The synthetic material had an avian vasodepressor potency of approximately 0.5 unit/mg, the same as that previously reported for acetone-oxytocin.[8] To test for the liberation of oxytocin from the synthetic material, 9.05 mg of the compound was dissolved in 9.0 ml of 0.25% acetic acid and heated at 90° for 30 min. The solution was lyophilized, and the product was subjected to partition chromatography on Sephadex in the manner previously described for the purification of oxytocin.[13] The conditions were as follows: solvent, 1-butanol–benzene–pyridine–0.1% aqueous acetic acid (6:2:1:9) at 25°; column size, 1.05 × 52.9 cm; hold-up volume, 12.2 ml; flow rate, 3.5 cc/hr; fraction size, 1.0 ml; aliquots for Folin–Lowry determination, 0.05 ml; solvent for regeneration of column, pyridine–0.2 *N* aqueous acetic acid (3:5). One peak was detected with R_f 0.28, the same value obtained under these conditions with an authentic sample of oxytocin. The R_f value for acetone-oxytocin under these conditions is about 0.7, well ahead of the position of oxytocin.[8] The material isolated from the eluates represented by the peak with R_f 0.28 weighed 6.4 mg and had an avian vasodepressor potency of approximately 500 units/mg. These results are practically identical with those previously reported for the regeneration of oxytocin from acetone-oxytocin.[8]

Acknowledgments. The authors wish to thank the following members of this laboratory for their cooperation: Mr. Joseph Albert for the elemental analyses, and Miss Margitta Wahrenburg, Mrs. Maxine Goldberg, and Mrs. Jessie Lawrence for the avian vasodepressor assays under the direction of Dr. W. Y. Chan.

Communications to the Editor

The Effect of Alcohol on Proton Exchange Reactions in Dimethyl Sulfoxide. I. Low Alcohol Concentrations

Sir:

Chemical reactions in solutions prepared by dissolving alkoxides in dimethyl sulfoxide (DMSO) have been widely studied.[1] Measurements of rates of proton transfer from carbon acids have been made,[2,3] and equilibrium constants have been measured.[4] Although the "active" base in these solutions has generally been assumed to be alkoxide, recent work by Ritchie and Uschold has indicated that an appreciable amount of the "kinetic" and equilibrium basicity may be due to the presence of methylsulfinylcarbanion, $CH_3SOCH_2^-$, the conjugate base of DMSO.[3c]

We have previously measured the rate of proton exchange between DMSO and $CH_3SOCH_2^-$ by ^{13}C satellite proton nmr line broadening.[5] Our method of measurement allows a unique insight into proton-transfer processes in these solutions because rates can be measured under equilibrium conditions while reactions are proceeding continuously. In this communication we wish to report the effect of added *t*-butyl alcohol (ROH) on the rate of proton removal from carbon acids in the presence of $CH_3SOCH_2^-K^+$. For total base strengths in the range ~0.01–~0.25 *M*, *addition of ROH causes a significant increase in the rate of proton removal from DMSO.* This effect reaches a maximum at ~2 equiv of ROH/equiv of base. The rates then decrease rapidly, but even at ROH:base of 5:1 the rates are faster than those in the absence of ROH. At its largest, the acceleration amounts to a factor of about 20. Typical results are summarized in Table I.

The rates of proton abstraction were determined by measuring the width of the ^{13}C satellite of DMSO.[5] The constant half-width of an internal standard showed that neither paramagnetic impurities nor viscosity effects were responsible for the line broadening. The increased rate of exchange is clearly demonstrated by the observation that the ^{13}C satellite of DMSO is substantially broadened when ROH is added to a solution of $CH_3SOCH_2^-K^+$ in DMSO. This additional broadening implies that the lifetime of the protons of DMSO is shortened. Results from solutions made from RO^-K^+ + ROH were identical with those from solutions made from $NH_2^-K^+$ + ROH or KH + ROH.[6]

Table I. Width at Half-Height of ^{13}C Satellite (0.0153 *M* Base)[a]

Expt	*t*-BuOH, *M*[b]	Width, Hz
317	0	1.4
319	0.0134	4.0
320	0.0209	6.1
321	0.0271	6.8
322	0.0362	2.9
323	0.0576	2.8
324	0.0842	1.6

[a] Solutions made from KNH_2 + DMSO. [b] *t*-BuOH added to original solution.

We are unable to specify the kinetically active base under these conditions. However, the absence of an OH peak in the nmr spectrum implies that RO^-K^+ is involved to some extent in the exchange process. A rather sharp maximum in rate at ROH:base of 2:1 suggests possible formation of a kinetically reactive 2:1 complex which becomes less reactive, or is destroyed, as ROH is further increased.

We have obtained additional evidence that *proton removal from other carbon acids in DMSO is also ac-*

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(1) See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, for a good general discussion and references; A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(2) J. E. Hofmann, R. J. Muller, and A. Schriesheim, *J. Am. Chem. Soc.*, **85**, 3002 (1963).

(3) C. D. Ritchie and R. E. Uschold: (a) *ibid.*, **86**, 4488 (1964); (b) *ibid.*, **89**, 1730 (1967); (c) *ibid.* **89**, 2960 (1967).

(4) E. C. Steiner and J. M. Gilbert, *ibid.*, **85**, 3054 (1963); **87**, 382 (1965); E. C. Steiner and J. D. Starkey, *ibid.*, **89**, 2751 (1967).

(5) J. I. Brauman and N. J. Nelson, *ibid.*, **88**, 2332 (1966).

(6) Solutions were made up and handled entirely with vacuum line techniques. Solutions were filtered prior to placement in nmr tubes; base concentrations were determined by titration. Spectra were obtained with a Varian A-60 spectrometer.

celerated by ROH. This is shown clearly by the following experiments. Triphenylmethane (0.44 *M*) in a solution of 0.33 *M* $CH_3SOCH_2^-K^+$ in DMSO has an nmr spectrum which is the superposition of the spectra of Ph_3CH and $Ph_3C^-K^+$. The methine peak is not broadened. Irradiation of the main DMSO peak causes no decrease in the methine height (the ^{13}C satellite does diminish as expected).[7-9] Thus, exchange is slow under these conditions. However, in a DMSO solution containing 0.44 *M* Ph_3CH, 0.29 *M* $CH_3SOCH_2^-K^+$, and 0.13 *M* ROH, the ratio of $Ph_3C^-K^+$ to Ph_3CH is smaller, indicating a less basic medium, and both the aromatic and methine peaks are broadened. The broadening of the methine is shown to be due ultimately to exchange with DMSO by irradiation of the main DMSO peak which now causes the methine to diminish to about 10% of its former height. Consequently, in these solutions exchange is fast. We estimate the acceleration to be at least as great as that observed for DMSO itself. Broadening of the methine peak persists even when very little $Ph_3C^-K^+$ is present.

It thus appears that, in general, although the equilibrium basicity of this medium with respect to carbon acids is lowered, the "kinetic basicity" is enhanced when small amounts of alcohol are added. The catalysis by ROH has been observed for all base concentrations examined. At present, it is difficult to interpret our results in terms of the previous measurements of Ritchie.[8c] Large differences in concentrations may be responsible for profound effects in this system as in others.[8] Further results are discussed in the accompanying communication.[10] Finally, we wish to point out that for synthetic work involving proton removal, solutions of *t*-BuO^-K^+ in DMSO can be as effective as or more effective than solutions of $CH_3SOCH_2^-K^+$, and they are much easier to prepare.

Acknowledgment. We are grateful to the National Science Foundation (Grant GP 6736) and to the Petroleum Research Fund, administered by the American Chemical Society (Grant 2917-A4), for support of this research.

(7) This double-resonance technique permits observation of slow rate processes by saturation at one site followed by chemical exchange.[8]

(8) J. I. Brauman, D. F. McMillen, and Y. Kanazawa, *J. Am. Chem. Soc.*, **89**, 1728 (1967), and references cited therein.

(9) Double-resonance experiments were carried out with a Varian HA-100 spectrometer; we thank Dr. Lois J. Durham for her help with them.

(10) J. I. Brauman and N. J. Nelson, *J. Am. Chem. Soc.*, **90**, 491 (1968).

(11) Stauffer Fellow, 1965–1966; National Institutes of Health Predoctoral Fellow, 1966–1967.

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The Effect of Alcohol on Proton Exchange Reactions in Dimethyl Sulfoxide. II. High Alcohol Concentrations

Sir:

In the accompanying communication[1] we reported the accelerating effect of small amounts of *t*-butyl alcohol (ROH) on the rate of proton removal from dimethyl sulfoxide (DMSO) and from triphenylmethane in the presence of $CH_3SOCH_2^-K^+$. In this communication we report the effects of relatively large amounts of ROH on proton transfers of DMSO in the DMSO–ROH system.

At least three proton exchange reactions can occur in these solutions (eq 1–3). *We observe that even in solutions containing ~10% ROH, with 0.1 M base, ap-*

$$\mathrm{ROH} + \mathrm{RO^-K^+} \rightleftharpoons \mathrm{RO^-K^+} + \mathrm{ROH} \qquad (1)$$

$$\mathrm{DMSO} + \mathrm{CH_3SOCH_2^-K^+} \rightleftharpoons \mathrm{CH_3SOCH_2^-K^+} + \mathrm{DMSO} \qquad (2)$$

$$\mathrm{DMSO} + \mathrm{RO^-K^+} \rightleftharpoons \mathrm{CH_3SOCH_2^-K^+} + \mathrm{ROH} \qquad (3)$$

preciable proton exchange occurs between DMSO and $CH_3SOCH_2^-$ *(eq 2).* This follows directly from an analysis of the relative broadening of the peaks corresponding to the protons of DMSO and ROH. In these solutions it is possible to observe, by nmr, a peak corresponding to the hydroxylic proton of ROH. This peak is appreciably broadened in comparison with its width in the absence of base; the extent of broadening is highly dependent on ROH concentration, decreasing as ROH increases. The width of the OH peak can be associated with the lifetime of the proton on oxygen by use[2] of eq 4; eq 1 cannot contribute to this broadening

$$1/T_2' = (1/T_2) + (1/\tau_{\mathrm{ROH}}) \qquad (4)$$

since in eq 1 the chemical environment of the proton is unchanged. Presumably, then, the entire OH broadening is due to eq 3. The measured lifetime, τ_{ROH}, thus refers only to protons exchanged with DMSO. Given τ_{ROH} it is possible to determine $\tau_{\mathrm{DMSO\text{-}3}}$, the lifetime of a proton on DMSO due to eq 3, by considerations of detailed balancing (eq 5). It is, in addition, possible to determine the "total" lifetime

$$\tau_{\mathrm{DMSO\text{-}3}} = \tau_{\mathrm{ROH}} 6[\mathrm{DMSO}]/[\mathrm{ROH}] \qquad (5)$$

of a proton on DMSO, τ'_{DMSO}, by measuring the width of the ^{13}C satellite.[1,3] In these solutions, τ'_{DMSO} is clearly shorter than $\tau_{\mathrm{DMSO\text{-}3}}$, indicating that some protons on DMSO are being exchanged without the intervention of ROH. Qualitatively this is seen as follows. The OH broadening must be accompanied by a broadening of the ^{13}C satellite (proportional to the concentration of ROH and DMSO). In fact, the ^{13}C satellite is much broader than one would expect on the basis of OH broadening; the most likely pathway for the additional exchange is eq 2. The lifetime for this exchange, $\tau_{\mathrm{DMSO\text{-}2}}$, can be obtained by use of eq 6. In

$$1/\tau_{\mathrm{DMSO\text{-}2}} = (1/\tau'_{\mathrm{DMSO}}) - (1/\tau_{\mathrm{DMSO\text{-}3}}) \qquad (6)$$

Table I are summarized some typical results. It can

Table I. Lifetimes of Protons on DMSO and ROH

Base, *M*	[*t*-BuOH]/[base]	τ_{ROH}, sec	τ'_{DMSO}, sec	$\tau_{\mathrm{DMSO\text{-}3}}$, sec	$\tau_{\mathrm{DMSO\text{-}2}}$, sec
0.316	5.0	0.022	0.84	1.0[a]	5.9[a]
0.282	5.6	0.024	0.84	1.1[a]	3.6[a]
0.203	7.5	0.034	1.06	1.6	3.0
0.108	14.1	0.060	1.2	2.9	2.1

[a] Under these conditions, within experimental error, $\tau'_{\mathrm{DMSO}} \approx \tau_{\mathrm{DMSO\text{-}3}}$.

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(1) J. I. Brauman, N. J. Nelson, and D. C. Kahl, *J. Am. Chem. Soc.*, **90**, 490 (1968).

(2) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 10.

(3) J. I. Brauman and N. J. Nelson, *J. Am. Chem. Soc.*, **88**, 2332 (1966).