79839-57-9; 9, 19297-11-1; 3-methyl-4-propylcyclohex-2-en-1-one, 79839-58-0.

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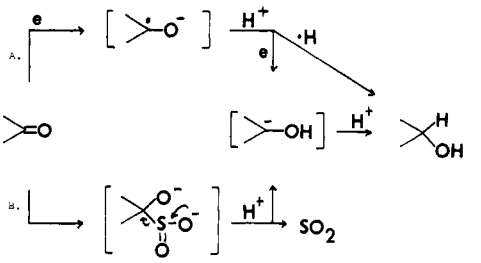
Mechanism of Sodium Dithionite Reduction of Aldehydes and Ketones

Summary: A reduction mechanism involving an α-hydroxy sulfinate intermediate has been suggested for the title reaction, on the basis of a radical ring-opening probe and the source of the hydrogen.

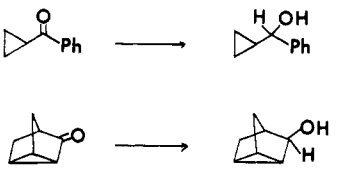
Sir: Sodium dithionite is a readily available, inexpensive reducing agent which is capable of reducing a variety of functional groups, e.g., nitro,[1] nitroso,[1] diazonium salts,[2] various pyridinium salts,[3] imines,[4] oximes,[4] aldehydes and ketones,[5] and α-halo ketones.[6] The reducing power of $Na_2S_2O_4$ is known to be generally enhanced in basic pH.[5,6] Sodium dithionite is a unique reducing agent in that it reduces a variety of pyridinium salts exclusively to the 1,4-dihydropyridine.[3,7] This reactivity has been explained in terms of the 1,4-addition of the SO_2 dianion equivalent to form a sulfinate intermediate, followed by the loss of SO_2.[8] More recently, however, Krapcho and Seidman studied the stereochemistry of the $Na_2S_2O_4$ reduction of cyclic ketones and found that cyclohexanones yielded mainly equatorial alcohols while bicyclic ketones gave primarily endo alcohols. On the basis of this stereochemical result, they suggested that reduction of the carbonyl group by $Na_2S_2O_4$ proceeded by an electron-transfer mechanism in a manner similar to that of Li–liquid NH_3–alcohol reduction of the ketones.[9]

In connection with our interest in the mechanism of the NADH-dependent alcohol dehydrogenase reactions utilizing the coenzyme recycling method with excess $Na_2S_2O_4$,[10] we have also examined the mechanistic possibilities of $Na_2S_2O_4$ reduction of carbonyl compounds. We have considered two basically distinct mechanisms. The first mechanism involves stepwise electron transfer from the reducing agent to the carbonyl group to form a ketyl radical intermediate. The ketyl radical then can either abstract a hydrogen atom from the medium, dimerize to pinacol, or undergo further reduction (Scheme I, pathway A). The second pathway involves a nucleophilic addition of the SO_2 dianion or its equivalent to the carbonyl group to form an intermediate α-hydroxy sulfinate which then loses SO_2 to give the carbanionic species (Scheme I, pathway B).[11]

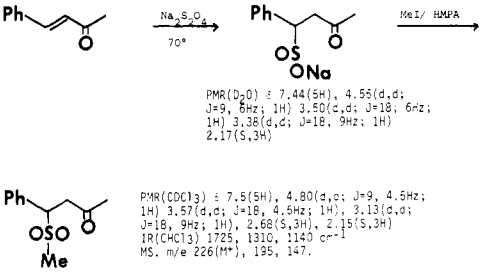
Scheme I



Scheme II



Scheme III



We have reasoned that if the ketyl radical were involved as a distinct intermediate as in dissolving-metal reductions,[13] the $Na_2S_2O_4$ reduction of cyclopropyl ketones should yield the ring-opened products. Thus, reductions of phenyl cyclopropyl ketone and nortricyclanone were carried out with $Na_2S_2O_4$ and $NaHCO_3$ in aqueous DMF solution at 120 °C under N_2.[9] The reduction products were found to be phenylcyclopropylcarbinol and *exo*-nortricyclyl alcohol, respectively, and careful product analyses by GC and NMR failed to reveal the presence of any ring-opened products (Scheme II).

Next, the source of the hydrogen in the reduced product was examined by running the $Na_2S_2O_4$ reduction of benzaldehyde in D_2O–DMF (1:1 by volume) at 105 °C in the presence of excess $NaHCO_3$. The benzyl alcohol product showed the following properties: mass spectrum, *m/e* (relative intensity) 108 (47.0), 109 (72.3), 110 (5.9), 111 (0.7); ^1H NMR ($CDCl_3$) δ 2.18 (br s, 1 H, OH), 4.60 (t, 1 H, J = 1.8 Hz, CHD), 7.31 (br s, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 64.91 (t, J = 22 Hz), 126.87, 127.54, 128.45, 140.68. These spectral data unambiguously indicate that the protic hydrogen of D_2O rather than the hydrogen atom of DMF was selectively incorporated into the benzylic position of the product.[14] The above results suggest that

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(2) Grandmougin, E. *Chem. Ber.* **1907**, *40*, 422.
(3) Mauzerall, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261.
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(5) Minato, H.; Fujie, S.; Okuma, K.; Kobayashi, M. *Chem. Lett.* **1977**, 1091; De Vries, J. G.; van Bergen, T. J.; Kellogg, R. M. *Synthesis* **1977**, 246.
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(9) Krapcho, A. P.; Seidman, D. A. *Tetrahedron Lett.* **1981**, 179.
(10) Taylor, K. E.; Jones, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 5689.
(11) Although dithionite ions are known to dissociate reversibly to SO_2 anion radicals in aqueous solution,[12] the identity of the immediate reducing species is not yet clear. Electron exchange may be possible between the anion radicals to form SO_2 and the SO_2 dianion as reducing species.
(12) Atkins, P. W.; Horsfield, A.; Symons, M. C. R. *J. Chem. Soc.* **1964**, 5220.
(13) Bellamy, A. J.; Campbell, E. A.; Hall, I. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1347. Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 374.

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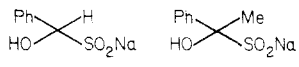
if the ketyl radicals are involved in these reductions, their lifetimes are extremely short, most likely due to rapid second electron transfer to form the carbanion. However, this possibility is rather unlikely in view of the fact that the dissolving-metal reduction of cyclopropyl ketones invariably gives the ring-opened product despite the well-known efficiency of the second electron redution of the conditions.[13].

When the progress of the $Na_2S_2O_4$ reduction of benzaldehyde was monitored by ^1H NMR, the benzaldehyde signal (δ 10.10) was quickly replaced, after mixing, by a signal at δ 5.50 (s, 1 H), which could be most reasonably ascribed to the α-hydrogen in addition product 1. Similarly, the acetophenone signal at δ 2.66 (s, 3 H) was replaced by a singlet at δ 1.97 (s, 3 H), which could again be attributed to the methyl group of the adduct 2. The rapid adduct formation has also been observed in the attempted $Na_2S_2O_4$ reduction of α,β-unsaturated ketones. Conjugated ketones have been found to be resistant to the reduction by $Na_2S_2O_4$, and the reason for this behavior appears to be due to formation of the 1,4-adduct in which reducibility of the carbonyl group is greatly diminished (Scheme III).[15]



1 2

(14) Similar results were obtained from the $Na_2S_2O_4$ reductions of benzaldehyde in D_2O–dioxane and of acetophenone in D_2O–DMF.

In summary, we suggest that pathway B (Scheme I) is more likely in operation in the $Na_2S_2O_4$ reduction of the "normal" carbonyl group, although the stepwise electron-transfer process (pathway A) may become available if the adduct formation becomes difficult due to steric reasons.

Acknowledgment is made to the Robert A. Welch Foundation (Grant No. A-752) and the National Institutes of Health for the financial support of this work.

Registry No. 1, 14339-77-6; 2, 79855-25-7; $Na_2S_2O_4$, 7775-14-6; phenyl cyclopropyl ketone, 3481-02-5; nortricyclanone, 695-05-6; benzaldehyde, 100-52-7; benzyl alcohol, 100-51-6; acetophenone, 98-86-2; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; sodium 1-phenyl-3-ketobutylsulfinate, 79855-26-8; methyl 1-phenyl-3-ketobutyl sulfone, 79855-27-9; 4-methyl-3-penten-2-one, 141-79-7; sodium 2-methyl-4-ketopent-2-ylsulfinate, 79855-28-0; methyl 2-methyl-4-ketopent-2-yl sulfone, 68152-40-9.

Supplementary Material Available: Experimental details for the preparation and the reduction of the substrates (2 pages). Ordering information is given on any current masthead page.

(15) The 1,4-adduct obtained from mesityl oxide was similarly methylated to give the sulfone product, $Me_2C(SO_2Me)CH_2C(O)CH_3$: ^1H NMR ($CDCl_3$) δ 2.92 (s, 2 H), 2.83 (s, 3 H), 2.22 (s, 3 H), 1.57 (s, 6 H); IR ($CHCl_3$) 1720, 1295, 1108 cm^{-1}; mass spectrum, m/e 178 (M^+, not observed), 99 ($M^+ - SO_2Me$), 43.

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Additions and Corrections

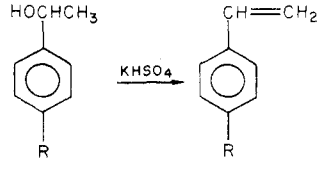
Vol. 45, 1980

Robert V. Hoffman,* Richard D. Bishop, Patricia M. Fitch, and Richard Hardenstein. Anhydrous Copper(II) Sulfate: An Efficient Catalyst for the Liquid-Phase Dehydration of Alcohols.

Page 917. Professor R. Arshady has kindly called attention to the fact that there are several references in the literature to instances where potassium bisulfate gives styrenes by dehydration in yields higher than those reported for this catalyst in our paper.[1-4]

1. D. Bailey, D. Tirrel, and O. Vogel, *J. Polym. Sci. Polym. Chem. Ed.*, **14**, 2725 (1973).
2. B. B. Corson, W. G. Hentzelman, L. H. Schwartzman, H. E. Tiepenthal, R. J. Lokken, J. E. Nickel, G. R. Atwood, and F. G. Pavlic, *J. Org. Chem.*, **23**, 544 (1958).
3. P. Ferruti and A. J. Fere, *J. Polym. Sci. A-1*, **9**, 3671 (1971).
4. R. Arshady and A. Ledwith, *Makromol. Chem.*, **179**, 819 (1978).

In particular he cites the dehydration of para-substituted 1-phenyl ethanols i which give the corresponding styrenes ii in 71–77% yields. With exception of ref 1, all these dehydrations involve activated phenyl ethanols. We have not tested these particular substrates, but we note that for those activated compounds we have tested, yields of dehydration with copper(II) sulfate increase noticeably.



i ii

R = H, OAc, $OCH_2C_6H_5$, CH_2OCH_3

C. H. Heathcock,* C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe. Acyclic Stereoselection. 7. Stereoselective Synthesis of 2-Alkyl-3-hydroxy Carbonyl Compounds by Aldol Condensation.

Page 1066. Abstract, "(±)-ephedrine (**51**)".
Page 1077. Table VIII, the column headings should be interchanged.
Page 1079. Line 5 of second column, "9.36 g of 2-(1-ethoxyethoxy)-2-methylpropionitrile".
Page 1079. Line 14 of second column, "pure hydroxy ketone **38**".

Daniel H. Rich,* Byung Jo Moon, and Amrit S. Boparai. Synthesis of (2*S*,3*R*)-3-Amino-2-hydroxy-5-methylhexanoic Acid Derivatives. Application to the Synthesis of Amastatin, an Inhibitor of Aminopeptidases.

Page 2289. The values given for the 3-amino-2-hydroxy-5-methylhexanoic acid derivatives are assigned to the wrong diastereomers in Table I. The properties of **5a** and **5b** should be interchanged; **6a** and **6b** should also be interchanged. These errors were introduced while preparing the original table and have no effect on the other published results.