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α-LITHIO-δ-SULTONES: HIGH PREFERENCE FOR EQUATORIAL VS. AXIAL LITHIUM

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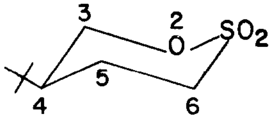
Recently Hartmann and Eliel[1] reported that metallation of conformationally fixed 1, 3-dithianes with n-butyllithium in THF led virtually exclusively to the introduction of the lithium in the equatorial position as judged by subsequent reaction with D_2O and CH_3I.

Our interest in selective metallation of one of the hydrogens of a methylene group α to sulfur functions[2] coupled with a ready synthesis of conformationally fixed δ-sultones[3] prompted us to investigate the reaction of these compounds with n-BuLi. The results are of interest since they parallel those of the dithiane series[1], allow the establishment of a lower limit for the energy differences (Li eq. vs. Li ax) for sultones in THF and reveal a facile epimerization of lithium from the axial to the equatorial position (carbanion inversion).

The sultone 1[4], prepared in 45% yield by cyclization of the dimesylate of 2-t-butyl-1, 3-propanediol[5] with BuLi in THF[3] was reacted with n-BuLi in THF at -78° for 1 min. The resultant clear solution of the lithio derivative 2 was then allowed to react with excess CH_3I, acetone or D_2O for 1 min. The yields of purified product were 81, 87 and 85% respectively. In each case the new substituent was introduced solely in the equatorial position.



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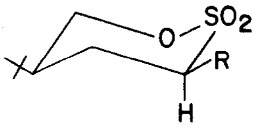


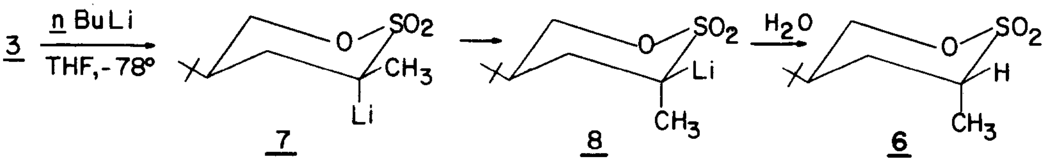
2, R = Li
3, R = CH_3
3a, R = CD_3
4, R = $(CH_3)_2C$-OH
5, R = D

The structural assignments are based primarily on n.m.r. data. The methylated sultone 3 had peaks in the n.m.r. at δ = 0.94 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H), 2.8 - 3.2 (m, 1H) and 4.25 - 4.40 (2H). The axial stereochemistry of the 6- hydrogen was clearly revealed by examination of the n.m.r. spectrum of the perdeuteromethyl sultone 3a during deuterium decoupling. The observed splittings of 11.7 and 3.7 Hz are consistent only with an axial-axial and axial-equatorial coupling. The same hydrogen in the hydroxy sultone 4 occured at δ = 3.11 with J_{aa} = 11.8 and J_{ae} = 3.8 Hz; in the α-deuterio sultone 5,the relevant couplings were 11.8 and 4.6 Hz. The other n.m.r. peaks in the latter two compounds were as expected.

The intermediate lithio derivative is assigned structure 2 (lithium equatorial), each of the electrophiles replacing lithium with retention[6]. This behaviour constrasts with that of α-lithiobenzyl methyl sulfoxide where D_2O was shown to react with retention and CH_3I with inversion of the C-Li (carbanion) configuration[2]. Methylation of cyclohexyl lithio compounds apparently occurs exclusively with retention of the C-Li configuration[7], the inversion processes is sterically extremely unfavorable.

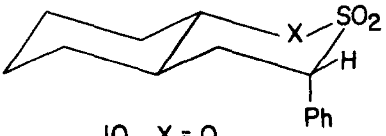
When the equatorially methylated sultone 3 was reacted with n-BuLi at -78° for 1 min. and then quenched with H_2O an isomer of 6 having the methyl group in the axial position was formed. No trace of the equatorial isomer 3 was observed in the n.m.r. spectrum of the total reaction product. The n.m.r. spectrum of 6 showed absorption at δ = 0.94 (s, 9H), 1.43 (d, J = 7.2 Hz, 3H), 3.0 - 3.4 (1H) and 4.25 - 4.40 (2H). The close similarity with the spectrum of 3 confirmed that the two compounds were indeed isomers.

In this interconversion the axially lithiated sultone 7 is presumeable formed first but readily isomerizes (inverts) to the more stable equatorially substituted lithio derivative 8; the $\Delta G^{\neq}$ for the inversion being less than 12 Kcal/mole[8]. The preference of the lithium for an equatorial position is sufficient to force the methyl group into the unfavorable axial position. Equatorial to axial methyl isomerization via lithiation was also observed by Hartmann and Eliel in the dithianes but, because of the slow metallation reaction, the ease with which the isomerization occured could not be observed.



The equatorial preference of the lithium in these compounds is even more dramatically illustrated by the complete isomerization of the sultone 9 (phenyl equatorial), benzylic H at 4.30 (d, J = 11.0 and 4.5 Hz) to the sultone 10 (phenyl axial), benzylic H at 4.50 (d, J = 5.0 and 2.4 Hz) on treatment with n-BuLi followed by hydrolysis. From this example it is possible to estimate the minimum energy difference for lithium equatorial vs. lithium axial in the six membered ring sultones as greater than 2.7 Kcal.[9]

9, X = O
11, X = CH_2



10, X = O
12, X = CH_2

Preliminary results indicate that a similar situation exists in six-membered sulfones. Thus the sulfone 11 was found to undergo essentially complete conversion to 12 when treated with n-BuLi and then quenched with H_2O[7], again indicating very strong preference for lithium (i.e. carbanion) in the equatorial position. This result contrasts strongly with the results of Katritzky et al[10] who have shown that the rates of base-catalyzed exchange in DMSO-d_6-tBuOD of the α axial and equatorial hydrogen in a six-membered ring sulfone do not differ greatly, thus indicating little difference in the relative stability of the two carbanion intermediates under these conditions. Similar large solvent effects on the relative stability of diastereomeric α-sulfinyl carbanions have been reported[2b].

The very large preference of lithium for the equatorial position cannot be completely ascribed to a large steric requirement resulting for strong solvation or agregation. Although only limited data are available, the conformational preference in ether solution of a lithium substituent in cyclohexanes does not appear to be excessive. For example, n.m.r. studies and CO_2 quenching experiments on menthyllithium in dimethyl ether at -78° gave a ratio of equatorial to axial lithium of 5.7 : 1[11], i.e. an A value of about 1 kcal. The related cyclohexyl grignard and dicyclohexyl magnesium derivatives show A values between 0.25 and 0.78 kcal in ether solvents[12]. Thus an additional feature in these compounds must favour the lithium in the equatorial position. In this configuration lithium lies on the internal bisector of the O=S=O angle. Ab initio calculation have indicated maximum carbanion stability for such an arrangement.[14]

Further studies to determine the equatorial preference of lithium in these and related sulfur compounds are in progress.

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4. All new compounds had acceptable analytical and spectroscopic data.
5. Prepared by condensation of tBuCH(Li)CO_2Li [e.g. P.L.Creger, J.Amer.Chem.Soc., 89, 2500 (1967)] with anhydrous formaldehyde followed by $LiAlH_4$ reduction.
6. The same results would have been obtained if lithium prefers the axial position and each electrophile was introduced with inversion of the C-Li configuration. Since the D_2O and acetone quench of sulfoxide and sulfone carbanion occur with retention[2, 7, 13] except in very unusual circumstances, this possibility is considered highly unlikely.
7. (a) W.H.Glaze, C.M.Selman, A.L. Bell and L.E. Bray, J.Org.Chem. 34, 649 (1969).
   (b) R. Viau, unpublished observations.
8. Obtained by assuming a maximum half-life of 15 sec for the lithium axial to lithium equatorial interconversion.
9. (a) This estimate is arrived at as follows: The ratio of 9 to 10 obtained upon quenching ought to reflect closely the equilibrium between axial and equatorial lithium salt in solution.[2] Since less than 5% of 9 was obtained the axial Li is more stable than equatorial Li by at least 1.2 Kcal. To this must be added the approximately 1.5 Kcal (one half of phenyl A value) to compensate for the unfavorable axial phenyl interaction in equatorial compared to the axial lithio sultone.
   (b) Metallation of 2-t-butyl-cis-4,6-dimethyl-1,3 dithiane yields only the equatorial 2-lithio derivative (t-butyl axial) indicating that the thermodynamic tendency of 2-lithium in 1,3-dithianes is greater than 4 Kcal. (E.L.Eliel, IUPAC Meeting, Boston, 1971; Pure and Applied Chemistry, 1971, in press.) These workers have also observed high kinetic preference for the abstraction of 2 equatorial vs. 2-axial hydrogen in a number of 1,3-dithianes.
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