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CONVINCING EVIDENCE THAT THE ALKYLATION STEREOCHEMISTRY OF CYCLIC α-LITHIO SULFOXIDES IS GOVERNED BY THEIR CHELATED STRUCTURE

Gérard Chassaing, Robert Lett and Andrée Marquet

C.N.R.S.-C.E.R.C.O.A. 2-8, rue H. Dunant 94320 Thiais (France)

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The stereochemistry of electrophilic substitutions of α-lithio sulfoxides has been extensively studied by several groups. The electrophiles (D_2O, ICH_3, CO_2, $(CH_3)_2CO$) were first thought to quench the equilibrium between diastereomeric lithiated intermediates and therefore to reflect the stabilities of the corresponding pyramidal carbanions (1).

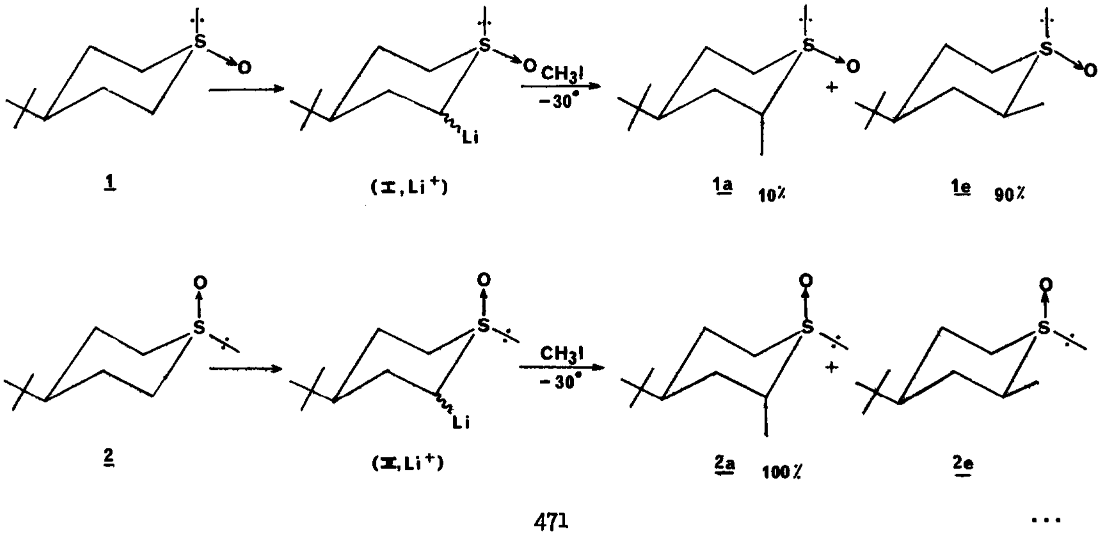
However, such interpretations did not allow the rationalization of many experimental facts, specially the stereoselectivities that we observed with D_2O and ICH_3 in a number of α-substituted 4-t-butyl thiacyclohexane S-oxides (2). We postulated that the course of the reactions could depend on the anion-cation interactions (2b).

Further work of the groups of T. DURST (3) and J.F. BIELLMANN (4) demonstrated the influence of added lithium salts or strong solvating agents on the stereoselectivity of deuteration and methylation of α-lithio benzylmethyl sulfoxide, for which J.F. BIELLMANN and J.J. VICENS proposed a chelate structure.

We bring here a convincing confirmation of the contribution of the cation to the stereochemistry of the methylation. A rationalization is proposed, based on a chelated α-lithiosulfoxide with a *planar* metallated carbon, deduced from our NMR studies.

In our previous work on 4-t-butylthiane oxides, we showed that methylation of the α-lithio carbanions with CH_3I occurs always trans to the S→O bond with a high stereoselectivity (2a) (scheme I), even in highly crowded compounds (2b).

Scheme I



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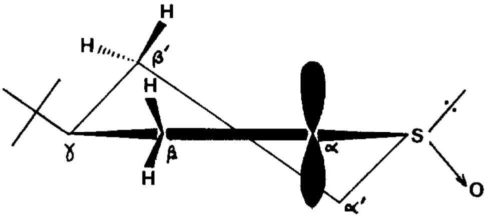
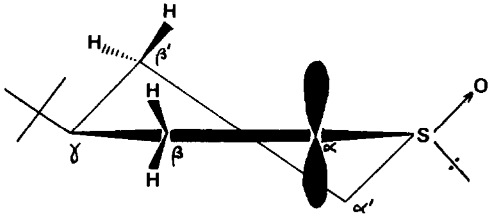
Our ^1H NMR studies of the lithio species (I, Li^+) and (II, Li^+) led us to propose the half-chair structures (I') and (II') with a planar metalated carbon (5).



I'



II'

These compounds have now been studied by ^{13}C NMR. The large increase, with respect to the initial sulfoxide, of the $^1J^{13}C$-H coupling constant of the anionic carbon (ΔJ=+18-19 Hz) confirms its planarity[*]. Furthermore, the whole set of ^1H and ^{13}C NMR data indicate very similar ring geometries for (I, Li^+) and (II, Li^+) and are consistent with structures (I') and (II')[†] (7).

The directing effect of the sulfoxide on the alkylation of these planar carbanions could be due to repulsive effects between the $\overset{+}{S}\rightarrow\overset{-}{O}$ dipole and the developing negative charge of the leaving group I^- or (and) to a large steric hindrance by S→O coordinated to Li^+ externally solvated, very likely in a stable chelated structure.

Indeed, at a given temperature, no or negligible variations of the stereochemistry of methylation by CH_3I and no important kinetic activation of the reaction are observed if HMPA, DABCO or lithium salts are added (7). These results, supporting the hypothesis that the same lithiospecies is always involved[≠], are consistent with a chelate as the reacting species, but they do not bring a direct evidence for it[÷].

Therefore, it was of interest to compare the stereochemistry obtained with CH_3I and with a reagent needing an electrophilic assistance by the Li^+ cation to be reactive. J.F. BIELLMANN and J.J. VICENS already observed that for α-lithiobenzylmethyl sulfoxide in THF, at 0°C, the ratio of methylated products is reversed from 5/1 with CH_3I to 1/1.5 with $O=P(OCH_3)_3$ (9).

We here report analogous results for (I, Li^+) and (II, Li^+) where more pronounced effects are observed (Table I).

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[*] This is consistent with further NMR results concerning other simple α-lithio dialkyl or benzylalkylsulfoxides (6).

[†] The spectra have been run in a 3/1 THF-benzene mixture. We checked that the addition of benzene does not modify the alkylation stereochemistry.

[≠] Consistently, no appreciable variation of ^1H and ^{13}C chemical shifts and H-H, ^{13}C-H coupling constants are observed in THF, with the temperature (7).

[÷] A chelated structure with a planar metalated carbon was also deduced from a detailed ^{13}C NMR study that we have carried out on Ø$SOCH_2Li$. This structure is stable in the presence of HMPA or added lithium salts, and is only broken by cryptates (8).

TABLE I

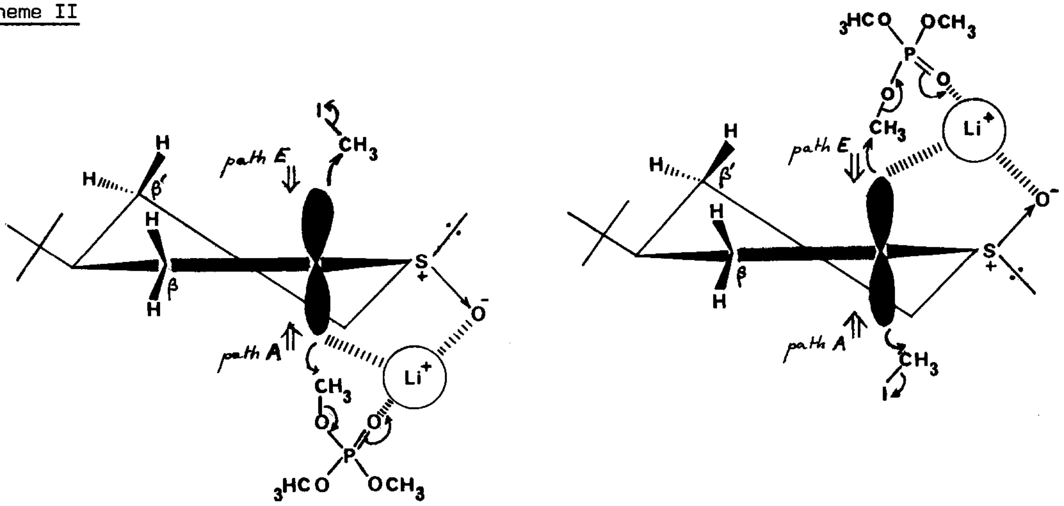
Stereoselectivity of methylation of 4-t-Butyl thiacyclohexane oxides at 20°C*

alkylating agent	medium	1a	1e	2a	2e
CH_3I	THF	20	80	100	0
$(CH_3O)_3P{=}O$	THF	93	7	30	70
$(CH_3O)_3P{=}O$	THF + 10 eq $LiClO_4$	40	60	92	8

* The ratio of isomers is determined by G.L.C. In these experiments, a mixture of αα'-dimethylated isomers (total amount < 10 %) is also present.

Under the same reaction conditions, at 20°C†, the stereoselectivity observed with CH_3I is completely reversed with $O{=}P(OCH_3)_3$: 93 % instead of 20 % of 1a for (I, Li^+), 30 % instead of 100 % of 2a for (II, Li^+). In contrast, in the presence of a large excess of $LiClO_4$ (c.a. 10 eq), the stereochemistry is again that of CH_3I for (II, Li^+) and a weak stereoselectivity is found for (I, Li^+). No salt effect is observed for the reaction with CH_3I. The results may be rationalized as depicted in scheme II.

Scheme II



(I, Li^+)

(II, Li^+)

The approach of methyliodide, governed by steric hindrance, is trans to the chelated face whereas trimethylphosphate, which requires coordination to Li^+, attacks cis to the S→O bond. If trimethylphosphate is activated by an external lithium salt, the directing effect of the chelated lithium cation is lost.

The reaction with CH_3I is much more stereoselective for (II, Li^+) than for (I, Li^+). In contrast, an almost symmetrical situation occurs with $O{=}P(OCH_3)_3$: (I, Li^+) reacts much

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† The reaction with $O{=}P(OCH_3)_3$ is sluggish even at 20°C. A lower temperature could not be used.

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more selectively (93/7) than (II, Li^+) (30/70). This may be due to the difference of steric conformational effects, in an axial type approach between paths A and E, in the half-chairs I' and II' (scheme II). The steric interactions in the transition state are higher for path E in both cases, the corresponding face being hindered by $H\beta'_{ax}$ and the t-butyl group. Thus the steric hindrance difference between both pathes is higher in the case of (II, Li^+).

The same steric factors may also lead to a stronger chelate interaction in I' than in II'. In (I, Li^+) the most favoured intramolecular electrophilic assistance could remain competitive with the assistance of external Li^+, even in large excess, thus giving a more efficient intramolecular electrophilic assistance which could explain why the reaction with $O=P(OCH_3)_3$ in the presence of $LiClO_4$ is more stereoselective with (II, Li^+) than with (I, Li^+).

We think that the results reported here are good evidence for chelated structures in α-lithiosulfoxides and for the predominant role of the cation to explain the alkylation stereochemistry.

REFERENCES

(1) a) R. VIAU, T. DURST, J. Am. Chem. Soc., 95, 1346 (1973) and ref. cit.
    b) K. NISHIHATA and M. NISHIO, Tetrahedron Letters, 1695 (1976) and ref. cit.
(2) a) S. BORY, R. LETT, B. MOREAU and A. MARQUET, Tetrahedron Letters, 4921 (1972).
    b) S. BORY and A. MARQUET, Tetrahedron Letters, 4155 (1973).
(3) T. DURST and M. MOLIN, Tetrahedron Letters, 63 (1975).
(4) J.F. BIELLMANN and J.J. VICENS, Tetrahedron Letters, 2915 (1974).
(5) R. LETT and A. MARQUET, Tetrahedron Letters, 1579 (1975).
(6) R. LETT, G. CHASSAING and A. MARQUET, J. of Organometal. Chem., 111, C 17 (1976).
(7) R. LETT, G. CHASSAING and A. MARQUET, full paper to be published.
(8) G. CHASSAING and A. MARQUET, to be published.
(9) J.J. VICENS, PhD Thesis, Strasbourg, 1977.