Tetrahedron, 1958, Vol. 3, pp 317–321. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATIONS

Sulfoxides as nucleophiles*

(*Received* 15 *March* 1958)

We wish to record the novel and interesting behavior of dimethylsulfoxide (DMSO) as a nucleophilic ionizing solvent for reactions with alkyl halides or arenesulfonates (RX). Judging ionizing power from relative rates of acid production from *p*-methoxyneophyl toluenesulfonate,[1] which is disposed toward anchimerically[2] assisted ionization, dimethylsulfoxide falls below the common solvolysing solvents, acetic acid and ethanol[3] (Table 1). On the other hand, it displays greater ionizing power than such solvents as dimethylformamide and dry acetone. The relatively high nucleophilicity of dimethylsulfoxide is evident from the solvent sequence observed with other substrates, such as 1,1-diphenyl-2-propyl *p*-bromobenzenesulfonate[4] and ethyl *p*-toluenesulfonate[5]

TABLE 1. SOLVENT RATE SEQUENCE IN SOLVOLYSIS OF SEVERAL ARENESULFONATES

Compound	Relative rates				
	AcOH	EtOH	Me_2SO	$HCONMe_2$	Me_2CO
p-Methoxyneophyl OTs, 75°	9·23[1]	3·42[1]	(1·00)	0·27	0·0468
1,1-Diphenyl-2-propyl OBs, 75°	1·02[4]	0·491[4]	(1·00)	0·084	0·0055
Ethyl OTs, 50°	0·00158[5]	0·101[5]	(1·00)		

(Table 1). With these materials, rates of reaction in DMSO are substantially greater than in ethanol. The tendency for nucleophilic solvent participation by DMSO in the rate-determining step of the reaction of RX molecules, is further evident from the structural rate sequence,[3,5] Me, 3 > Et, 1 < Pr^i, 1·5, for the alkyl toluenesulfonates in DMSO at 50°.

The action of DMSO on simple RX molecules gives rise to two different types of derivatives, both with the proper elementary analysis for 1:1 adducts of RX and DMSO (Table 2). O-alkyl derivatives (I) are obtained conveniently in yields of 50–90 per cent by isolation of the product of reaction of methyl, ethyl or benzyl arenesulfonates in DMSO at the proper stage. By the use of methyl iodide and silver nitrate in DMSO, the O-methyl nitrate is derived. More stable isomeric S-alkyl adducts of DMSO(II) may also be obtained. This type of derivative is derived from benzyl toluenesulfonate in DMSO after long reaction periods. With methyl iodide, the S-alkyl product is the only one which we have been able to isolate. Treatment of this derivative with silver arenesulfonate or silver nitrate in water gives rise to the S-alkyl arenesulfonate or nitrate (Table 2).

In water or aqueous ethanol the O-alkyl adducts hydrolyse rapidly to produce one equivalent of acid (Table 2), while the S-alkyl derivatives are quite inert. In fact, they may be recrystallized from water. The O-alkyl derivatives tend to isomerize in solution to the S-alkyl variety, the tendency for

* Research supported by the National Science Foundation.

[1] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.* **78**, 2763 (1956); S. Winstein and R. Heck, *J. Amer. Chem. Soc.* **78**, 4801 (1956); A. H. Fainberg, Unpublished work.
[2] S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *J. Amer. Chem. Soc.* **75**, 147 (1953).
[3] S. Winstein, E. Grunwald and H. W. Jones, *J. Amer. Chem. Soc.* **73**, 2700 (1951).
[4] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *J. Amer. Chem. Soc.* **74**, 1113 (1952.)
[5] S. Winstein and H. Marshall, *J. Amer. Chem. Soc.* **74**, 1120 (1952).

such isomerization decreasing in the order of anions, $I^{\ominus} > \overset{\ominus}{O}NO_2 > \overset{\ominus}{O}Ts$. While other mechanisms may also be possible, the available data suggest than an important route from O- to S-alkyl derivatives involves reversibility of formation of the O-alkyl adduct and competing formation of the S-alkyl derivative. During reaction of 0·037 M methyl iodide in DMSO at 50°, the O → S conversion is so important that only 7 per cent of acid-producing O-adduct, formed rapidly, can be detected kinetically. In contrast, 94 per cent of O-adduct can be detected with 0·030 M methyl *p*-bromobenzenesulfonate in DMSO at 50°.

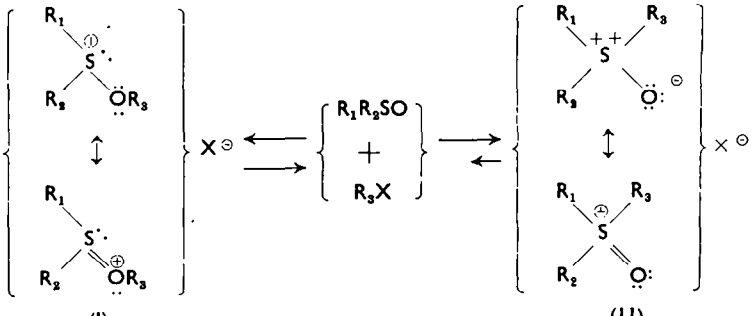
TABLE 2. SUMMARY OF SULFOXIDE ALKYLATION PRODUCTS

R_1R_2SO	R_3X	O-alkyl derivatives		S-alkyl derivatives m.p. (°C)
		m.p. (°C)	Acid* (per cent)	
$(CH_3)_2SO$	CH_3I	—	—	220†
	CH_3ONO_2	66–68	92·4	220·0–220·5
	CH_3OTs	48–54	95·0	165–167
	CH_3OBs	98–99	98·2	232–233
	C_2H_5OTs	83–89	97·6	—
	$C_6H_5CH_2OTs$	92–93‡	97·5	119·5–120
$C_6H_5CH_2SOCH_3$	CH_3OTs	79–80‡	98·0	

* Percentage of one equivalent of acid by titration of an aqueous solution to the phenolphthalein end-point.
† Depends upon rate of heating.
‡ Mixed m.p. 72–74°.

The present observations indicate that the O- and S-alkylation products (I) and (II) are associated with kinetic and thermodynamic control of products, respectively, with the range of RX molecules so far explored. The only other report of similar alkylation of DMSO of which we are aware is the very recent one of Kuhn's,[6] which appeared after the present work was essentially complete. Kuhn and Trischmann[6] made the important observation that methyl iodide reacts in DMSO solution and have isolated a methiodide and several other derivatives prepared by metathetical reactions of the methiodide. Because methyl iodide was the only RX molecule investigated and the methiodi de was inevitably the S-alkyl variety, the duality of possible alkylation products was not observed.

The identification of the O- and S-alkyl derivatives (I) and (II) is clear from both physical and chemical evidence. The proton magnetic resonance (NMR) absorption spectrum of the O-adduct of DMSO and methyl *p*-bromobenzenesulfonate in chloroform displays three peaks in addition to the single solvent peak. The areas of these peaks in the order of increasing shielding are in the ratio



(I) (II)

R. Kuhn, *Angew. Chem.* **17**, 570 (1957); R. Kuhn and H. Trischmann, *Liebigs Ann.* **611**, 117 (1958).

4 : 3 : 6. These correspond to the aromatic, O-methyl and S-methyl protons, respectively, of the O-methyl derivative(I). The NMR spectrum of a fresh solution of the S-adduct of DMSO and methyl nitrate in deuterium oxide shows only one type of proton, corresponding to the S-methyl derivative(II).

The comparison of the initial adducts from DMSO and benzyl *p*-toluenesulfonate, on the one hand, and benzylmethylsulfoxide, methyl iodide and silver *p*-toluenesulfonate, on the other, supplies further evidence regarding the O- or S-alkyl nature of the adducts from kinetic control of products. The two adducts containing the benzyl group differ in melting point (Table 2) as well as in behavior in hydrolysis. Benzyl alcohol is obtained from the DMSO–benzyl toluenesulfonate product, and methanol is derived from the benzylmethylsulfoxide–methyl toluenesulfonate adduct. Since the two adducts would be identical if S-alkylation were involved, the chemical evidence agrees with the NMR results in favor of the O-alkyl designation (I) for the adducts from kinetic control of products.*

The dialkyl-alkoxysulfonium and trialkyl-oxosulfonium salts (I) and (II) represent interesting new materials. For example, they may be of some interest as alkylating agents. Further, the trimethyl-oxosulfonium nitrate (II; $R_1 = R_2 = R_3 = CH_3$; $X^{\ominus} = \overset{\ominus}{N}O_3$) undergoes very rapid exchange of deuterium for protium even in neutral deuterium oxide solution. The rate of this exchange may be estimated from the change in the NMR spectrum of the solution with time, since the C–H absorption disappears and an O–H absorption appears as exchange proceeds. In this way, a rough first-order rate constant of ca. 6×10^{-4} sec^{-1} was estimated for the exchange at room temperature (ca. 28°). The exchange in this case is faster by a factor of ca. 20 than that observed by Doering and Hoffmann[7] with trimethylsulfonium iodide at 26·8° in deuterium oxide, 0·2615 M in sodium deuteroxide. One could anticipate powerful acceleration of deuterium exchange by the addition of an oxygen atom to trimethylsulfonium ion, and the available facts make it clear that the oxygen substituent in the trimethyl-oxosulfonium derivative(II) accelerates deuterium exchange by at least several powers of ten.

The new sulfoxide derivatives, especially the O-alkyl variety (I), may play important roles as intermediates in other reactions occurring in DMSO or other sulfoxide solvents. Possible examples are the relatively efficient olefin formation from many alkyl arenesulfonates in DMSO as solvent[8] or the conversion of phenacyl bromides to phenylglyoxals in DMSO reported recently by Kornblum.[9]

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* The S-methyl designation (II) for the thermodynamically favored adduct turns out to be in agreement with Kuhn and Trischmann's[6] structural assignment to the DMSO methiodide on the basis of their treatment of the methiodide with hot concentrated hydriodic acid, a reaction of questionable validity for proof of structure.

[7] W. von E. Doering and A. H. Hoffmann, *J. Amer. Chem. Soc.* 77, 521 (1955).
[8] S. Smith and J. Takahashi, Unpublished work.
[9] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand and W. M. Weaver, *J. Amer. Chem. Soc.* 79, 6562 (1957).

Optical rotatory dispersion studies—XVIII*

Demonstration of conformational mobility in 2-chloro-5-methyl*cyclo*hexanone†

(*Received* 28 *March* 1958)

ON the basis of extensive rotatory dispersion measurements of halogenated steroid ketones,[1] an empirical rule has been proposed,[2] which states that the sign of the single Cotton-effect curve[3] of the parent *cyclo*hexanone is not altered by introduction of equatorial bromine or chlorine in the α or α′ positions, but that axial halogen can invert the sign in a predictable manner. Since all earlier work[1]

* Paper XVII, C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *J. Amer. Chem. Soc.* In press.

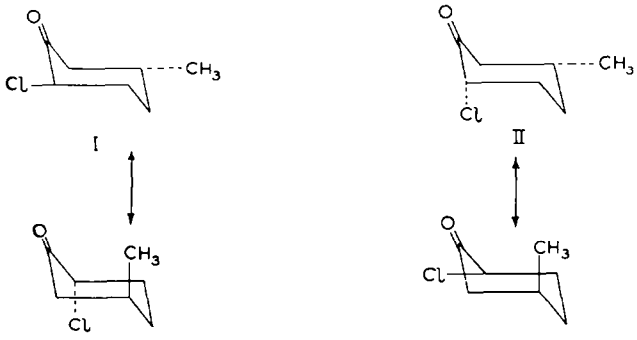
† Supported by grant No. CY-2919 of the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

[1] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **80** (1958).
[2] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* 79, 1506 (1957).
[3] For nomenclature, see C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957).

has been carried out with polycyclic systems of rigid conformation, it was of considerable interest to extend such observations to monocyclic *cyclo*hexanones.

Chlorination of (−)-3-methyl*cyclo*hexanone with sulfuryl chloride in carbon tetrachloride gave 2-chloro-5-methyl*cyclo*hexanone (m.p. 68–69°, $[\alpha]_D$ +6·4° ($CHCl_3$). (*Anal.* Found for $C_7H_{11}OCl$: C, 56·97; H, 7·71; O, 11·07; Cl, 23·80 per cent,) which was dehydrochlorinated with 2,4-dinitrophenylhydrazine to give optically active 5-methyl-2-*cyclo*hexen-1-one 2,4-di-nitrophenylhydrazone (m.p. 143–145°, $[\alpha]_D$ −211° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 380 mμ. *Anal.* Found for $C_{13}H_{13}O_4N_4$: C, 53·79; H, 4·83; N, 19·31 per cent).

Two pairs of conformational isomers are possible for the chloroketone, one of them *trans* (I, III) and the other (II, IV) *cis*. Ultraviolet and infrared measurements* indicate—in agreement with expectation[4]—that the amount of axial isomer predominates in a non-polar medium (octane) and is reduced in a polar solvent (methanol). The spectral measurements do not, however, distinguish



between the two possible axial (II *or* III) or the two equatorial (I *or* IV) conformers and a unique solution to this problem can be secured by optical rotatory dispersion measurements.

According to our earlier empirical rule,[2] (I), (II) and (IV) should have a positive Cotton effect[8] curve—as does the starting ketone (+)-3-methyl*cyclo*hexanone[5,6] itself—while only conformer (III) should exhibit a negative curve. Since the spectral measurements* indicate a preponderance of the axial form in octane, the rotatory dispersion of 2-chloro-5-methyl*cyclo*hexanone was first measured in octane solution and found to exhibit a strong, single negative Cotton-effect curve[3] (trough at $[\alpha]_{330}$ −1092°), from which it follows that conformer (III) rather than (II) represents correctly the axial form of the chloroketone. Most strikingly, when the dispersion curve was measured in methanol solution, where the spectral data* indicate a considerable amount of the equatorial isomer, it proved to be positive (peak at $[\alpha]_{305}$ +626°).†

This dramatic inversion of the sign of the Cotton-effect curve on changing from a non-polar to a polar solvent can best be rationalized by assuming that in the former solvent the *cyclo*hexanone exists to a large extent as (III) and in the polar medium as the "flipped-over" conformer (I). The energy difference between (I) and (III) is rather small—the "3-alky ketone" effect[7] in (III) roughly counterbalancing the unfavorable electrostatic effect of the equatorial chlorine atom in (I), thus allowing for the polarity of the solvent[4] to be the decisive factor.

Further work with optically active halogenated *cyclo*hexanones is in progress, but it is pertinent

* Details will be published in our complete paper.

† That no isomerization of axial to equatorial chlorine in the same conformer (*trans* (III) to *cis* (IV)) had occurred was demonstrated by dissolving the substance in methanol, evaporating (after 45 min) to dryness *in vacuo* and quickly measuring the dispersion in octane (starting with the characteristic trough in the 330 mμ region), which again proved to be negative.

[4] J. Allinger and N. L. Allinger, *Tetrahedron* **2**, 64 (1958). Extensive personal discussion with these authors is gratefully acknowledged.

[5] H. S. French and M. Naps, *J. Amer. Chem. Soc.* **58**, 2303 (1936).

[6] C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957).

[7] W. Klyne, *Experientia* **12**, 119 (1956).

to point out at this time that this represents still another example of the great utility of the rotatory dispersion technique[6] in the examination of conformational problems.[8]

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[8] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* In press; see also Paper XVII, C. Djerassi *et al.*

Kinetics of a nucleophilic replacement of an aromatic nitro group

(*Received* 18 *April* 1958)

SODIUM methoxide reacts with 1:4-dinitronaphthalene in methanol solution to give only the nitrite ion and 4-nitro-1-naphthyl methyl ether. The reaction may be followed by sampling at convenient intervals into toluene and water, with subsequent absorptiometric determination of the nitrite ion in the aqueous phase by a diazotisation–coupling process as described by Rider and Mellon.[1]

The kinetics are of second order, viz.:

$$\text{rate} = k[\text{methoxide}]\,[1:4\text{-dinitronaphthalene}]$$

and salt effects appear to be absent. The Arrhenius parameters have been calculated from determinations of the specific rate at six temperatures and are:

Activation energy = 19·2 kcal/g mole
Frequency factor ($\log_{10} A$) = 11·4

It is interesting to compare these values with those for *p*-dinitrobenzene, given by Bolto and Miller[2] as 22·4 kcal/g mole and 12·6, respectively.

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[1] B. F. Rider and M. G. Mellon, *Industr. Engng. Chem.* (*Anal.*) **18**, 96 (1946).
[2] B. A. Bolto and J. Miller, *Aust. J. Chem.* **9**, 74 (1956).

1-Methoxyvinyl esters*

(*Received* 21 *May* 1958)

WE have found that mercuric salts catalyse the addition of carboxylic acids to methoxyacetylene (I) in methylene chloride solution, the reaction constituting the first general method for the preparation of 1-methoxyvinyl esters† (II). The following examples illustrate the marked catalytic effect of mercuric ions in the formation of II. Whereas the uncatalysed addition of acetic acid (1 mole) to I (2 moles) gave only 25 per cent of IIa (the remainder being anhydride), the addition of 2 mole per cent of mercuric acetate (based on acid) gave 95 per cent IIa. Previous attempts to prepare the analogous 1-ethoxyvinyl acetate have been reported as unsuccessful.[6] In the case of *p*-phenylazobenzoic acid, negligible reaction occurred when a suspension of 1 mole in methylene chloride was

* Contribution No. 1501 from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut.

† Until recently,[1–5] 1-alkoxyvinyl esters were not described in the literature.

[1] G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Amer. Chem. Soc.* **76**, 1715, 1720 (1954).
[2] R. Broekema, S. van der Werf and J. F. Arens, *Rec. Trav. Chim.* **77**, 258 (1958).
[3] J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.* **23**, 635 (1958).
[4] A. S. Kende, *Chem. and Ind.* 1053 (1956).
[5] F. D. Cramer and K. G. Gärtner, *Chem. and Ind.* 560 (1958).
[6] J. F. Arens and P. Modderman, *Proc. Koninkl. Nederland. Akad. Wetenschap.* **53**, 1163 (1950); *Chem. Abstr.* **45**, 6152*d* (1951); G. Eglinton, E. R. H. Jones, B. L. Shaw and M. C. Whiting, *J. Chem. Soc.* 1862 (1954).

stirred for 12 hr with 2·5 moles of I. However, with the addition of 0·5 and 5 mole per cent of mercuric acetate (based on acid), the reaction was complete in 9, and 1·5 hr respectively, and negligible amounts of anhydride were formed. The 1-methoxyvinyl esters prepared by this general method are recorded in the accompanying table. They all exhibit a sharp band at ca. 5·95 μ in the infrared which is as intense as that due to the ester carbonyl.

The activity of the esters (II) as acylating agents is exemplified by the reaction of a slight excess of IIa with benzylamine (vigorously exothermic); β-naphthylamine (2 hr at 80°); 2,4-dinitrophenol (8 hr at room temperature); and *p*-nitrobenzyl alcohol (3 hr at 80°). After removal of any volatiles,

TABLE 1

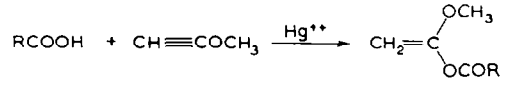
R	II	Yield (%)*	b.p. or m.p.	Calcd.			Found		
				C,	H,	N or Cl	C,	H,	N or Cl
CH_3	a	75	79° (85 mm)	51·7	6·9		51·8	6·8	
C_6H_5	b	98	95–96° (0·5 mm)	67·4	5·7		67·7	5·8	
p-$NO_2C_6H_4$	c	66	76·5–78°	53·8	4·1	6·3	53·7	4·3	6·4
3,5-$(NO_2)_2C_6H_3$	d	98	93·5–95·5°	44·8	3·0	10·4	45·0	3·2	10·3
p-$C_6H_5N{=}NC_6H_4$	e	80	93·5–94·5°	68·1	5·0	9·9	68·0	5·1	9·9
$(C_6H_5)_2CCl$	f	71	63–63·5°	67·4	5·0	11·7	67·5	4·9	11·5
†	g	85	136·5–137·5°	72·9	9·1		73·3	9·1	

* Although the yields of the crude esters were almost quantitative, some loss resulted in the removal of small amounts of contaminating anhydride.

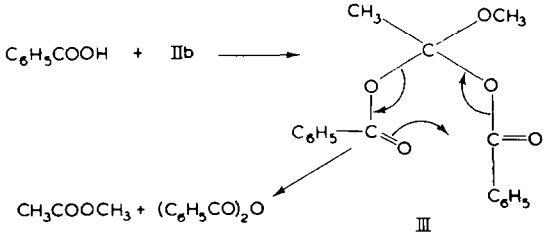
† IIg = 1-methoxyvinyl 3β-acetoxy-Δ^5-bisnorcholenate.

nearly quantitative yields of the acetyl derivatives were obtained. The use of the esters (II) as intermediates in the synthesis of peptides offers attractive possibilities.[3,5]

Compounds corresponding to II have been postulated as intermediates in the useful conversion of an acid to its anhydride by I.[6] Indeed, the reaction of acetic acid and benzoic acid with IIa and IIb respectively, gave nearly quantitative yields of the corresponding anhydrides. This conversion undoubtedly occurs by intermediate formation of III, followed by subsequent decomposition to anhydride via a cyclic transition state, rather than by direct attack of acid at the carbonyl carbon atom of II, as the following results show. When 1 mole of IIb was treated with 1 mole of benzoic acid containing 1·06 at. per cent excess ^{18}O per oxygen, benzoic anhydride containing 0·53 at. per cent excess ^{18}O per oxygen was recovered and the methyl acetate concurrently formed was found to contain 0·52 at. per cent excess ^{18}O in the carbonyl oxygen.



I II



III

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