compensates for the electron repulsion of even directly bonded carbanion centers. Thus, dicarbanions can be generated with surprising ease *when they are stabilized within an ion triplet of this type.*

In the ion triplets from the indenofluorenes one cesium cation is expected to be close to one 9-fluorenyl-type position, and the other cesium cation is expected to be on the opposite side of the molecular ring plane close to the other 9-fluorenyl-type position (Figure 3). In such a structure, each cation is close to one anion center *but relatively far from the other.* The electrostatic stabilization within the ion triplet is therefore reduced and the second pK's are larger. The difference in pK^2_{CsCHA} between **3b** and **4b** is probably associated with their relationship to the *m*- and *p*-xylene dianions, respectively. In the meta system the carbanion electrons are placed in two nonbonded Hückel MO's; accordingly, *m*-xylene is dimetalated more readily than *p*-xylene.[6]

These principles based on Figure 1 should be applicable generally and undoubtedly rationalize the facile formation of many polylithiated organic compounds; that is, such compounds may be simply envisaged as ion multiplets.[7] Moreover, this view also explains the many examples where a second metalation occurs close to the first.[8]

Acknowledgment. We thank Dr. Bon-Su Lee for preliminary experiments. This research was supported in part by NSF Grants 79-10814 and 82-05696.

(6) Klein, J.; Medlik, A.; Meyer, A. Y. *Tetrahedron* **1976**, *32*, 51.
(7) See: (a) Kost, D.; Klein, J.; Streitwieser, A., Jr.; Schriver, G. W. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 3922. (b) Schleyer, P. v. R.; Kos, A. J. *J. Chem. Soc., Chem. Commun.* **1982**, 448 and papers cited therein.
(8) Some especially pertinent examples are as follows: Shirley, D. A. *J. Org. Chem.* **1960**, *25*, 1189, 2238; **1962**, *27*, 4421. Shatzmiller, S.; Lidor, R., personal communication. See also ref 7b.

Kinetics, Thermodynamics, and Stereochemistry of the Allyl Sulfoxide–Sulfenate and Selenoxide–Selenenate [2,3] Sigmatropic Rearrangements

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The thermodynamic relationships between the II and IV oxidation states (eq 1, Y = S, Se) play a dominant role in determining

(1)

chemical behavior of sulfoxides, sulfinic, and sulfenic acids and esters, as well as their selenium analogues. It can be argued on the basis of bond strengths that the equilibrium of eq 1 should be more to the right for selenium than for sulfur, and this is supported by some experimental evidence.[2]

We report here the results of a study aimed at quantifying the equilibrium of eq 1, using the system shown in eq 2. Since for Y = Se only the selenenate isomer was detectable at equilibrium it was necessary to employ a kinetic technique (measurement of both k_{12}^{Se} and k_{21}^{Se} to determine the thermodynamic relationship

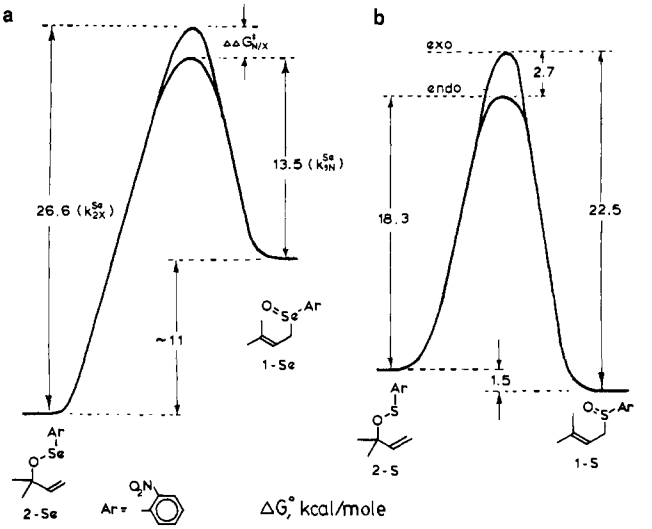
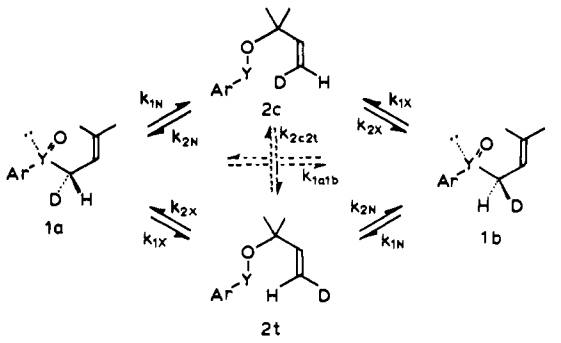
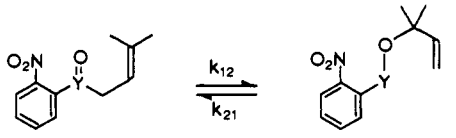


Figure 1. Free energy diagrams for the equilibration of (a) selenoxide **1**-Se and selenenate **2**-Se at −80 °C; (b) sulfoxide **1**-S and sulfenate **2**-S at −30 °C.

Scheme I



between the isomers. The rate constants k_{12}^{Se} could be directly measured. *o*-Nitrophenyl prenyl selenide was oxidized to the selenoxide **1**-Se (*m*-CPBA, −85 °C), which could be briefly observed at −80 °C by 270-MHz NMR, and the rate was measured ($t_{12} \approx 6$ min, $k_{12}^{Se} = 0.002$ s^{-1}) for its isomerization to **2**-Se.



(2)

1-S Sulfoxide
1-Se Selenoxide
2-S Sulfenate
2-Se Selenenate

The rate constant for the reverse process was estimated from the cis–trans isomerization (k_{2c2t}^{Se}) measured between 51 and 80 °C of the deuterium-labeled selenenate **2**c-Se (Scheme I).[3]

1a → 2t
exo (X)
1a → 2c
endo (N)

Unfortunately this is not a direct measure of k_{21}^{Se}. To achieve cis–trans isomerization, **2**c-Se must proceed to **1**-Se by the exo transition state and return endo, or vice versa.[5] Simply proceeding to **1**-Se and returning via the lowest pathway[6] results in no de-

(1) These results were taken in part from the Ph.D. Thesis of S. Wollowitz, University of Wisconsin–Madison, 1980.
(2) (a) Selenenate–selenoxide: Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154. Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570. Reich, H. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 3112. Reich, H. J.; Wollowitz, S. *Ibid.* **1982**, *104*, 7051. (b) Sulfenate–sulfoxide: Tang, R.; Mislow, K. *Ibid.* **1970**, *92*, 2100. (c) Selenenic anhydride–selenolseleninate: Reich, H. J.; Hoeger, C. A.; Willis, W. W., Jr. *Ibid.* **1982**, *104*, 2936. Reich, H. J.; Willis, W. W., Jr.; Wollowitz, S. *Tetrahedron Lett.* **1982**, *23*, 3319. Kice, J. L.; McAfee, F.; Slebocka-Tilk, H. *Ibid.* **1982**, *23*, 3323.

(3) Prepared from *cis*-2-methyl-3-buten-2-ol-3,4-d_2 (from 2-methyl-3-butyn-2-ol reduction with $LiAlD_4$ followed by D_2O quench)[4a] and *o*-nitrobenzeneselenenyl chloride.[4b] The 3-deuterio substituent is omitted in Scheme I.
(4) (a) Borden, W. T. *J. Am. Chem. Soc.* **1970**, *92*, 4898. Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *Ibid.* **1967**, *89*, 4245. (b) Behaghel, O.; Seibert, H. *Chem. Ber.* **1933**, *66*, 708.

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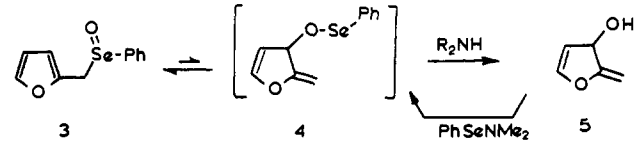
tectable change. It can be shown that the observed and [2,3] sigmatropic rate constants are related as follows, provided that $k_N \gg k_X$:[6] $k_{2c2t}^{Se} \approx 2k_{2X}^{Se}$ and $k_{12}^{Se} \approx k_{1N}^{Se}$. Using the directly measured value for k_{12}^{Se} and the value for k_{2X}^{Se} obtained by extrapolating k_{2c2t}^{Se} to −80 °C ($\Delta H^{\ddagger} = 24.9$ kcal/mol, $\Delta S^{\ddagger} = -7.0$ eu), it is possible to construct a partial free-energy diagram for the **1**-Se/**2**-Se equilibration (Figure 1a). The free-energy difference of interest separating selenoxide and selenenate is 12.5 $- \Delta\Delta G^{\ddagger}_{N/X}$ kcal/mol, where $\Delta\Delta G^{\ddagger}_{N/X}$ is the separation between the endo and exo transition states (i.e. k_N/k_X).

Since k_N/k_X cannot be directly measured for Y = Se, we decided to provide a partial answer by studying the sulfur analogue for which K_{eq} is directly measureable. The sulfenate ester **2**-S was prepared from 2-methyl-3-buten-2-ol and *o*-nitrobenzenesulfenyl chloride at −50 °C, and the rate of equilibration ($k_{12}^S + k_{21}^S$) with sulfoxide **1**-S was measured at −29.7 °C ($k_{12}^S + k_{21}^S = 0.000\,216\ s^{-1}$, $K_{eq} = 23.9$). When the deuterium-labeled compound **2c**-S[7,9] was used, only a single diastereomer[6] of **1**-S was formed (>98%). Equilibration (k_{1a1b}^S) occurred at higher temperatures, and the rate was extrapolated to −29.7 °C ($\Delta H^{\ddagger} = 21.7$ kcal/mol, $\Delta S^{\ddagger} = -1.6$ eu). From the three experimentally determined numbers k_{21}^S, k_{1a1b}^S, and K_{eq}^S, it was possible to calculate the [2,3] sigmatropic rate constants and construct the free-energy diagram (Figure 1b).

The most striking finding is the high value (275) of k_N^S/k_X^S,[6] corresponding to a $\Delta\Delta G_{N/X}^{\ddagger}$ of 2.7 kcal/mol. The k_N/k_X value represents the maximum possible asymmetry transfer from chiral sulfur to chiral carbon (if there is one) of the sulfenate. That such high values have been rarely achieved by using optically active sulfoxides for the synthesis of chiral allyl alcohols[5] could be due in part to the inefficient cleavage of allyl sulfenates, but more likely reflect some peculiarityof the present system.[5b,10]

Returning now to the original question of the selenenate–selenoxide equilibration we can esimate $\Delta\Delta G_{N/X}^{\ddagger} \approx 2$ kcal/mol, and thus $\Delta G^{\circ}_{1Se/2Se} \approx 11$ kcal/mol. Because of the long temperature extrapolation involved, we estimate a possible error of ±2.5 kcal/mol. Since $\Delta G^{\circ}_{1S/2S} = -1.5$ kcal/mol, the equilibrium of eq 2 shifts by 12 kcal/mol on going from S to Se. The two principal contributors are the weaker C–Se bond strength compared to C–S and the smaller degree of multiple bonding in the dipolar Se–O vs. S–O bond. Some of the more dramatic differences between S and Se chemistry can be traced to the effect discussed here, (e.g., the fact that selenoxide syn eliminations are irreversible and much more rapid than those of sulfoxides[11]).

The isomerization of selenoxide to selenenate can be facile even in situations where the double bond is part of an aromatic ring such as furan or phenanthrene. Even though the selenoxide **3** is the only species detected by NMR,[12] it is in rapid equilibrium with its selenenate isomer **4** since treatment with pyrrolidine gives alcohol **5** in a crude (NMR) yield of 87%.[13] Purification by distillation is usually accompanied by some isomerization to furfuryl alcohol, as well as reversal to selenoxide **3**. 9-Phenanthrenylmethyl phenyl selenoxide can similarly be converted to 9-methylene-10-hydroxy-9,10-dihydrophenanthrene.



3 4 5

Acknowledgment. We thank the National Institutes of Health, The National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Supplementary Material Available: Tables of observed and calculated rate constants used to construct Figure 1 (2 pages). Ordering information is given on any current masthead page.

(5) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Goldmann, S.; Hoffmann, R. W.; Maak, N.; Geueke, K.-J. *Chem. Ber.* **1980**, *113*, 831. (c) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1970**, 526.

(6) We have no direct evidence on which is the lower to the two transition states (i.e., whether **1a**-S or **1b**-S is formed from **2c**-S). From the results reported for the *cis*- and *trans*-2-butenyl[5a] and -octenyl[5b] sulfoxides, it is almost certainly the endo (**1a**-S). The most pertinent evidence is that **2c**-S rearranges to the diastereomer of **1**-S with D replacing the downfield H ($CDCl_3$) of the sulfoxide AB (X) pattern (δ_A 3.90, δ_B 3.61, $J_{AB} = 13.0$ Hz, $J_{AX} = 8.0$ Hz, $J_{BX} = 8.5$ Hz).

(7) Prepared from 1,1-dibutyl-2,3-dihydro-3,3-dimethyl-2-oxastannole[8] by treatment with *n*-butyllithium/D_2O.

(8) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.

(9) Isotope effects are small in sigmatropic rearrangements (e.g., for [3,3], $k_H/k_D = 0.97$–1.1 per D): Malojcic, R.; Humski, K.; Borcic, S.; Sunko, D. E. *Tetrahedron Lett.* **1969**, 2003; *J. Am. Chem. Soc.* **1970**, *92*, 6534.

(10) The X-ray structure of methyl *o*-nitrobenzenesulfenate shows a close NO_2–S approach. Hamilton, W. C.; LaPlaca, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 2289.

(11) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

(12) The loss of aromatic stabilization (15.8 and 17.3 kcal/mol for furan and phenanthrene) exceeds the predicted energy gain on conversion to selenenate. Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley-Interscience: New York, 1972, p 131.

(13) 1-Alkenyl-1-cyclopropyl phenyl selenoxides behave similarly to selenoxide **3**. Here the strain of the alkylidene cyclopropane makes the rearrangement endothermic. Halazy, S.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 2135.

Spectroscopic Observation of the Tautomer of 7-Deoxydaunomycinone from Elimination of Daunosamine from Daunomycin Hydroquinone[1]

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Anaerobic reduction of daunomycin (**1**) in microsomes by NADPH[2,3] and in solution by dithionite gives 7-deoxydaunomycinone (**2**).[4] In vivo reductive elimination has been proposed to occur from the semiquinone (**3**) by some[5-7] and from the hydroquinone (**4**) by others[7,8] and to be at least in part responsible for covalent binding of the drug to DNA.[6-8]

Earlier we reported the efficient reduction of daunomycin to 7-deoxydaunomycinone by **6** and kinetic evidence that the reduction occurred possibly via hydride transfer.[9] The kinetic measurements presumed no long-lived intermediates as suggested by prior electrochemical studies.[10] This presumption has now been found to be inaccurate. Kinetics and spectroscopy establish that the reducing agent is **7**[11] and reveal the elusive tautomer **5** of 7-deoxydaunomycinone.

A rigorously oxygen-degassed, methanol-*d* solution containing 1.79×10^{-4} M **1**, 1.79×10^{-3} M **6**, and 2.0×10^{-3} M trisma buffer (1:1 Tris/Tris·HCl) at 25.0 ± 0.1 °C gave the spectral changes shown in Figure 1 during the time regime 10–130 s with scans every 10 s. The sequence of events was a fall in the absorption at 480 nm coupled with a short rise at 420 nm followed by a substantial rise at 380 and 608 nm. During the 380- and 608-nm band rise, the 420-nm band disappeared. Scans beyond 130 s

(1) Support: NCI, CA-24665, Developmental Therapeutics Program; University of Colorado, CCRW; 3M Co.

(2) Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Mol. Pharmacol.* **1977**, *13*, 901.

(3) Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Cancer Res.* **1978**, *38*, 1745.

(4) Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653.

(5) Bachur, N. R.; Gordon, S. L.; Gee, N. V.; Kon, H. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 954.

(6) Pan, S.-S.; Pederson, L.; Bachur, N. R. *Mol. Pharmacol.* **1981**, *19*, 184.

(7) Sinha, B. K.; Gregory, J. L. *Biochem. Pharmacol.* **1981**, *30*, 2626. Sinha, B. K. *Chem.-Biol. Interact.* **1980**, *30*, 67.

(8) Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527. Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(9) Barone, A. D.; Atkinson, R. F.; Wharry, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 1606.

(10) Rao, G. M.; Lown, J. W.; Plambeck, J. A. *J. Electrochem. Soc.* **1978**, *125*, 534.

(11) Koch, T. H.; Olesen, J. A.; DeNiro, J. *J. Am. Chem. Soc.* **1975**, *97*, 7285. Burns, J. M.; Wharry, D. L.; Koch, T. H. *Ibid.* **1981**, *103*, 849.

0002-7863/83/1505-2504$01.50/0