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Reduction of Aldehydes and Ketones by Sodium Dithionite

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Conditions have been developed for the effective reduction of aldehydes and ketones by sodium dithionite, \( \text{Na}_2\text{S}_2\text{O}_4 \). Complete reduction of simple aldehydes and ketones can be achieved with excess \( \text{Na}_2\text{S}_2\text{O}_4 \) in \( \text{H}_2\text{O} \)/dioxane mixtures at reflux temperature. Some aliphatic ketones, for example, pentanone and 4-heptanone, are reduced only sluggishly under these conditions. Good conversions can be achieved, however, by adding dimethylformamide to the reaction mixture, again held at reflux. The reductions of 17 compounds are described and the scope of the reaction is discussed. \( \alpha \)-Hydroxy sulfinates are suggested as probable intermediates in these reductions.

In 1870 Schützenberger described the reducing powers of a solution of sodium bisulfite in which zinc turnings had been dissolved. The reducing substance, which Schützenberger named sodium hydrosulfitre, was isolated and was assigned the erroneous formula \( \text{NaHSO}_2\cdot\text{H}_2\text{O} \). This substance, later obtained pure by others, was shown in fact to be \( \text{Na}_2\text{S}_2\text{O}_4 \cdot2\alpha \cdot\text{H}_2\text{O} \), commonly known as sodium dithionite.

Over the years sodium dithionite has found many applications. It has achieved commercial importance as a reducing agent in vat dyeing and as a bleaching agent. In biochemistry sodium dithionite is used to prepare the reductant in NADH recycling experiment.26

Table I. For satisfactory yields to be obtained, the aqueous reaction medium must be mildly basic to prevent decomposition in aqueous solution to chiefly thiosulfate and sulfite.27

R' \( = \) alkyl, \( \alpha \)-alkyl, aryl or H

\[
\text{R}^2 = \text{alkyl, aryl or H}
\]
Reduction of Aldehydes and Ketones


Table I. Reductions of Aldehydes and Ketones to Alcohols with Na₂S₂O₄

| entry no. | substrate | product | solvent | yield, %
|-----------|-----------|---------|---------|-----
| 1         | n-hexanal | n-hexanol| H₂O     | 83  |
| 2         | benzaldehyde | benzyl alcohol | H₂O-dioxane | 84  |
| 3         | 2-furfuryl aldehyde | 2-furyl alcohol | H₂O | 90  |
| 4         | cyclohexanone | cyclohexanol | H₂O | 80  |
| 5         | 4-tert-butylocyclohexanone | 4-tert-butylocyclohexanol (cis/trans = 13/87) | H₂O-dioxane | 84b |
| 6         | adamantanone | 2-adaman tanol | H₂O-dioxane | 97c |
| 7         | camphor | no reaction owing to sublimation | H₂O-dioxane |  |
| 8a        | 4-heptanone | 4-heptanol | H₂O-dioxane | 25d |
| b         | 2-pentanone | 2-pentanol | H₂O-dioxane | 33d |
| b         | 10          | 2-octanone | 2-octanol | H₂O-DMF | 85a |
| b         | 11a        | cyclopentanone | cyclopentanol | H₂O-dioxane | 75f |
| b         | 12a        | 2-norbornanone | 2-norbornanol (exo/endo = 17/83) | H₂O-dioxane | 44d |
| b         | 13a        | cycloheptanone | cycloheptanol | H₂O-dioxane | 40h |
| b         | 14         | levulic acid (4-oxopentanoic acid) | (4-hydroxy pentanoic 1,4-lactone) | H₂O | 54i |
| b         | 15a        | acetophenone | 1-phenylethanol | H₂O-dioxane | 30d |
| b         | 16a        | benzophenone | diphenylmethanol | H₂O-dioxane | 50d |
| b         | 17         | 4-bromobenzophenone | (4-bromophenyl)phenylmethanol | H₂O-DMF | 94 |
| 18        | ethyl phenylglyoxalate | ethyl mandelate | H₂O | 24  |

a Isolated yields of pure product unless otherwise indicated; purity was at least 99% as determined by GLC. b Isolated as a mixture of cis and trans isomers. The major isomer was obtained in pure form by crystallization from n-heptane and identified as the trans isomer by means of 1H NMR. c An acid-soluble impurity, likely 2-(dimethylamino)pentane, was also formed in 13% yield and was removed by acid washing. d 2-(Dimethylamino)octane isolated as byproduct in 14% yield. e Dimethylcyclopentylamine isolated as byproduct in 48% yield. f Isolated as a mixture of exo/endo isomers. Stereochemistry assigned by GLC comparison with product mixture obtained from reduction of 2-norbornanone with LiAlH₄. g Isolated by continuous extraction with ether. h mp 65.5-66.5 °C (authentic sample, mp 69 °C). i Reaction carried out at room temperature; complete after 6 h. Apparently considerable hydrolysis occurs.

In hot aqueous solution aldehydes are reduced smoothly to the corresponding alcohols (entries 1–3 in Table I) and the carbonyl group of levulinic acid is also readily reduced (entry 14) as are the carbonyl groups of cyclohexanone, 4-tert-butylocyclohexanone, and adamantanone (entries 4–6). These conditions are not adequate, however, for conversion of other aliphatic and aromatic ketones (Table I, entries 8a, 9a, 11a–13a, 15a, 16a).

We finally found that the problem of incomplete conversion could be abated by using dimethylformamide (DMF) as a 1:1 cosolvent with H₂O. Conversions of aromatic ketones under these conditions are virtually complete and the degree of conversion of other ketones is raised considerably. On the other hand the use of cosolvents such as chlorinated hydrocarbons, ethers, alcohols (ethanol, n-propanol, or n-butanol), or tetramethylurea, each as a 1:1 mixture with H₂O, led only to decreased yields.

With DMF as cosolvent some reductive amination reminiscent of that seen in the Leuckart reaction occurs, especially with methyl ketones and cyclopentanone (footnotes e–g, Table I). Apparently, Na₂S₂O₄ serves also a reductant in this reaction (eq 2). These amines formed as side products are easily removed, however, by extraction with acid.

The reactions of Na₂S₂O₄ with either benzonitrile or ethyl benzoate led only to hydrolysis of these substrates: diphenylacetone, N-methylpyrrolidone, and benzoic acid were not reduced. Both phenacyl bromide and phenacylphenylmethylsulfonium tetrafluoroborate were reduced to acetophenone at room temperature in H₂O with Na₂S₂O₄, but phenacyl benzoate was unaffected under these conditions.

B. Mechanism of Reduction. It has long been known that the reaction of Na₂S₂O₄ with some aldehydes and ketones under aqueous basic conditions at room or lower temperature can lead to α-hydroxy sulfinates (1) as shown in eq 3.

For examination of the possibility that α-hydroxy sulfinates could be intermediates in the reductions reported here, 1a derived from benzaldehyde was synthesized. This was added to a refluxing mixture of dioxane-H₂O. The reaction product consisted of a 65/35 mixture of benzyl alcohol and benzaldehyde (eq 4). The formation of 1a is known to be reversible, explaining the presence of benzaldehyde. The results of the above experiment

provide in our opinion good suggestive evidence for \( \alpha \)-hydroxy sulfinates in the reactions examined by us. The absence of detectable amounts of pinacol products in this or other reductions argues against direct transfer of a hydrogen atom to an \( \alpha \)-hydroxyalkyl radical formed by one electron transfer steps.

The reductive decomposition of an \( \alpha \)-hydroxy sulfinate (eq 5) involves (possibly concerted) loss of SO\(_2\) and is represented by the reaction:

\[
S_2O_4^{2-} + \text{H}_2 \text{O} \rightarrow \text{HSO}_3^- + \text{HSO}_3^-
\]

(6)

Little known of the thermal chemistry of \( \alpha \)-hydroxy sulfinates, but precedent for the postulated loss of SO\(_2\) can be found in the reported thermal decompositions with loss of SO\(_2\) of several allylic sulfinic acid derivatives. 34-37

There is abundant evidence that SO\(_2\) \(-\) rapidly fragments in aqueous solution; the kinetic schemes are complicated and the product bands are often not complete. 65 In neutral or mildly acidic solution eq 6 and 7 have been suggested as important contributors to the overall decomposition. The sulfoxylate anion, HS\(_2\O\), should be sufficiently nucleophilic to lead to the \( \alpha \)-hydroxy sulfinate (eq 8) in a manner analogous to bisulfitie (HS\(_2\O\)).

\[
S_2O_4^{2-} + \text{H}_2 \text{O} \rightarrow \text{HSO}_3^- + \text{HSO}_3^-
\]

(7)

\[
\text{HSO}_3^- + \text{SO}_4^{2-} \rightarrow \text{HSO}_3^- + \text{SO}_3^{2-}
\]

(8)

Addition. Decomposition as shown in eq 7 could account for the need of roughly 5 equiv of Na\(_2\)S\(_2\O\)\(_4\) necessary for complete reduction of a carbonyl compound.

The importance of the reactions of eq 6 and 7 has been questioned, however, chiefly on kinetic grounds. 38 Rate expressions for S\(_2\)O\(_4\) \(-\) decomposition usually contain terms one-half order in S\(_2\)O\(_4\) \(-\). Moreover, the SO\(_2\) \(-\) radical anion (2) is readily detected by electron spin resonance in solutions of decomposing S\(_2\)O\(_4\) \(-\). These observations are in accord with eq 9 being an important (reversible) step.

The radical anion 2 has also been convincingly implicated as the reductant of various biological materials. 4

The reaction steps given in eq 9-11 represent another sequence for the formation of \( \alpha \)-hydroxy sulfinates with 2 as the reductant. Decomposition as illustrated in eq 5 affords alcohol obtained as an end product.

\[
\text{S}_2\text{O}_4^{2-} \rightarrow 2\text{SO}_2^-
\]

(9)

**Experimental Section**

Melting points were determined on a Mettler FP-2 melting-point apparatus equipped with a Mettler FP-21 microscope. Elemental analyses were performed in the microanalytical department of this laboratory. Infrared spectra were recorded on a Unicam SP-2000 infrared spectrophotometer or a Perkin-Elmer 237 grating infrared spectrophotometer. \(^1\)H NMR spectra were recorded on a Varian A-60, a JOEL C-60HL, or a Hitachi Perkin-Elmer R242B spectrometer. Tetramethylsilane (Me\(_4\)Si) was used as an internal standard. A Varian XL-100 was used for recording the \(^{13}\)C NMR and 100-MHz \(^1\)H NMR spectra. Mass spectra were obtained on an AEI MS-902 instrument.

**General Procedure for Reduction of Aldehydes and Ketones with Na\(_2\)S\(_2\O\)\(_4\)**

A solution of substrate (50 mmol) in dioxane (175 mL) or DMF for more difficulty reducible substrates is added to water (175 mL) containing NaHCO\(_3\) (27.5 g). When DMF was used as cosolvent, in some cases it was necessary to add some more water during the reduction to prevent gel formation.) When no cosolvent is used, the substrate is added neat. Sodium dithionite (12.5 g) is added and the reaction mixture refluxed for 4 h during which time three additional 12.5-g portions of Na\(_2\)S\(_2\O\)\(_4\) are added. (A total of three 12.5-g portions of Na\(_2\)S\(_2\O\)\(_4\) sufficed for the reductions of benzaldehyde, furfuraldehyde, 4-tert-butylcyclohexanone, adamantane, and norbornanone.) The reaction is carried out under an atmosphere of nitrogen. After the mixture cooled to room temperature, water is added until the solution becomes clear and thereafter the solution is extracted with ether (furfuryl alcohol and \( \gamma \)-valerolactone were isolated by continuous extraction with ether for 7 and 72 h, respectively). When DMF is used as cosolvent the ether extracts are back-washed twice with water to remove traces of DMF.

After the solution is dried (MgSO\(_4\)) and the ether is removed, the products are isolated by either distillation or recrystallization. Identification is based on melting or boiling points, infrared and \(^1\)H NMR spectra, and comparison with authentic materials. All reductions were carried out on a 2-mmol scale and for purposes of isolation were also done on a 50-mmol scale. When products were not isolated GLC was used to determine the degree of conversion and/or product ratio. In all those cases a 6 ft \( \times \) 1/8 in. Carbowax 20 M on Chromosorb WAW 80-100-mesh column was used.

**Reduction of 2-Octanone**

2-Octanone (6.41 g, 50 mmol) was subjected to the conditions described above for the reduction of aldehydes and ketones; DMF was used as cosolvent. After workup by the usual procedure, the combined ethereal layers were extracted with two 50-mL portions of 2 N HCl followed by washings with water and saturated NaHCO\(_3\). The ethereal extract was dried (MgSO\(_4\)) and was removed. The residue was subjected to kugelrohr distillation to give 4.90 g (37.6 mmol, 75% yield) of 2-octanone. The combined acid layers were washed once with ether and then neutralized with a 2 N NaOH solution. The aqueous solution was extracted twice with ether and the combined ethereal layers were washed with water. After the solution was dried
(Na₂SO₄) and solvent was removed, the residue was subjected to kugelrohr distillation to give 1.11 g (7.0 mmol, 14% yield) of mp 232.3-233.1 °C (lit.4 mp 240 °C). 2-(dimethylamino)octane: 1470, 2770, 2870, 2960 cm⁻¹; 'H NMR (CDCl₃) 5 2.09 (s, 6 H), 1.24 (br C, 76.18; H, 14.75; N, 8.94.

Analysis. Calcd for C₁₀H₁₉N: C, 76.36; H, 14.74; N, 8.90. Found: C, 76.18; H, 14.75; N, 8.94.

Synthesis and Decomposition of Sodium Benzyloxydibenzosulfinate (1a). Compound 1a was synthesized by following Bazlen’s method: IR (KBr pellet) 655, 690, 895, 1050, 2600-3700 cm⁻¹ (no absorption due to benzaldehyde carbonyl could be detected). To 40 mL of a refluxing dioxane-H₂O (1:1) mixture 4.80 g of Na₂S₂O₄ was added and the mixture was stirred under nitrogen. To the solution upon GLC analysis; this comes from reversible for-

Reduction of Phenacyl Bromide with Na₂S₂O₄. A solution of phenacyl bromide (400 mg, 2 mmol) in 7 mL of ether was added to a solution of 1.10 g of NaHCO₃ in 7 mL of H₂O; 2.00 g of benzyl alcohol the solution upon GLC analysis; this comes from reversible for-

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Registry No. la, 14339-77-6; Na₂S₂O₄, 7775-14-6; 2-(dimethylamino)octan-1-ol, 7378-97-4; phenacyl bromide, 70-11-1; methylphenacylp phenylsulfonium tetrafluoroborate 45 was carried out as described above for phenacyl bromide. The sulfonyl salt was added neat to the mixture because of its insolubility in ether. After 1.5 h the mixture was worked up as usual. The sulfonyl salt (666 mg, 2.00 mmol) gave 486 mg of liquid residue, the sole constituents of which were acetonaphenone (108 mg, 0.9 mmol, 45% yield).

At 1% of the solvent w,w removed, the residue was subjected to GLC (Carbowax, vide supra) and 1H NMR. Both benzyl alcohol and benzaldehyde were present in a 65:35 ratio. A solution of 1a in cold dioxane-water did not contain benzyl alcohol, though a marked amount of benzaldehyde was found to be present in the solution upon GLC analysis; this comes from reversible forma-

R(3-

Reactions of the Cyclopropanone Hemiketal Magnesium Salt with Some Nucleophilic Reagents

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Cyclopropanone (5), 1-(arylethynyl)cyclopropanone (7), 1-(3-hydroxypropyl)cyclopropanone derivative 10, 1-(2-propynyl)cyclopropanone (14), cyclopropanone cyanoacrydine, benzyldencyclopropanes 32, and ethyl cyclopropyldienecetate (38) have been prepared from the magnesium salt of cyclopropanone hemiketal 3. 3-Cyclopropyldiene-1-propenyl (12) and 3-cyclopropyldiene-1-propyne (16) have been obtained from the cyclopropanes 10 and 14, respectively. Some reactions of this new synthon were specific. On the other hand, 3 did not undergo the nucleophilic addition of sulfur and nitrogen ylides; it underwent oxidizing ring opening with Br₂ZnCH₂COOEt and induced the decomposition of diazomethane.

The formation of cyclopropanone from ketene and diazomethane in inert solvent at -75 °C has been proven spectroscopically. But, in spite of its considerable interest, this three-membered-ring ketone is not sufficiently

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