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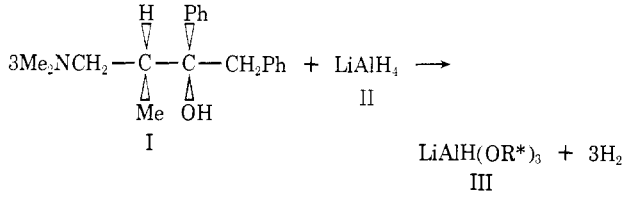
A Reversal in Stereoselectivity Depending upon the Age of a Chiral Lithium Alkoxyaluminohydride Reducing Agent[1]

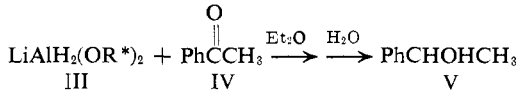
Sir:

We have observed a remarkable time-dependent reversal in stereochemistry during the asymmetric reduction of methyl phenyl ketone with the chiral reducing agent formed by adding an ether solution of 2–3 equiv of (+)-(2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol[2] (I, R* = OH) to approximately 1 mol of lithium aluminum hydride ($LiAlH_4$, II). This reagent is symbolized by $LiAl(OR^*)_2H_2$ or $LiAlH(OR^*)_3$, where R*O represents the chiral alkoxy group from I.[3]



Červinka and coworkers[4] have studied a series of reagents made by treating lithium aluminum hydride with various alkaloids, while Landor and coworkers[5] have studied chiral reductions using reagents prepared from lithium aluminum hydride and various sugar derivatives. Asymmetric reductions using these reagents have been reviewed.[6] In these previous studies no mention was made of dependence of stereoselectivity upon the age of the chiral reagent such as we have observed and report in this communication.

Treatment of methyl phenyl ketone (IV) with reagent III[3] (prepared by mixing 1 molar equiv of lithium aluminum hydride with 2.3 molar equiv of I) within 3 min after its preparation at 20, 3, and −65° gave (*R*)-(+)-methylphenylcarbinol (V) which was 57, 68, and 75% enantiomerically pure, respectively. However,



when this chiral reagent was allowed to stand for 10 min or more, the reaction gave the *S*-(−) enantiomer of V up to a 66% excess, after 1 hr. Thus, either the *R*-(+) or *S*-(−) isomer of V can be obtained by asymmetric reduction in reasonable enantiomeric excess by using the same reagent but varying the age of that reagent between 3 min and 1 hr or more. This same stereochemical reversal was observed when the $LiAlH_4$:I molar ratio was either 1:2 or 1:3. Upon mixing $LiAlH_4$ and I in molar ratios from 1:2 to 1:3 by adding the aminocarbinol I in ether solution to a reasonably concentrated solution of $LiAlH_4$ in ether, the theoretical amount of hydrogen is evolved and a thick precipitate forms. This precipitate goes into solution on standing, on refluxing, or upon addition of a ketone substrate. However, the reversal in stereoselectivity is not associated solely with the nonhomogeneous *vs.* homogeneous nature of the reaction mixture, since a reduction conducted in a large excess of ether immediately after preparing the reagent was homogeneous and gave the *R*-(+) isomer but with reduced stereoselectivity, 29% enantiomeric excess (29% ee).

In a typical experiment a solution containing 1.02 g (3.6 mmol) of I, $[\alpha]^{27}D$ +7.96° (*c* 11.05, EtOH),[2] in 2.0 ml of ether at 0° was added to 3.0 ml of a filtered ethereal solution of lithium aluminum hydride (1.56 mmol) under nitrogen. A thick white precipitate was formed along with an immediate evolution of 3.4 mmol of hydrogen. The flask containing I was rinsed with 1.0 ml of ether and added to the mixture. Three minutes after initial mixing, 120 mg of methyl phenyl ketone (IV) in 1.0 ml of ether was added to the reagent; the precipitate disappeared almost immediately. (*R*)-(+)-Methylphenylcarbinol, 100 mg, 82% yield, $[\alpha]^{20}D$ +29.3° (*c* 8.15, cyclopentane), and the chiral inducing alcohol I, $[\alpha]^{25}D$ +7.93° (*c* 1.6, EtOH), 0.95 g, 94% recovery, were obtained after hydrolysis and work-up of the reaction mixture. Since the maximum rotation of pure V is $[\alpha]^{20}D$ +43.1° (*c* 7.19, cyclopentane), this represents 68% excess of the *R*-(+) enantiomer (68% ee). The same reaction except at −65° gave 75% ee and at room temperature 57% ee. When this reagent was made exactly as above but stirred for various lengths of time before the ketone was added, the stereoselectivity changed as follows: 4 min, 20% ee *R*-(+); 8 min, 15% ee *S*-(−) (the precipitate just dissolves after swirling for 8 min; 40 min, 62% ee *S*-(−); reflux 10 min and stirred overnight, 66% ee.

Superficially this phenomenon resembles that reported by Mislow and coworkers[7] in the asymmetric hydroboration of *cis*-3-hexene using the chiral reagent "di-3-pinanylborane"; use of freshly prepared reagent followed by oxidation gave (*R*)-(−)-3-hexanol, 20.6% ee, while use of the same reagent which had been warmed and allowed to stand 21 hr gave the (*S*)-(+)-3-hexanol, 10.7% ee. A similar finding was reported for the hydroboration of benzonorbornadiene.

The fundamental reason behind the time-dependent stereochemical reversals in these asymmetric hydroborations and our present examples of asymmetric reduction may be related or entirely different. In any event, these results point out the care required in defining reaction conditions in such stereochemical studies and

(1) We gratefully acknowledge support of these studies by the National Science Foundation, Grant No. NSF GP-27448.

(2) A. Pohland and H. R. Sullivan, *J. Amer. Chem. Soc.*, 73, 4458 (1953); 77, 3400 (1955).

(3) This formulation is intended to define the combining ratio of the reagents used in its preparation but explicitly should not be interpreted as indicating a specific structure or state of aggregation of the reagent.

(4) (a) O. Červinka, *Collect. Czech. Chem. Commun.*, **30**, 1684 (1965); O. Červinka and O. Bělovský, *ibid.*, **32**, 3897 (1967); **30**, 2487 (1965).

(5) (a) S. R. Landor, B. J. Miller, and A. R. Tatchell, *Proc. Chem. Soc.*, 227 (1964); (b) S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. C*, 1822 (1966); 197 (1967); (c) S. R. Landor and A. R. Tatchell, *ibid.*, 2280 (1966).

(6) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 202–210.

(7) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Amer. Chem. Soc.*, **90**, 4877 (1968).

the necessity for reporting homogeneity or nonhomogeneity in such reaction mixtures. These findings introduce an added caution in the application of such systems for stereochemical correlations and in the proposal of precise transition-state stereochemistries to explain such results until extensive studies on the system have been completed. We are currently engaged in exploring the many variables involved in this and related systems.

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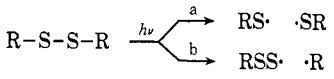
Photo-CIDNP from Carbon–Sulfur Cleavage of Alkyl Disulfides

Sir:

The literature on the photolysis of simple disulfides, which serve as a model for studying the photoreactions of sulfur-containing proteins, is sparse but identifies two distinct photochemical processes (Scheme I).

Scheme I



Sulfur–sulfur photocleavage[1] (path a), both direct and sensitized, to yield thiyl radicals is well known in both gas[2] and liquid[3] phases. Carbon–sulfur cleavage (path b) during photolysis has been observed[4] and shown to be a sensitized process for certain disulfides in the liquid phase.[5] Important mechanistic details, such as the nature of the excited state, the mode of its deactivation, and the relationship between the sensitized and unsensitized photolyses, remain to be elucidated, however, before the role of this process in the photodynamic inactivation of enzymes can be evaluated.

We wish to report photo-CIDNP evidence which provides additional insight into the mechanism of C–S cleavage in solution. The spectrum in Figure 1 was recorded[6] during photolysis of 0.08 *M* *tert*-butyl disulfide **1** in benzene solution inside the modified probe of an HA-60 spectrometer, using the unfiltered beam of

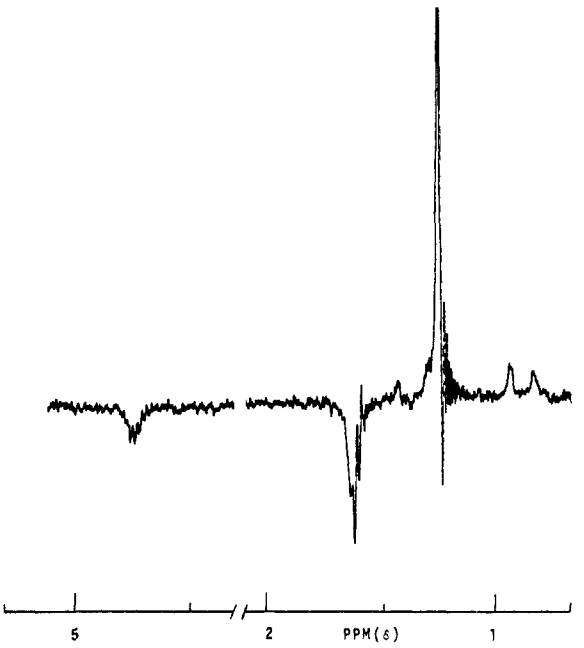


Figure 1. Photo-CIDNP spectrum recorded during irradiation of 0.08 *M* *tert*-butyl disulfide in benzene. The peak at δ 1.25 (s) is starting material, the peaks at δ 1.63 and 4.75 are isobutylene, and the peak at δ 0.90 (d) is isobutane. When irradiation is interrupted, only the peak at δ 1.25 remains.

a 1000-W high-pressure mercury arc lamp. Photolysis in the presence of either acetophenone or benzophenone yielded similar but more strongly enhanced signals. The polarized products are isobutylene (**3**, CH_3 and vinyl protons emission) and isobutane (**4a**, CH_3 protons enhanced absorption). Application of the simple rules based on the radical pair model of CIDNP[7] suggests a cage disproportionation between *tert*-butyl[8] and *tert*-butylperthiyl[9] radicals proceeding from a *triplet* excited state of the disulfide as the source of the isobutylene polarization. Cage escape by *tert*-butyl radical to yield polarized isobutane (possibly by hydrogen abstraction from starting material[10]) is also consistent with this mechanism (Scheme II).

Diffusive encounters of *tert*-butyl and *tert*-butylperthiyl radicals are an additional source of the polarized products, but one which can be diminished by the use of scavengers. The addition of 0.025 *M* *n*-butanethiol decreased the polarization of **3**, most probably because *tert*-butyl radicals are scavenged efficiently. Indeed, the polarization of **4a** was slightly increased, presumably because the shorter lifetime of the *tert*-butyl radical allowed less proton relaxation in the radicals escaping from a geminate encounter. The addition of higher concentrations of the mercaptan (up to 0.3 *M*), however, caused no further change in the intensity of the isobutylene lines. This residual polarization must result from a triplet–geminate pair interaction which is not disturbed by moderate scavenger concen-

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(2) P. M. Rao, J. A. Copeck, and A. R. Knight, *Can. J. Chem.*, **45**, 1369 (1967).
(3) C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1137 (1959).
(4) A. B. Callear and D. R. Dickson, *Trans. Faraday Soc.*, **66**, 1987 (1970).
(5) (a) G. W. Byers, H. Gruen, H. G. Giles, H. N. Schott, and J. A. Kampmeier, *J. Amer. Chem. Soc.*, **94**, 1016 (1972); (b) H. Gruen, H. N. Schott, G. W. Byers, H. G. Giles, and J. A. Kampmeier, *Tetrahedron Lett.*, 3925 (1972).
(6) This photolysis apparently is not solvent sensitized since similar spectra (isobutylene, methylene) are obtained in carbon tetrachloride and in cyclohexane. It also seems unlikely that the polarization observed is due to the presence of an impurity capable of sensitizing this reaction since the polarization from **3** during photolysis of **1** is not smaller in more highly purified samples. Secondary photolysis of products was not occurring since the spectra reported were obtained immediately after irradiation was started and remained unchanged for several minutes afterward. Deoxygenation of the samples by nitrogen bubbling produced no change in the observed spectra.
(7) H. R. Ward, *Accounts Chem. Res.*, **5**, 18 (1972); R. G. Lawler, *ibid.*, **5**, 25 (1972).
(8) g = 2.0025: R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).
(9) g = 2.01 by analogy to ethyl thiyl radical: A. Torikai, S. Sawada, F. Fueki, and Z. Kuri, *Bull. Chem. Soc. Jap.*, **43**, 1617 (1970).
(10) Stronger isobutane polarization is observed in the presence of greater amounts of starting compound despite the unchanging isobutylene polarization, indicating more rapid scavenging of *tert*-butyl radicals by **1** or a minor impurity such as *tert*-butylthiol.