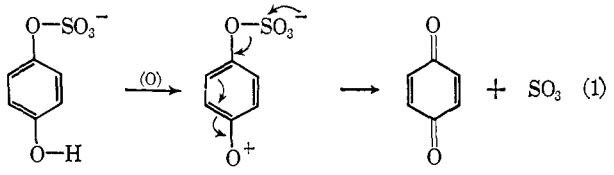
The Oxidative Cleavage of Hydroquinone Monosulfate Ester. A Model Reaction for Sulfate Transfer

Sir:

Sulfate transfer in biological systems from 3′-phosphoadenosine 5′-phosphosulfate (PAPS) to acceptor compounds is catalyzed by enzymes known as sulfokinases; this process has been extensively studied.[1] Lipmann has shown that PAPS, a mixed anhydride of sulfuric and phosphoric acids, is the actual transferring agent in these enzymic systems.

The recent work on the oxidative cleavage of quinol monophosphates[2-5] and resultant transfer of phosphate to acceptor compounds suggests that similar reactions might be achieved with quinol monosulfates.[6] The oxidation of a quinol monosulfate could conceivably take place by a mechanism such as that indicated in reaction 1. In this scheme the S–O bond is cleaved



$$SO_3 + \text{acceptor} \longrightarrow \text{sulfonated acceptor} \qquad (2)$$

with the resultant release of SO_3 which could then sulfonate an acceptor present in the reaction medium (reaction 2). If sulfate transfer to an acceptor is achieved one has then essentially carried out an "oxidative sulfonation." The biological transfer of sulfate does not appear to involve oxidation, although recently it was suggested that the oxidative cleavage of L-ascorbic acid 3-sulfate may be biologically important as a means of transferring sulfate.[7] Nevertheless, the transfer of sulfate from a quinol monosulfate to another compound by oxidative cleavage of the quinol sulfate can be examined as a possible model reaction for *in vivo* sulfate transfer. To test this hypothesis we have synthesized the potassium salt of hydroquinone monosulfate ester[8] ($HQ-SO_3K$) and have studied the action of various oxidants on this substrate. Preliminary experiments indicated that $HQ-SO_3K$ was oxidized by $NaIO_4$, $NaIO_3$, Br_2, and ceric sulfate.

At a periodate concentration of 0.151 *M* the oxidation of $HQ-SO_3K$ (8×10^{-3} *M*) at pH 1.0 and 25.0° obeys first-order kinetics with a pseudo-first-order rate constant of 4.85×10^{-3} sec^{-1}. The periodate oxidation of hydroquinone under similar conditions and concentrations is also first order with a pseudo-first-order rate constant of 9.45 sec^{-1}.[9] Thus, the periodate oxidation of $HQ-SO_3K$ is approximately 2×10^3 times slower than that of hydroquinone. A kinetic dependence on the periodate concentration is also observed in the oxidation of $HQ-SO_3K$. These experimental observations provide strong evidence that an oxidative cleavage of $HQ-SO_3K$ is occurring, rather than hydrolysis of the sulfate ester, followed by oxidation of the hydroquinone produced by the hydrolysis.

The periodate oxidation of $HQ-SO_3K$ was carried out at pH 1.3 in water enriched in the oxygen-18 isotope (1.6 atom % ^{18}O). The sulfate produced by the oxidative cleavage was isolated as $BaSO_4$ after reduction of excess periodate and iodate by the addition of NaI and $HClO_4$. The oxygen in the $BaSO_4$ was converted to CO_2 by treatment of the $BaSO_4$ with $Hg(CN)_2$ and $HgCl_2$ at 400°.[10,11] Mass spectrometric analysis of the CO_2 indicated that less than 10% S–O bond cleavage had occurred. Therefore, the bulk of the sulfate obtained under these conditions was formed by aryl–oxygen cleavage (*i.e.*, it was generated as bisulfate and not as SO_3).

It is possible to oxidize $HQ-SO_3K$ with periodate in the nonaqueous solvent, methanol. In this solvent we find that some of the solvent is sulfonated, resulting in monomethyl sulfate, $CH_3OSO_3^-$. The reaction was carried out as follows: 1 mmole of $HQ-SO_2K$ and 2 mmoles of $NaIO_4$ in 15 ml of methanol were stirred for 8 hr at room temperature. At the end of this period the reaction was complete, the solution was filtered, and the solvent was evaporated from the filtrate. The remaining solid together with exactly 1 mmole of added sodium acetate was taken up in D_2O, and an nmr spectrum was run on the resulting solution. Integration of the CH_3 peak of the $CH_3OSO_3^-$ relative to the acetate peak indicated an 80% yield of $CH_3OSO_3^-$. This determination was possible through the use of nmr, since the methyl resonances of methanol, $CH_3OSO_3^-$, and $(CH_3O)_3SO_2$ do not overlap in D_2O.

The most plausible explanation for sulfonation of the methanol would be that SO_3 is generated by the oxidative cleavage and then attacks the solvent. In order to check this, an experiment was done with 1 mmole of $NaHSO_4$ substituted for the $HQ-SO_3K$. No $CH_3OSO_3^-$ was detected by nmr. Therefore, it appears that bisulfate does not act as a sulfonating agent for methanol under these conditions.

Further sulfate transfer studies have been done using N,N-dimethylformamide (DMF) as a solvent and bromine as the oxidant. Oxidation of equimolar amounts of $HQ-SO_3K$ and methanol in DMF with Br_2 and analysis by nmr indicated that approximately 65% of the methanol had been converted to $CH_3OSO_3^-$, with the remaining methanol left unchanged. Nmr integration was not carried out due to the nearness of the low τ methyl peak of DMF to the $CH_3OSO_3^-$ methyl peak.

Detailed studies on the oxidative cleavage and transfer reactions of hydroquinone and other quinol monosulfate esters are in progress.

Acknowledgment. We wish to thank Mr. Dennis R. Patterson for his assistance with the ^{18}O tracer studies.

(1) F. Lipmann, *Science*, **128**, 575 (1958).
(2) V. M. Clark, G. W. Kirby, and A. R. Todd, *Nature*, **181**, 1650 (1958).
(3) V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. Todd, *J. Chem. Soc.*, 715 (1961).
(4) V. M. Clark, D. W. Hutchinson, and A. R. Todd, *ibid.*, 722 (1961).
(5) T. Wieland and F. Patermann, *Angew. Chem.*, **70**, 313 (1954).
(6) In recent elegant work C. D. Snyder and H. Rapoport (*J. Am. Chem. Soc.*, **89**, 1269 (1967)) have shown that the involvement of quinones in oxidative phosphorylation must proceed with the original carbon–oxygen bonds of the quinone remaining intact. It is certainly unclear at the present time how quinol phosphates are formed, if they are indeed formed during oxidative phosphorylation.
(7) E. A. Ford and P. M. Ruoff, *Chem. Commun.*, 630 (1965).
(8) S. Yamaguchi, *Nippon Kagaku Zasshi*, **80**, 171 (1959).
(9) E. T. Kaiser and S. W. Weidman, *J. Am. Chem. Soc.*, **86**, 4354 (1964).
(10) M. Anbar and S. Guttman, *Intern. J. Appl. Radiation Isotopes*, **5**, 233 (1959).
(11) F. R. Williams and L. P. Hager, *Science*, **128**, 1434 (1958).

S. W. W. wishes to thank the Research Committee at the University of Missouri at St. Louis for their support.

(12) Predoctoral Fellow of the National Institutes of Health.

S. W. Weidman
Department of Chemistry, University of Missouri at St. Louis St. Louis, Missouri

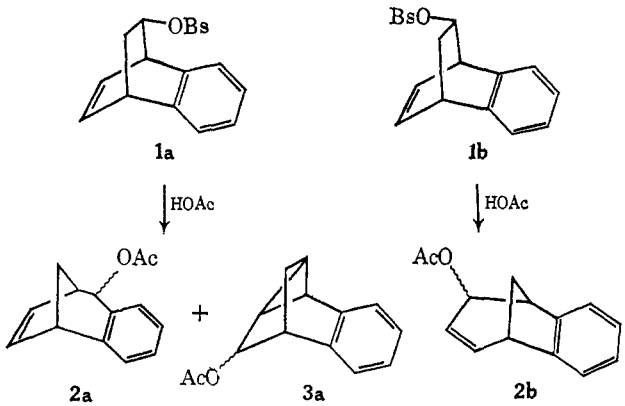
D. F. Mayers,[12] O. R. Zaborsky,[12] E. T. Kaiser
Department of Chemistry, University of Chicago Chicago, Illinois

Received May 15, 1967

An Unusual Rearrangement of a Benzobicyclo[2.2.2]octadienol

Sir:

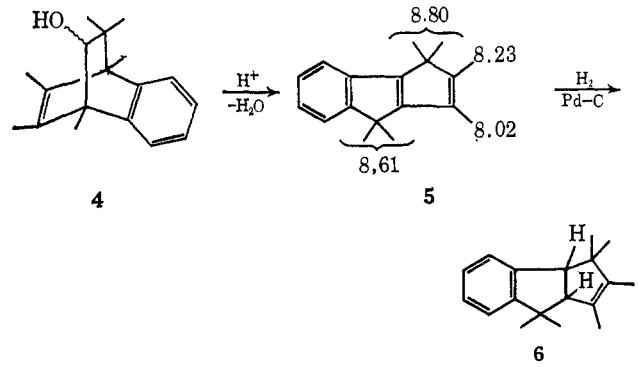
Carbonium ion reactions in the bicyclo[2.2.2]-2-octyl series generally lead to products which have either retained the [2.2.2] ring structure or rearranged to the [3.2.1] ring system.[1] In a recent meticulous study, Tanida[2] found that the group which migrates is *anti* to the leaving group. Thus **1a** gave the [3.2.1] vinyl migration product **2a**, whereas **1b** gave the [3.2.1] aryl migration product **2b**. In addition, **1a** gave minor



amounts (17%) of cyclopropylcarbinyl product **3a**.[3]

We wish to describe an unexpected, profound, but facile, rearrangement of a highly methyl-substituted derivative of **1**; the product is a benzodihydropentalene.

Addition of benzyne[4] to hexamethyl-2,4-cyclohexadienone[5] gave an adduct, mp 108–108.5°, in 73% yield.[6] Reduction with $LiAlH_4$ in ether at 0° afforded a nearly quantitative yield of the alcohol mixture **4** in which the epimer with OH *anti* to the aryl ring predominated (63:37).[7] The alcohol mixture[8] on treatment with strong acid afforded a crystalline hydrocarbon, mp 101–102°, in 45% yield.[9] It analyzed for $C_{18}H_{22}$; its mass spectrum showed a strong parent peak (*m/e* 238), a base peak at *m/e* 223, and other strong peaks at *m/e* 208, 193, and 178, indicating a fairly stable carbon framework with at least four pendant methyl groups. The nmr spectrum consisted of an aromatic multiplet (τ 2.77–3.02, 4 H), two quartets due to homoallylically coupled methyls (τ 8.02 and 8.23, J = 1 cps, 3 H each), and two very sharp singlets (τ 8.61 and 8.80, 6 H each). The nmr spectrum quickly eliminated all anticipated structures.[10] The ultraviolet spectrum showed an unusually intense long-wavelength band (λ_{max} 321 mμ (log ϵ 4.35)), as well as other bands at λ 246 (log ϵ 3.89), 238 (4.10), and 203 mμ (4.21). On the basis of these data and further conversions, we assign structure **5** to the dehydration product of **4**.[11]



Compound **5** readily absorbed 1 mole of hydrogen (ethanol, 5% Pd–C, room temperature, 1 atm) to give, as the major product, a dihydro derivative (mass spectroscopy) which still had two homoallylically coupled methyl groups (τ 8.28 and 8.45) as well as four separate unsplit aliphatic methyl peaks (τ 8.62, 8.77, 8.92, and 9.41). Thus the hydrogens (AB quartet at τ 6.50 and 6.89) must have added to a tetrasubstituted double bond which did not have any methyl substituents. The ultraviolet spectrum (λ 273 (log ϵ 3.33), 266 (3.33), 260 (3.26), 253 (3.20), and 208 mμ (3.95)) showed that the dihydro compound lacked a styrene chromophore; it is assigned structure **6**.[12]

One of the allylic methyl groups of **5** (τ 8.02) underwent complete exchange when **5** was in contact with excess 80% D_2SO_4–D_2O at room temperature for 3 hr. Since the most stable carbonium ion from protonation

(1) For a survey of the earlier literature, see J. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 213–226.

(2) H. Tanida, K. Tori, and K. Kitahonoki, *J. Am. Chem. Soc.*, **89**, 3212 (1967).

(3) We have encountered similar rearrangements with substituted derivatives of **1a** and **1b**; see T. Kakihana, M.S. Thesis, Michigan State University, 1966.

(4) L. Friedman and F. M. Logullo, *J. Am. Chem. Soc.*, **85**, 1549 (1963); M. Stiles, R. G. Miller, and U. Burckhardt, *ibid.*, **85**, 1792 (1963).

(5) H. Hart, P. M. Collins, and A. J. Waring, *ibid.*, **88**, 1005 (1966).

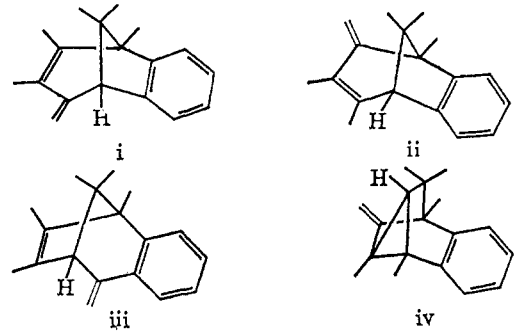
(6) All new compounds gave satisfactory microanalyses and infrared and nmr spectra consistent with the assigned structures.

(7) A complete nmr assignment for each epimer was attained with the aid of syntheses using 3-CD_3 and 5-CD_3 dienone;[5] analysis of the epimeric mixture was based on nmr.

(8) Chromatographic separation of the epimers has thus far failed; attempts using derivatives of **4** are in progress.

(9) The best yield was obtained by adding a $CHCl_3$ solution of the alcohols to a 50:50 sulfuric–trifluoracetic acid mixture at room temperature over 15 min, followed by dilution with ice.

(10) Products of phenyl migration (i or ii), vinyl migration (iii), or double bond participation (iv), followed by proton loss, should have two vinyl protons.



(11) Space limitations preclude presentation of all the supporting evidence for the structural and nmr assignment.

(12) Another dihydro-**5** (from 1,4 addition of hydrogen) and a tetrahydro-**5** have also been identified.