by ca. 3 kcal/mol compared to hydrogen as the substituent.[32] An effect of this size could result in the rate changes seen both in the gas phase and in solution.

An alternative explanation assumes that the transition state, while biased toward the BB extreme, still retains some BM

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(30) Gajewski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4393. The substitution of enthalpies in place of free energies for the neutral systems that the equation was derived for results in a near-constant shift in $\Delta H^{\ddagger}$, making it typically 4 kcal/mol too large when calculated from eq 4. The inclusion of entropy in eq 4 favors the looser BB extreme by ca. 6 eu (J. J. Gajewski, personal Communication).

(31) Bricese, S. M. J.; Riveros, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 230. Sullivan, S. A.; Beauchamp, J. L. *Ibid.* **1977**, *99*, 5017.

(32) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493.

character. If it is envisioned in a reasonable conformation, as a pseudo-chair **8**, then the anionic oxygen can assume either an equatorial or axial position. If the usual conformational rules apply, the alkoxide functionality in the secondary system should prefer a pseudo-equatorial orientation as in **8**, while for the tertiary system with both a methyl and an alkoxide group present on C-3, **9** with the anionic group in an axial orientation should compete in energy with the equatorial alkoxide conformer. Such positional dependence has been observed in the Cope rearrangement of 3,4-dimethyl-1,5-hexadiene, where the methyls prefer being equatorial in the chair-like transition state relative to the axial positions by 9:1.[2c] The mechanism by which an axial oxyanion should result in a more favorable transition state than an equatorial one is not immediately evident, but presumably it would involve some sort of secondary orbital interaction. Most of the solution-phase examples of this reaction are capable of such a conformation, and this postulate is testable by design of conformationally locked systems, with the oxyanion alternately axial and equatorial.

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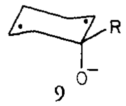

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Other MNDO calculations have been performed on these systems which shed further light on the nature of the rearrangement. Geometry optimization using MNDO calculations on **1a**, arranged with a starting geometry in a chair-like form, results in a structure where the C1–C2 double bond has rotated about the C2–C3 bond approximately 120° into a pseudo-exo geometry, presumably to avoid steric interactions with the C6 carbon. The interesting point is that the C3–C4 single bond (the bond that is broken in the BB intermediate) has appreciably lengthened to 1.613 Å, and the C1–C2–C3–O atoms (the enone in the BB intermediate) are coplanar. The optimized structure thus resembles a planar enone with an allylic moeity near it. The negative charge remains primarily on the oxygen We are not aware of any crystal structures to verify such a large bond lengthening in a homoallylic alkoxide, but the fact that the lengthening does not occur for the C2–C3 bond, rather only for the bond leading to the most stable components, would seem to indicate that the reactive nature of the alkoxide is reflected in its structure. If the BM intermediate **3** is arranged in a chair conformation, geometry optimization with the MNDO method results in the product enolate **4** being the most stable structure located, irrespective of whether the oxyanion is axial or equatorial. Since semi-empirical calculations are strictly parameterized only for minima on potential energy surfaces, one must be careful in interpreting them for other parts of the surface. Nevertheless, qualitatively this indicates that the BM intermediate is on the product side of the reaction coordinate. A similar optimization of a planar enone and allyl moeties arranged to mimic a BB transition state results in relaxation to either the reactant alkoxide or product enolate, depending on small changes in the starting geometry.

In conclusion, we find that the acceleration of the Cope rearrangement due to the presence of an anionic group on C3 occurs in the gas phase as well as in solution. Alkyl substitution at C3 results in an apreciable rate difference between the prototypical anionic Cope rearrangement systems **2a** and **2b** in both the gas and condensed phases, ascribable to an intrinsic structural effect and not to relative ion-pairing or solvation effects. The question of whether this change is due to methyl stabilization of the intermediate or to a stereoelectronic conformational effect should be amenable to testing by suitably designed models with conformationally locked anionic substituents.

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Complete Kinetic Analysis of Thermal Stereomutations among the Eight 2,3-Dideuterio-2-(methoxymethyl)spiro[cyclopropane-1,1′-indenes]

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Abstract: Two isomeric cyclopropanes with stereochemical labels at each of three ring carbons, (−)-(1*S*,2*S*,3*S*)-*trans*,-*trans*-2,3-dideuterio-*cis*-2-(methoxymethyl)spiro[cyclopropane-1,1′-indene] and (+)-(1*R*,2*S*,3*R*)-*cis*,*trans*-2,3-dideuterio-*trans*-2-(methoxymethyl)spiro[cyclopropane-1,1′-indene], were synthesized in optically pure form and pyrolysed at 198.9 °C. The relative concentrations of stereoisomers in product mixtures were determined as a function of time by using a combination of analytical techniques: vapor phase chromatography, polarimetry, NMR spectroscopy, and NMR spectroscopy in the presence of an optically active lanthanide shift reagent. The stereochemical reaction kinetics reveal that the Smith mechanism is not a plausible model for one-center epimerization; two trimethylenes, produced through two distinct cyclopropane C-C bond cleavages, are implicated, since all three possible one-center epimerizations are seen: from the cis isomer, k_1, k_2, and k_3 ($\times 10^5$ s) are 0.95, 2.34, and 0.17, while from the trans isomer, k_1', k_2', and k_3' ($\times 10^5$ s) are 0.32, 0.80, and 0.19.

The energy gap between molecules having either a tetrahedral or a planar tetracoordinate carbon is diminished if that atom resides in a cyclopropane ring or at C(5) of a cyclopentadiene ring.[1] These conclusions have been drawn from early theoretical analyses based on single-determinant calculations[1] and from later studies employing configuration interaction.[2] When both structural features are present, as in a spiro[2.4]hepta-4,6-diene system, the energy-gap reducing influences are in large part cumulative: for the series methane, cyclopropane, cyclopentadiene, and spiro-

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(1) Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475–1485. Hoffmann, R.; Alder, R. W.; Wilcox, C. F., Jr. *Ibid.* **1970**, *92*, 4992–4993.

(2) Crans, D. C.; Snyder, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7152–7154. See also: Collins, J. B.; Dill, J. D.; Jemmis, E. D.; Apeloig, Y.; Schleyer, P. R.; Seeger, R.; Pople, J. A. *Ibid.* **1976**, *98*, 5419–5427 and references therein.