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KINETIC versus THERMODYNAMIC ACIDITY OF α-SULPHONIUM PROTONS

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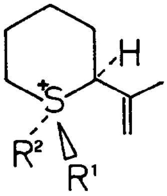
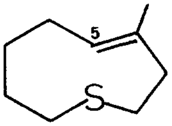
Abstract: The kinetic acidity of structurally different, or stereochemically different, protons α to a sulphonium function may not parallel their thermodynamic acidity.

The stereochemistry of the ring enlargement by 3,2-sigmatropic rearrangement of sulphonium ylides may depend on the method of ylide generation from the parent sulphonium salt.[1] When a 6:1 trans:cis isomeric mixture of **1** and **2** was treated at -70°C with t-BuOK in THF/t-BuOH (10/1 v.v.) (Method I) or with lithium diisopropylamide (LDA) in THF at -70°C (Method II) the product was a 1:4.3 or, respectively, a 6:1 mixture of E- and Z-4-methylthiacyclonon-4-ene, **5** and **6**.[1]



1: $R^2 = CH_3$; R^1 = lone pair
2: $R^1 = CH_3$; R^2 = lone pair
3: $R^2 = CD_3$; R^1 = lone pair
4: $R^1 = CD_3$; R^2 = lone pair



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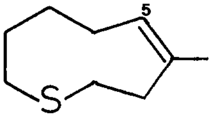

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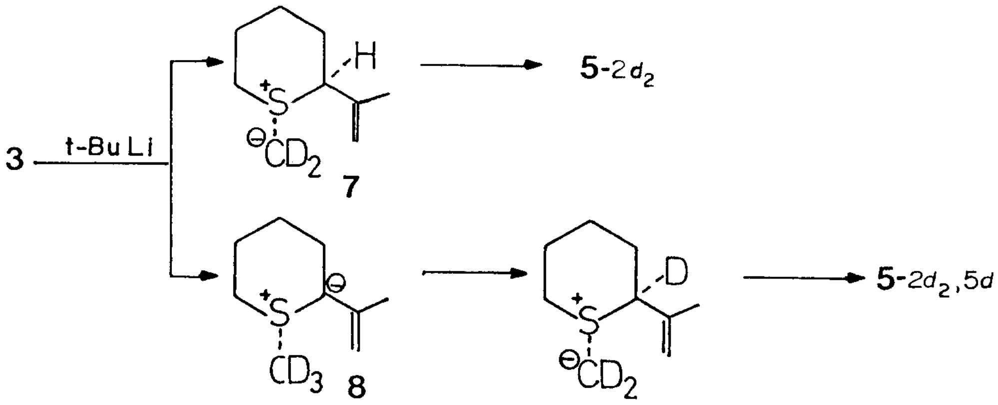
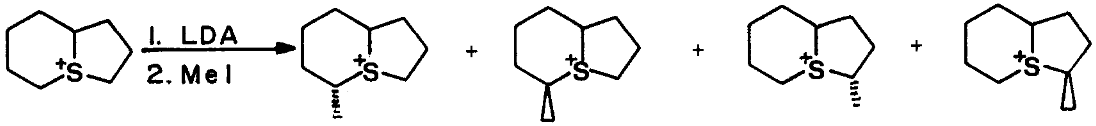
We have now established that other strong, essentially irreversible bases [t-BuLi, KDA, $NaN(SiMe_3)_2$] behave like LDA insofar as the product distribution reflects the composition of the starting material. Since **1** and **2** are expected to rearrange stereospecifically[1] (**1** → **5**; **2** → **6**) the finding that with method I the product from the trans salt (**1**) largely consist of the Z olefin (**6**) means that, before rearranging, **1** largely undergoes epimerization to **2**, most likely via reversible removal of the allylic proton at C_2.[2] On the other hand, when the ylide is generated irreversibly with Method II (LDA, t-BuLi, ...) epimerization does not occur to any appreciable extent, implying that either the allylic proton is not removed rapidly or, if it is, reprotonation occurs (possibly intramolecularly) with configurational retention.

To establish which of the alternative routes (Scheme) is actually followed, a 6:1 mixture of the deuteromethyl sulphonium salts **3** and **4** was treated with t-BuLi (THF, -70°) and the deuterium content of the separated[1] product olefins analyzed by ^{2}H NMR. The Z and E thiacyclononenes had deuterium in the α-methylene region, δ 2.6 and 2.4 , respectively, but no detectable deuterium in the olefinic region (<1% of the respective α-methylene peaks). As any formation of the allylide **8** would show up as deuterium at C_5, these results rule out **8** as an intermediate and establish the direct formation of the methylide **7**.[3] Accounting for kinetic H/D isotope effect, the conclusion must be that kinetically, towards t-BuLi, the S-Me H's are more acidic than the allylic H by a factor greater than about one hundred. On the other hand, the stereochemical results obtained with t-BuOK in THF/t-BuOH are compatible with the allylic proton being removed rapidly.[5] If, as it is reasonable to assume, the allylide is more stable than the methylide, the parallelism between kinetic and thermodynamic acidity appears to be followed in the case of t-BuOK in THF/t-BuOH but not in that of t-BuLi in THF.[7]

Scheme



That kinetic and equilibrium acidities of α-sulphonium H's may not necessarily parallel each other is supported by an independent study which, as the sequel will show, does not require any assumption as to which ylide is more stable in which solvent. We have reported that iodomethane quenching of the ylide formed (THF, -70°) by LDA deprotonation of a *cis*-1-thioniabicyclo[4.3.0]-nonane salt (**9**) yields three α-methylated products, **10**, **11** and **12** in a ∼9:3:1 ratio.[10]



9 10 11 12 13

At the time of our report[10] no attention had been paid to the time gap between deprotonation and quenching. We have now found that if quenching occurs immediatly (∿5 sec) after deprotonation, all four products, **10-13**, are present (in a∿2.5:1:2.5:1 ratio); if, however, the ylide is quenched after some time, the yield of the C_2-methylation products, **10** and **11**, increases at the expenses of C_9-methylation products, **12** and **13**. Eventually, quenching after 10 min or more at -70°, produces only C_2-alkylation products, although the total alkylation yield (75-80%) is unaffected.[11] This result conclusively shows that, while the protons at the two α-regions (C_2 and C_9) have comparable kinetic acidities towards LDA, the equilibrium acidity largely favors the C_2 region.

The parallelism between kinetic and thermodynamic acidities is a fundamental tenet of physical organic chemistry.[12] It is often implied in estimates of pK_a values for setting up acidity scales,[12] and it is invariably postulated in theoretical studies (our own included)[13] where the relative kinetic acidity of diastereotopic protons is related to the calculated stability of the corresponding carbanions (or ylides). Our present results, showing kinetic and thermodynamic acidities do not necessarily parallel each other, issue a word of caution in using arguments where such parallelism is implied.

References and Notes

1. V. Cerè, C. Paolucci, S. Pollicino, E. Sandri and A. Fava, J.Org.Chem., **46**, 3315 (1981).

2. Id., ibid., **44**, 4128 (1979).

3. This finding may be contrasted to that by Bates and Feld[4] indicating the allylic H of dimethyl-(3,3-dimethylallyl)sulphonium bromide is abstracted by BuLi faster than the S-Me H's by an estimated factor of 9.

4. R.B. Bates and D. Feld, Tetrahedron Lett., 417 (1968).

5. For the 1-methyl-2-vinylthiolanium cation, exchange experiments provide direct evidence that the α allylic H is removed faster than the α methyl H's (by hydroxide in aqueous medium)[6].

6. V. Cerè, C. Paolucci, S. Pollicino, E. Sandri and A. Fava, J.Org.Chem., **43**, 4826 (1978).

7. That the order or kinetic acidity may be base/solvent dependent has been long since recognized for diastereotopic protons, the phenomenon being especially conspicous in sulphoxides.[8] The available data,[8] however, provide no hint of whether the equilibrium acidity may also change in a way that, for any given base/solvent, the parallelism between kinetic and equilibrium acidities stil holds. The peculiarity of the system under investigation here is that the protons competing for the base are structurally different, enough that their relative equilibrium acidity may be assumed not to be reversed by a solvent change. Moreover, the conjugate base being an ylide rather than a carbanion, the interactions with the metal ion will be minimal compared with α-sulphinyl carbanions, where the counterion is known to exert a overwhelming effect.[9]

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9. a) T. Durst and M. Molin, Tetrahedron Lett., 63 (1975). b) J.F. Biellmann, J.J. Vicens, ibid., 467 (1978); c) G. Chaissaing, R. Lett and A. Marquet, ibid., 471 (1978).

10. V. Cerè, C. Paolucci, S. Pollicino, E. Sandri and A. Fava, J.Org.Chem., **47**, 2681 (1982).

11. Actually in the fast quenching experiments the yield is somewhat reduced due to some (~10%) unreacted sulphonium salt. On the other hand, long time gaps (>1 h) also lead to somewhat reduced yields due to ylide decomposition.

12. See for instance, T.H. Lowry and K.S. Richardson, "Mechanism and Theory in Organic Chemistry" 2nd Ed., Harper and Row, New York, 1981; pp. 257 ff

13. G.D. Andreetti, F. Bernardi, A. Bottoni and A. Fava, J.Am.Chem.Soc., **104**, 2176 (1982), and references therein.

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