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A New Synthesis of Dialkoxymethane. The Magnetic Nonequivalence of Methylene Protons in Certain Dialkoxymethane

Takeo SATO,* Yoshitaka SAITO,* Masatsune KAINOSHO** and Kazuo HATA*

* *Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Setagaya-ku, Tokyo*

** *Ajinomoto Co., Inc., Kawasaki*

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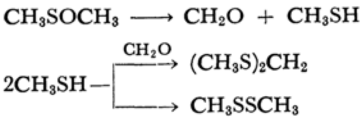
Dimethyl sulfoxide (DMSO), under acidic conditions, is known to yield formaldehyde as one of its decomposition products. A new method of synthesizing dialkoxymethanes, which consists of the treatment of alcohols with a DMSO-PPA (polyphosphoric acid) mixture, has been shown to be convenient and also generally applicable. Under mild conditions, five primary alcohols and four secondary alcohols are converted to the corresponding formals in 50—80 and 30—40% yields respectively. Dimethyl disulfide, bis(methylthio)methane and methylthiomethyl ether and an oxidation product of the alcohol have been shown to be the main by-products in this reaction. The examination of the NMR spectra has revealed that the acetal methylene protons of dialkoxymethanes made from (±)-secondary alcohols are observed as an AB quartet and as a singlet, each arising from meso and racemic compounds, respectively.

Customarily dialkoxymethanes (formaldehyde acetals) have been prepared by the treatment of formaldehyde with alcohol in the presence of an acid catalyst, such as hydrogen chloride, *p*-toluenesulfonic acid or ferric chloride. Our attention was directed to the observations that formaldehyde was obtained during the thermal decomposition of dimethyl sulfoxide (DMSO) when it was heated at 190°C for 72 hr,[1] and that the cleavage of sulfoxides into aldehydes and mercaptans was best achieved by the action of acid.[2,3] Thus, we expected that the treatment of alcohols with DMSO containing a suitable acid catalyst, one which generates formaldehyde *in situ*, might be useful for the synthesis of dialkoxymethanes.[4]

Dialkoxymethane Formation. In the present study, it has been shown that primary and secondary aliphatic alcohols were converted to the corresponding dialkoxymethanes using a DMSO-polyphosphoric acid (PPA) mixture under mild conditions. The results are tabulated in Table 1. A typical reaction was carried out in the following way. To a DMSO-PPA mixture, made from 54 g of 80% PPA[5] and 117 g (1.5 mol) of DMSO, 0.2 mol of alcohol was added, after which the mixture was heated on a water bath for several hours. In most cases the reaction mixture separated into two layers within 30 min. After it had then been diluted with water, the reaction mixture was extracted with isopropyl ether, in which DMSO was practically insoluble. The dialkoxymethanes were isolated by distillation and were characterized by their NMR and infrared spectra, which showed four or more characteristic absorptions between 1040—1200 cm^{-1},[6] and by gas chromatography using polyethylene glycol on celite column. All the products are known compounds and were finally identified by direct comparison with authentic materials prepared by the conventional method. The yield of acetal from primary alcohols was generally good, ranging from 50 to 80%. Those from secondary alcohols were obtained in somewhat lower yields. In these cases, however, the starting material was recoverable; for example, menthol and borneol were recovered in 37 and 14% yields respectively. As was expected, 1-octanol was recovered when it was heated in DMSO alone at 180°C for 10 hr. The treatment of the same alcohol with PPA for 5 hr at water-bath temperature resulted in the formation of polymeric hydrocarbon. As an analogous reaction, the dehydration of lower alcohols by heating them with PPA at atmospheric pressure[7] or under pressure[8] to give a polymer has been reported. A vigorous decomposition of DMSO occurred when phosphorus pentoxide was used instead of PPA.

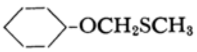
Side Reaction. In lower homologs, diethoxy- to dipentyloxymethanes, the distillate was always contaminated with dimethyl disulfide, bp 109.5°C; NMR spectrum δ 2.39 (SCH_3) and/or bis(methylthio)methane, bp 148°C; NMR spectra δ 2.08 (SCH_3) and 3.53 (SCH_2S). These by-products were assumed to be formed by the following reactions;[1]



$$CH_3SOCH_3 \longrightarrow CH_2O + CH_3SH$$

$$2CH_3SH - \begin{cases} \xrightarrow{CH_2O} (CH_3S)_2CH_2 \\ \longrightarrow CH_3SSCH_3 \end{cases}$$

Although a quantitative analysis of dialkoxymethane in the mixture was possible on the basis of the NMR data, the yields reported herein for these compounds were obtained with gas chromatography. The other by-products in this reaction were methylthiomethyl ethers of alcohols, which were isolated in certain cases. For example, the reaction with cyclohexanol afforded, in addition to dicyclohexyloxymethane, bp 144—145°C/15 mmHg, a distillate, bp 97—99°C/15 mmHg, in an 8.6% yield. The NMR spectra of this product consisted of two singlets, at δ 2.08 (SCH_3) and 4.58 (OCH_2S), together with the other typical signals; these spectra indicated structure I. The reaction with (−)-menthol also afforded methylthiomethyl ether (4.5% yield); bp 138—140°C/17 mmHg, with NMR signals appearing at δ 2.08 and 4.62 (both singlets). Oxidation products were also obtainable in some cases. Camphor was obtained in a 3% yield from the reaction with (+)-borneol.



(I)

The NMR Spectra of Dialkoxymethanes. The characterization of dialkoxymethanes by means of their NMR spectra was straight-forward. All the compounds reported herein showed satisfactory spectra.[9] In Table 1 the peaks for OCH_2O

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[1] V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964); 1, 3-Dioxolane was obtained in 54% yield by heating ethylene glycol in DMSO at 190°C for 72 hr.

[2] W. J. Kenney, J. A. Walsh and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961).

[3] During the present work was in progress Lunn [W. H. W. Lunn, *J. Org. Chem.*, **30**, 2925 (1965)] reported the formation of formaldehyde, which reacted with steroidal ketones and alcohols, from DMSO-BF_3 mixture.

[4] For reviews on the reaction of DMSO see: T. Sato, *Yuki Gosei Kagaku Kyokai Shi (J. Soc. Org. Synth. Chem. Japan)*, **23**, 768, 867 (1965); J.-C. Bloch, *Ann. Chim.*, **10**, 419 (1965).

[5] F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 322 (1958).

[6] E. D. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 161 (1952).

[7] J. W. Jean, U. S. Pat. 2373475 (1945).

[8] H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2965 (1950).

[9] NMR spectra were measured at 60 Mc on a Varian A-60 spectrometer as carbon tetrachloride solution and expressed in δ value (ppm) from tetramethylsilane as an internal reference. The spectra at 100 Mc were kindly measured by Dr. Y. Fujiwara using Varian HA-100 spectrometer at the University of Tokyo.

TABLE 1. THE FORMATION OF DIALKOXYMETHANES FROM ALCOHOLS WITH DMSO-PPA MIXTURE

Alcohol	g	DMSO g	PPA (80%) g	Reaction time hr	Dialkoxymethane				
					Yield %	Bp, °C (mmHg)	n_D (temp., °C)	$\delta_{\mathrm{OCH_2O}}$[e]	$\delta_{\mathrm{OCH_2C,OCH(C)_2}}$
Ethanol	13.8	175	81	4	52[b]			4.61 s	3.59 q
1-Propanol	12.0	117	54	3	—[b,c]			4.60 s	3.45 t
1-Butanol	14.8	117	54	5.5	79[b]			4.60 s	3.48 t
1-Pentanol	17.6	117	54	5.5	83[b]			4.59 s	3.48 t
(±)-2-Pentanol					—[d]	195—196	1.4189 (13.5)	4.60m	3.65m
1-Octanol	26.0	117	54[a]	5	68	141—145 (3)	1.4370 (15.5)	4.52 s	3.42 d
(±)-2-Octanol	13.0	39	19	7	40	122—124 (1)	1.4341 (18)	4.61m	3.67m
Cyclohexanol	33.0	175	81	5	44	144—145 (15)	1.4702 (22)	4.67 s	3.53m
(−)-Menthol	31.2	117	54	5	29	207 (23) [mp 58]	—	4.72 s	3.17m
(+)-Borneol	30.8	117	54	5	28	[mp 168]	—	4.62 s	3.88m

a) Commercial 70% PPA was used.
b) Analyzed by gas chromatography using 2 m of polyethylene glycol on celite 408 column.
c) Peaks for starting material and dipropoxymethane could not be resolved. Distillate (9 g), bp 103—109°C, contained 44% of dipropoxymethane as deduced from NMR.
d) Prepared by the conventional method using *p*-toluenesulfonic acid as acid catalyst.
e) Multiplicity is shown as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

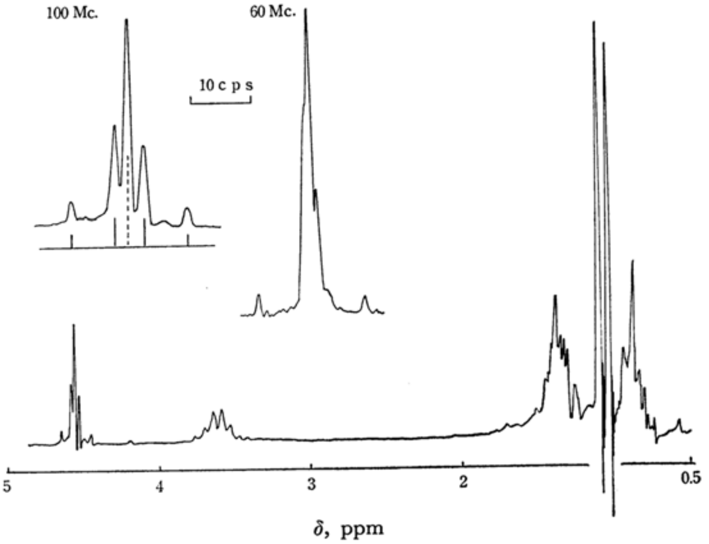

Fig. 1. NMR spectra of bis(1-methylbutoxy)methane (neat) at 100 Mc. Inserts are the acetal methylene signals at 60 Mc (CCl_4) and 100 Mc.

and OCH_2C (or methine protons) are tabulated. Methylene and methine protons at the α position of the alkoxy residue had signals at δ 3.42—3.55 and at 3.17—3.88 respectively in the expected multiplicity. The acetal methylene signal appeared at δ 4.6—4.7. It appeared as a sharp singlet, as was expected, for those compounds prepared from primary alcohols. Dicyclohexyloxymethane also showed a sharp singlet at δ 4.66. Those for bis(1-methylbutoxy)methane and bis(1-methylheptyloxy)methane, however, appeared as multiplets. Derived from the racemic secondary alcohols, they were mixtures of racemic and meso forms.[10] The multiplets at δ 4.60 and 4.61 respectively were shown to be separable into an AB quartet and a singlet. The quartet should be ascribed to non-equivalent methylene protons.[11] The AB quartet was analyzed, by means of the spectra obtained at 100 Mc, as follows:

bis(1-methylbutoxy)methane;

$$\nu_A - \nu_B = 9.2 \text{ cps}, \quad |J_{AB}| = 7.3 \text{ cps}$$

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10) Although no complete separation of the isomers was achieved by the gas chromatography of bis(1-methylbutoxy)methane, the peak appeared as a plateau by using 6 ft column packed with 20% β,β'-ODPN on GC-22 operating at 58°C in contrast to the sharp peaks observed for the uniform acetals.

11) F. A. Bovey, *Chem. and Eng. News*, Aug. **30**, 111 (1965).

bis(1-methylheptyloxy)methane;

$$\nu_A - \nu_B = 8.9 \text{ cps}, \quad |J_{AB}| = 7.3 \text{ cps}$$

In Fig. 1 the spectra for bis(1-methylbutoxy)-methane are shown, together with the partial expanded patterns for the acetal methylene group.

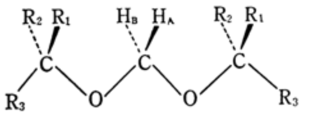
In the type-II compound, in which X* is a group with no plane or center of symmetry, methylene protons experience magnetic nonequivalence and usually show a different chemical shift.[12]

RCH_2X^*	$X^*CH_2X^*$	$X^*YCH_2YX^*$
(II)	(III)	(IV)

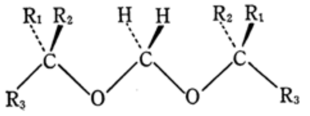
When R is displaced by X* (a type-III compound), methylene protons in the racemic compound become equivalent, because the nonequivalence created by X* is compensated for by the presence of the second X* of the same configuration, whereas in the meso form the two protons are still magnetically nonequivalent. The situation is indicated in the spectra of 2, 4-disubstituted pentanes and, more generally, vinyl chloride[13] or methacryl polymers,[14] whose tacticity has been discussed on the basis of their NMR spectra.[11]

In a type-IV compound,[15] when Y is the group lacking hydrogen(s) which enter spin-spin coupling with central methylene protons, a racemic compound would give a singlet, while the meso compound would show the AB quartet. Dialkoxymethanes prepared from (±)-secondary alcohols belong to this category.

As is illustrated in the formula, the meso compound V possesses a plane of symmetry which involves the acetal methylene group. On the other hand, VI has a two-fold axis of symmetry.



(V)



(VI)

If the above postulation for the observed magnetic nonequivalence is valid, the dialkoxymethanes prepared from optically active secondary alcohol would show a singlet signal for the acetal methylene protons, since they exist only as one of the enantiomers of the racemic form VI. In accord with this expectation, (−)-menthol and (+)-borneol afforded acetals which showed a sharp singlet for the methylene protons at δ 4.72 and 4.62 respectively.

Experimental

The experiments will be illustrated by the representative case of 1-octanol.

Dioctyloxymethane. Under cooling, 54 g of commercial 70% PPA was added to 117 g (1.5 mol) of DMSO, which had been distilled from calcium hydride under reduced pressure; 26 g (0.20 mol) of 1-octanol was then added to this mixture, and the new mixture was heated on a water bath for 5 hr. After 20 min the reaction mixture was separated into two layers. The reaction mixture was diluted with water and extracted with three portions of isopropyl ether. The extract, after being washed with water and dried over magnesium sulfate, was distilled to give 19 g (68%) of dioctyloxymethane, bp 141—145°C/3 mmHg; $n_D^{15.5}$ 1.4370; ν_{max}^{film} 1166, 1115, 1072 and 1040 cm^{-1} and no ν_{OH}; NMR spectra, δ 0.88 (CH_3 6H), 1.28 (CH_2 24H), 3.42 (CH_2O 4H) and 4.52 (OCH_2O 2H). It has been characterized by direct comparison with an authentic material prepared from paraformaldehyde and anhydrous ferric chloride.

A solution of 39 g (0.30 mol) of 1-octanol in 117 g (1.5 mol) of DMSO was heated at 180°C for 10 hr, but this process resulted in the recovery of only the starting material.

A mixture of 20 g (0.15 mol) of 1-octanol and 82 g of 79% PPA was heated on a water bath for 5 hr to give 2 g of a colorless oil, bp 98—128°C/18 mmHg. This product was deduced to be a polymeric hydrocarbon from its boiling point, its refractive index, and its infrared data, which showed bands only at 2925, 2850, 1460 and 1375 cm^{-1}.

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12) E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963) and references cited therein.

13) F. A. Bovey, E. W. Anderson and D. C. Douglass, *J. Chem. Phys.*, **39**, 1199 (1963).

14) F. A. Bovey and G. V. D. Tiers, *J. Polymer Sci.*, **44**, 173 (1960); A. Nishioka, H. Watanabe, K. Abe and Y. Sono, *ibid.*, **48**, 241 (1960); U. Johnsen and K. Tessmer, *Kolloid-Z.*, **168**, 160 (1960); U. Johnsen, *J. Polymer Sci.*, **54**, S6 (1961).

15) Magnetic nonequivalence of methylene protons due to long-range effect of the asymmetric grouping were discussed; G. M. Wittesides, D. Holtz and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964); J. C. Randall, J. J. Mcleskey, III, P. Smith and M. E. Hobbs, *ibid.*, **86**, 3229 (1964).