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STEREOELECTRONIC EFFECTS ON METALLATION OF 1,3-DIOXANES

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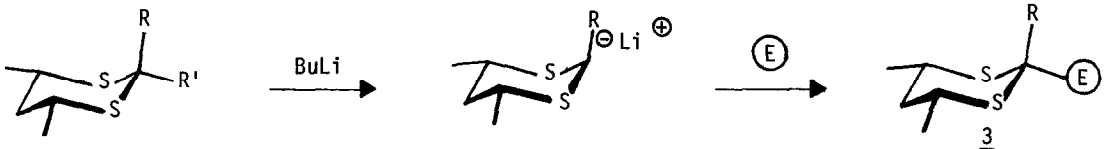
Summary: Metallation of the acetal (H-2) proton in 1,3-dioxolanes, 1,3-dioxanes and open chain acetals is possible only if the proton can occupy an "equatorial-like" conformation.

Several years ago, two of us[1a] described the large (>6 kcal/mol) thermodynamic preference for equatorial electrophilic substitution in conformationally homogeneous 1,3-dithianes after removal of either axially (1) or equatorially (2) situated protons followed by addition of an electrophile (Scheme 1). Kinetically, also, equatorial proton abstraction is preferred.



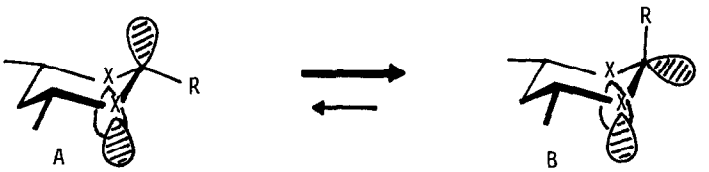
1, R = H, R' = alkyl (or H)
2, R'= H, R = alkyl (or H)

R = alkyl (or H)

R = alkyl (or H)

SCHEME 1

We ascribed these preferences to a stereoelectronic effect (gauche effect[2a]) and ab initio calculations[2b] have, indeed, confirmed that the equatorially disposed carbanion B (Scheme 2)

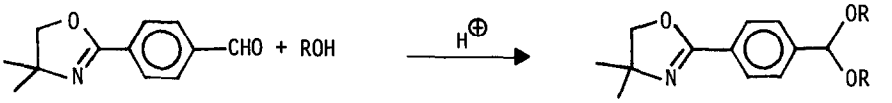


SCHEME 2

should be preferred over the axial one (A). Carbanion A (X = S) is destabilized by the anti-periplanar arrangement of the sulfur lone pair orbitals shown and the carbanion orbital (both filled) whereas carbanion B is stabilized by interaction of the filled carbanion orbital with the antibonding (σ^*) orbital of the S-C bond. According to theory, oxygen compounds should show the same preference for equatorial proton abstraction[2b] even though their overall acidity is less because of the lesser polarizability of O compared to S[2c]. So far, although the stereo-electronic effect has been demonstrated in 1,3-oxathianes[3], it has not yet been verified in purely α-oxygen substituted carbanions (Scheme 2, X = O).

We wish to describe experimental results which fully support Lehn's predictions in 1,3-oxa carbanions and show that considerable differences in proton acidity exist. A variety of 2-substituted acetals 5 was prepared using the p-formyl oxazoline 4[4] as described in Table 1. The use of these acetals was prompted by our earlier work[5] which demonstrated that stable

Table 1



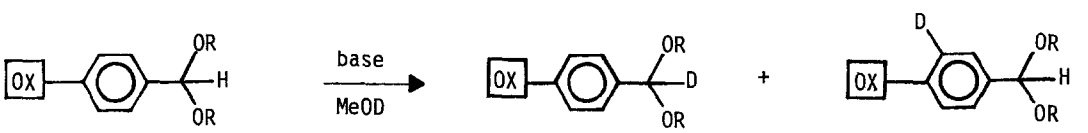
4 5

R-OH	Method[a]	5 (% yield)	mp or bp (°C)
MeOH	A	94	125-130/0.25 mm
$HOCH_2CH_2OH$	B	87	67-68
$HO-(CH_2)_3-OH$	B	94	121-122
$HOCH(CH_3)CH_2CH_2OH$	B	87[b]	70-72
$HOCH(CH_3)CH_2CH(CH_3)OH$	B	88[c]	89-94 (ee) 72-74 (ea)
$HOC(CH_3)_2CH_2CH(CH_3)OH$	B	85	115-116
$HOCH_2CH(Ph)CH_2OH$	B	72	162-163

a) Method of preparation; A $HC(OMe)_3$, p-TsOH, MeOH, reflux; B Diol, toluene, p-TsOH reflux; b) Mixture of equatorial-axial methyl isomers (9:1), determined by hplc (μ-Porosil) 20% $CHCl_3$-hexane, separated by hplc to give pure compound, mp 70-72°; c) Diequatorial methyl isomers (ee) crystallized from mixture. The equatorial-axial (ea) methyl isomer purified by hplc (silica gel, 15% acetone-hexane) mp 72-74°.

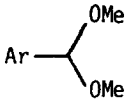
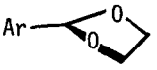
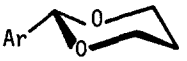
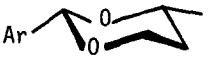
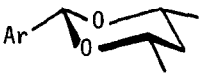
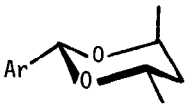
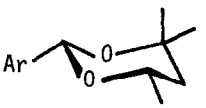
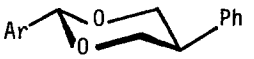
acetal carbanions can be generated thus rendering 5 as a potential acyl anion equivalent. Since all the acetals were prepared under equilibrating conditions, it is safe to assume that in those cases where the acetals are six-membered rings, the 2-aryl substituents occupy the preferred equatorial position.[6]

Metallation of 5 was accomplished either by n-BuLi (THF, -45°, 4 h) and quenching with CH_3OD at -45° or lithium diisopropylamide at -45°, allowing warming to 25° over a period of 24 h and then quenching with CH_3OD. When n-BuLi is used, metallation on the aromatic ring[7] may compete with acetal proton removal; whereas with LDA, no ring metallation occurs and either deuteriated acetal or starting material are the only products recovered (Table 2).



5 6 7

Table 2

Entry	$ArCH(OR)_2$, 5	Base[a]	% 6 (acetal-D)[c]	% 7 (o-D)
1		n-BuLi LDA	100 100	0
2		n-BuLi LDA	100 100	0
3		n-BuLi LDA	30 100[b]	70
4		LDA	0	
5		n-BuLi LDA	0 0	100
6		n-BuLi LDA	0	100
7		n-BuLi LDA	0 0	100
8		n-BuLi LDA	0	100

a) All metallations were complete in less than 2 h although reactions were run longer (n-BuLi, 4 h, LDA, 24 h); b) Slowly metallated and the carbanion decomposed over 24 hr, as evidenced by total disappearance of 2-H proton; c) Determined by H^1-nmr with ±2% accuracy.

Additional significant data for simple 2-phenyl-substituted 1,3-dioxanes are shown in Scheme 3. The numbers below the structures indicate the extent of deuteronation observed (by proton NMR spectroscopy) after treatment of the 1,3-dioxane in question with n-butyllithium (1.5 equivalents) in n-hexane - tetramethylethylene diamine[8] at -50°C for 6 hours followed by quenching with D_2O. (There was no interconversion of compounds 8 and 10 under these conditions.)

8 9 10

100% 25% 0%

SCHEME 3

The following conclusions may be drawn from the data in Table 2 and Scheme 3: 1) A 1,3-dioxane with equatorial H (8) will undergo proton abstraction with base. 2) Conformationally flexible compounds in which the acetal proton may assume "equatorial-like" positions also undergo deprotonation (entries 1 and 2 in Table 2). 3) 1,3-dioxanes with axial H do not undergo proton abstraction under any of the conditions studied (10, Scheme 3 and entries 4-8, Table 3); in the case of the oxazoline-substituted compounds (entries 5-8) ring deuteration occurs instead with BuLi. 4) Conformationally mobile 1,3-dioxanes (9, Scheme 3 and entry 3, Table 2) undergo deprotonation slowly and ring deprotonation may compete under appropriate conditions.

The data clearly support Lehn's prediction of preferred equatorial deprotonation, even in the case of carbanions α to oxygen.

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1. a) E.L. Eliel, A.A.Hartmann and A.G. Abatjoglou, J.Am.Chem.Soc., 96, 1807 (1974). b) See also A.G. Abatjoglou, E.L. Eliel and L.F. Kuyper, ibid., 99, 8262 (1977).

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4. The preparation of 4 was accomplished by treating 2-(p-bromophenyl)oxazoline [J.Org.Chem., 39, 2787 (1974)] with 1.1 equiv of n-BuLi in THF at -78° followed, after 30 min, with 1.5 equiv DMF. Workup by aqueous quenching gave 4 in 94% yield, mp 42-43°.

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7. A.I. Meyers and E.M. Mihelich, J.Org.Chem., 40, 3158 (1975); H.W. Geschwend and A. Hamdan, J.Org.Chem., 40, 2008 (1975).

8. Previously reported attempts to deprotonate 9 - D. Seebach, Angew.Chem.Int.Ed.Eng., 8, 639 (1969); J.N. Hines, M.J. Peagram, E.J. Thomas and G.H. Whitham, J.C.S. Perkin I, 2332 (1973) - either failed or led to cleavage reactions.

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