(24) E. R. Garrett, T. Suzuki, and D. J. Weber, *J. Amer. Chem. Soc.*, **86**, 4460 (1964).
(25) E. G. Sander and C. L. Deyrup, *Arch. Biochem. Biophys.*, **150**, 600 (1972).
(26) We thank Dr. R. T. B. Rye for taking the mass spectrum.
(27) R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **25**, 1583 (1960).
(28) R. Behrend, *Justus Liebigs Ann. Chem.*, **229**, 18 (1885).
(29) "International Critical Tables," **3**, 56 (1928).
(30) C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

Three-Membered Rings. VII. Solvent Control of the Cis–Trans Isomer Ratio in the Preparation of a Phosphonate Substituted Cyclopropane[1]

Eckhard W. Hellmuth, John A. Kaczynski, James Low, and Layton L. McCoy*

Department of Chemistry, University of Missouri—Kansas City, Kansas City, Missouri 64110

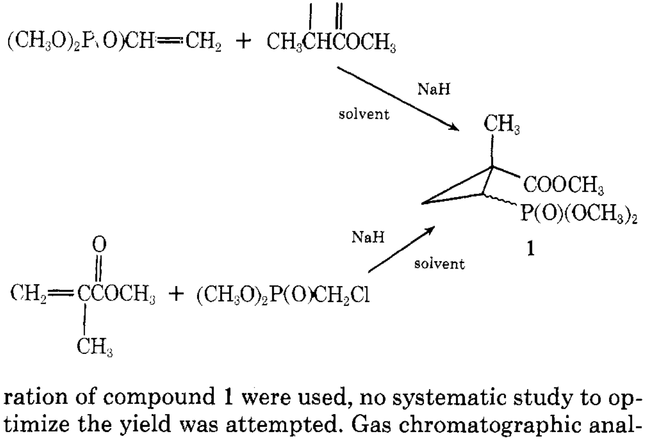
Received March 12, 1974

Dimethyl 2-methyl-2-carbomethoxycyclopropylphosphonate was prepared by the reaction of methyl methacrylate with dimethyl chloromethylphosphonate and sodium hydride in solvent mixtures varying from pure benzene through benzene–dimethylformamide to pure dimethylformamide. Two isomers were observed in all solvents. The stereochemistry proposed for them is based on analysis of their nuclear magnetic resonance spectra. The ratio of trans isomer to cis isomer was determined by gas chromatographic analysis and confirmed by nuclear magnetic resonance spectral analysis. Although log (trans isomer/cis isomer) produces a linear relationship when plotted against the Kirkwood–Onsager term, $(\epsilon - 1)/(2\epsilon + 1)$, for solvent polarity, the correlation is the inverse of nearly all such cases previously reported, *i.e.*, the cis isomer predominates in the polar solvent dimethylformamide and the trans isomer predominates in the nonpolar solvent benzene.

A general procedure for the preparation of polysubstituted cyclopropanes has been examined in earlier papers of this series[2] and in work reported by others.[3] The procedure involves treatment of an α-halo compound with an α,β-unsaturated compound in the presence of a base and solvent. All of the groups reported to "activate" the α-halogen compound and the olefinic compound might be termed carbon functional groups, *i.e.*, functional groups with a central carbon such as esters, amides, nitriles, and ketones. Cyclopropane products thus formed are at least difunctional. The functional groups, the "activating" groups, are on adjacent positions of the cyclopropane ring, oriented cis or trans. It has been observed that the cis/trans isomer ratio is dependent on the solvent: when the solvent is nonpolar, *e.g.*, benzene, the cis isomer predominates, while when the solvent is polar, *e.g.*, dimethylformamide, the cis/trans isomer ratio decreases, usually leading to a preponderance of the trans isomer.[2b] The present report gives an extension of the previous work to include a heteroatom functional group, the phosphonate moiety, and an examination of the solvent effect in this system.

The dimethyl phosphonate group was used to activate either the α-halo group or the olefinic group as shown in Scheme I.[4] Although a variety of conditions for the preparation of compound 1 were used, no systematic study to optimize the yield was attempted. Gas chromatographic analysis showed the presence of two isomers as expected. Complete separation of these isomers was not accomplished in either analytical or preparative scale gas chromatography, but separation was sufficient to determine isomer ratios (confirmed by integrated peak ratios in the nmr spectra of mixtures), to obtain the nmr spectra of each isomer, and to give enriched materials for subsequent saponification. The first isomer eluted in these separations is designated as isomer A, the second isomer B. Control experiments showed that these isomers do not interconvert under the preparative reaction conditions.

Scheme I



Preparation of compound 1 in solvents varying from *N,N*-dimethylformamide (DMF) through mixtures of DMF with benzene to benzene produced changes in the ratio isomer B/isomer A, as seen in Table I. Although these studies of the effect of solvent used the dimethyl chloromethylphosphonate pathway, the dimethyl vinylphosphonate pathway did show the same isomer preference in the nonpolar solvent benzene (the polar solvent dimethylformamide was not examined). In similar studies of isomer ratio–solvent relationships in the preparation of some cyclopro-

Table I
Solvent Composition, Kirkwood-Onsager Term Values, Yields, and Isomer Ratios for the Preparation of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate

Solvent ratio $HC(=O)NMe_2:C_6H_6$	$(\epsilon - 1)/(2\epsilon + 1)$	Yield of phosphonate, %	B/A (trans/cis)	Log (trans/cis)
10:0	0.4803	18	0.19	−0.72
9:1	0.4631	19	0.23	−0.64
8:2	0.4446	38	0.27	−0.57
7:3	0.4246	37	0.42	−0.38
6:4	0.4034	26	0.56	−0.25
5:5	0.3803	35	0.87	−0.06
4:6	0.3555	12	1.27	+0.10
3:7	0.3284	16	1.75	+0.24
2:8	0.2984	8	2.9	+0.46
1:9	0.2627	17	7.9	+0.90
0:10	0.2302	6	14.8	+1.17

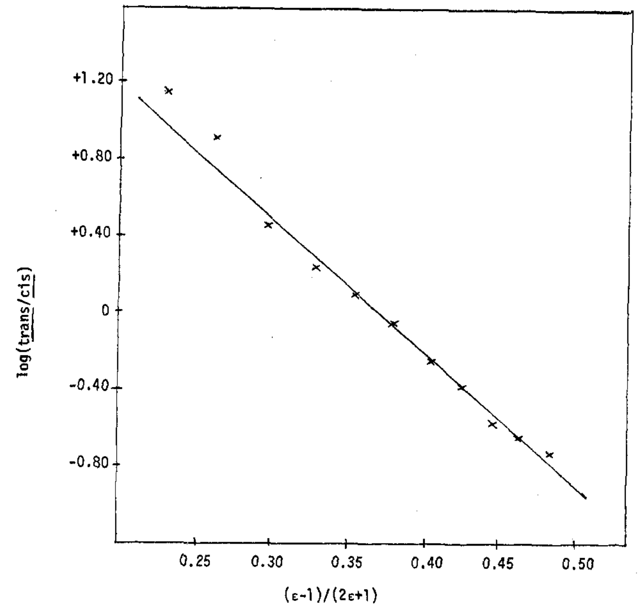


Figure 1. Correlation of isomer ratio [log (trans/cis)] with solvent polarity [(ε − 1)/(2ε + 1)] in the preparation of dimethyl 2-methyl-2-carbomethoxycyclopropylphosphonate.

panedicarboxylic esters, Inouye[5,6] showed that such relationships were consistent with the Kirkwood theory for the effect of the dielectric constant of the media on the reaction rate.[7] Thus, a plot of log (isomer B/isomer A) against the function (ε − 1)/(2ε + 1) where ε is the dielectric constant of solvent gives the result seen in Figure 1.

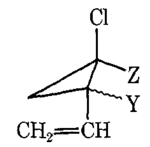
The proposed stereochemistry of the two isomers is based primarily on nmr studies. There are only minor differences in chemical shifts and coupling of the ring hydrogens and the carbomethoxy hydrogens of the two isomers. However, the *C*-methyl hydrogens and the phosphorus methoxy hydrogens in the two isomers are quite different. In isomer A, the *C*-methyl hydrogens appear as a singlet (δ 1.50) while in isomer B they appear as a doublet (δ 1.38, J_{P-H} = 2.3 Hz). On the basis of work by several groups[8] it appears that P–H coupling through two (or three) carbon atoms varies with the dihedral angle as in the Karplus relationship.[9] In the two possible isomers, the C–C–methyl and C–C–phosphorus dihedral angles were estimated at 0 and 105° from models. The largest coupling would occur at 0° and this would be expected to produce an observable doublet. Thus, in isomer B the *C*-methyl would be cis to the phosphonate group or on the basis of the previous discussion would be called the trans isomer (phosphonate and carbomethoxy groups trans). This assignment is consistent with the upfield shift of the doublet arising from through-space shielding of the methyl group by the phosphonate group cis to it.[10] In a somewhat different way, the P *O*-methyl hydrogens confirm this assignment. For isomer A these hydrogens appear as two sets of doublets (δ 3.72, J_{P-H} = 11.2 Hz; δ 3.73, J_{P-H} = 11.0 Hz) while in isomer B they occur as one doublet (δ 3.67, J_{P-H} = 11.2 Hz). P–H coupling will result in the doublets observed, while the appearance of two sets of doublets might be diastereotopic or due to restricted rotation of the phosphonate group. Models suggest that a cis arrangement of the two functional groups produces very severe crowding and possible hindrance to rotation of the phosphonate group; a trans arrangement leaves the phosphonate group much less restricted. Examination of the nmr spectra of isomer A at elevated temperatures (up to 180°) showed no change in the set of doublets, but examination of isomer B at low temperature (down to −70°) changes its nmr spectrum to give a set of doublets very similar to those observed for isomer A. This is consistent with the idea of hindered rotation for the phosphonate group, and the cis relationship of the two bulky functional groups in isomer A.[11]

Saponification of isomer B produced a triacid in which the *C*-methyl produces a doublet (δ 1.40, J_{P-H} = 1.8 Hz) in its nmr spectra. Saponification of isomer A was more difficult and a pure acid was not obtained. However, the nmr spectrum (in D_2O) of the crude acid isolated showed the C-methyl singlet at δ 1.47 and that one phosphonate methyl group (δ 3.70, d, J_{P-H} = 11 Hz) was still present, *i.e.*, unsaponified, possibly owing to the marked steric hindrance and charge concentration with the two functional groups oriented cis.

Thus, we propose that isomer A is the cis isomer and isomer B is the trans isomer. This leads to the interesting observation (Figure 1, Table I) that the effect of solvent on isomer formation apparently is the reverse of that observed previously,[2,3,5,6] *i.e.*, the cis isomer predominates in the polar solvent while the trans isomer predominates in the nonpolar solvent. Although unexpected, this result is not surprising. Application of the Kirkwood theory of solvent effects on reaction rates to the reactions studied here leads to the equation

$$\ln k_t/k_c = C_0 - 1/kT \cdot (\epsilon - 1)/(2\epsilon + 1) \cdot (\mu_c{}^{*2}/r_c{}^{*3} - \mu_t{}^{*2}/r_t{}^{*3})$$

where C_0, k, and T are constants for the present discussion, $\mu_i{}^*$ is the dipole for the transition state of the i reaction, $r_i{}^*$ is the radius of the same transition state, and ε is the dielectric constant for the solvent. Clearly, the slope of the line produced by plotting ln K_t/k_c *vs.* (ε − 1)/(2ε + 1) is determined by the relative dipoles and sizes of the transition states for the cis and trans reactions. Values for these dipoles and sizes can be estimated so as to rationalize observed results,[5] but it is unlikely that sufficiently precise values can be determined *a priori* so as to give reliable predictions. Nearly all previous studies have involved "nonactivating" substituents, *i.e.*, substituents other than the ester, nitrile, or keto functions defining the stereochemistry, which are alkyl groups, and in these cases the generalization of nonpolar solvent–cis isomer, polar solvent–trans isomer is consistent. However, it should be noted that when chlorine is one of the "nonactivating" substituents, although the solvent–isomer ratio trend is still present, the cis isomer predominates in *both* polar and nonpolar solvents.[2b] Further, more recently and subsequent to the completion of this work, Ducher, Sudre, and Vessiere[12] have reported a similar inversion of the solvent–isomer ratio relation. Thus for



with Y = $COOCH_3$ and Z = $COOCH_3$ or CN, only the cis isomer is formed independant of the solvent used ($PhCH_3$ or $[(CH_3)_2N]_3PO$) and with Y = CN the per cent of cis isomer in the isolated product is as follows,

	Z = $COOCH_3$	Z = CN
$PhCH_3$	35	30
$[(CH_3)_2N]_3PO$	62	74

i.e., the cis isomer predominates in the more polar solvent. Thus, the solvent polarity–isomer ratio relation established for systems having alkyl substituents and ester or nitrile activating groups appears not necessarily to be applicable with other types of polar substituents and activating groups. The present work is consistent with and supports the general concept of stereochemical control by transition state dipole–solvent polarity interaction proposed by Inouye.[5] However, in terms of the expression derived from the Kirkwood theory, it is not possible in the general case to make valid, reliable *predictions* as to the nature of the solvent–isomer ratio relation, *i.e.*, which isomer will predominate in which type of solvent, or even if there will be a change in isomer in going from one solvent to another.

Experimental Section

General. Nuclear magnetic resonance spectra were taken on a Varian T-60 spectrometer, or a JEOL JNM-4H-100 spectrometer; the esters were observed in carbon tetrachloride solution and the acids in D_2O unless otherwise mentioned. Gas–liquid chromatographic analyses were carried out on a Varian Aerograph A-90-P gas chromatograph.[13]

Preparation of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate. A. Dimethyl Chloromethylphosphonate.[14] The general conditions are essentially those of Inouye, *et al.*[6] Pertinent results are shown in Table I.

B. Dimethyl Vinylphosphonate.[15] General procedure A[2b] modified so as to filter out the sodium chloride rather than wash it out with water was used; a 57% yield of cyclopropane ester mixture was obtained (bp 122–129°, 1.8 mm).

Products from runs in solvent ratios of 5:5, 4:6, and 3:7 (Table I) were combined and distilled (bp 85–86°, 0.4–0.5 mm). Chromatographic analysis showed only the two isomer peaks in the ratio 51% trans, 49% cis (nmr analysis showed 49% trans). The sample was analyzed. *Anal.* Calcd. for $C_8H_{15}PO_5$: C; 43.25; H, 6.81; P, 13.94. Found: C, 43.13; H, 7.30; P, 13.59.

Saponification of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate. A. Saponification of an ester mixture containing a preponderance (90%) of trans ester occurred readily with aqueous methanolic sodium hydroxide upon slight warming. Concentration of the solution and then addition of concentrated hydrochloric acid precipitated most of the sodium chloride, which was removed. Concentration of the acid solution, solution of the concentrate in acetonitrile, and storage in a refrigerator produced a crystalline acid after a few days. Recrystallization from acetic acid containing a few drops of acetic anhydride resulted in the trans triacid, mp 159.5–160.5°. *Anal.* Calcd for $C_5H_9O_5P$: C, 33.35; H, 5.04; P, 17.20. Found: C, 33.24; H, 4.92; P, 17.12. The mother liquors from the trans triacid produced no further crystalline material. However, both the trans triacid and the mother liquors on treatment with diazomethane produced the triesters, the trans triacid giving pure trans triester and the mother liquors giving a mixture of triesters containing about 75% cis isomer.

B. Triester (76% cis) was saponified under the same conditions. A crystalline acid, mp 120–124°, was isolated; although a variety of solvents were used, the melting point could not be narrowed. An nmr spectrum of this material in dimethyl sulfoxide showed acidic protons at δ 8.43, with the area of this peak being two-thirds the area of the $P(O)(OCH_3)$ doublet (δ 3.55) or the ring methyl group singlet (δ 1.35).

Isomerization Control Experiments. A sample of the triester (65% cis) treated with sodium hydride for 74 hr at temperatures ranging from 25 to 85° showed no change in isomer ratio. Similarly, another sample (50% cis) refluxed with sodium methoxide in methanol for 48 hr showed no change in isomer composition. In several preparations of the triester, samples were removed while reaction was occurring; in all cases, the isomer ratios were essentially the same at all stages of reaction.

Nmr Temperature Studies. These studies were carried out with the JEOL instrument. The low-temperature studies (trans isomer) were carried out in $(CD_3)_2CO$ (15% v/v) with 1–5% tetramethylsilane added as an internal reference. The sample was cooled slowly by cold nitrogen vapor; below −80° the mixture became too viscous for study. Dimethyl sulfoxide was used for the high temperature, the solvent protons acting as reference (δ 2.5). The mixture was heated slowly to the boiling point (189°). For both the hot and cold studies, spectra were taken at room temperature and several intermediate temperatures.

Registry No.—*cis*-**1**, 52176-07-05; *trans*-**1**, 52176-08-6; *trans*-**1** triacid, 52176-09-7; dimethyl vinylphosphonate, 4645-32-3; dimethyl chloromethylphosphonate, 6346-15-2; methyl 2-chloropropanoate, 17639-93-9; methyl methacrylate, 80-62-6.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of John A. Kaczynski, Jr., University of Missouri—Kansas City, 1974, and the M.S. Thesis of James Low, University of Missouri—Kansas City, 1970.

(2) (a) L. L. McCoy, *J. Org. Chem.*, **25**, 2078 (1960); (b) L. L. McCoy, *J. Amer. Chem. Soc.*, **84**, 2246 (1962); (c) L. L. McCoy and G. W. Nachtigall, *J. Org. Chem.*, **27**, 4312 (1962).

(3) See footnote 1 of ref 2b for an extensive but not exhaustive list of such papers.

(4) The obvious combination of the α-halo and olefinic phosphonate compounds with base and solvent to give a diphosphonate substituted cyclopropane has been tried. Although a diphosphonate apparently is formed, we have been unable to purify and characterize it.

(5) Y. Inouye, S. Inamasu, M. Horiike, M. Ohno, and H. M. Walborsky, *Tetrahedron*, **24**, 2907 (1968).

(6) S. Inamasu, M. Horiike, and Y. Inouye, *Bull. Chem. Soc. Jap.*, **42**, 1393 (1969).

(7) J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934).

(8) (a) C. Benezra, *Tetrahedron Lett.*, 4471 (1969); (b) C. Benezra, *J. Amer. Chem. Soc.*, **95**, 6890 (1973); (c) J. A. Ross and M. D. Martz, *J. Org. Chem.*, **34**, 399 (1969); (d) D. Seyferth, R. S. Marmor, and P. Hilbert, *ibid.*, **36**, 1379 (1971).

(9) M. Karpulus, *J. Chem. Phys.*, **30**, 11 (1959).

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 88.

(11) There do not seem to be any clear-cut examples of hindered rotation of phosphonate groups reported. However, possible examples are found: (a) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, **36**, 1379 (1971); (b) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2270 (1961).

(12) S. Ducher, J. P. Suncre, and R. Vessiere, *C. R. Acad. Sci., Ser. C*, 537 (1974).

(13) A variety of columns and conditions were examined; most gave no or unsatisfactory separation. In some of the early work Apiezon L was used, but for the work reported here, phenyl diethanolamine succinate was used. It should be noted that the order of elution of the two isomers is reversed with these two column materials.

(14) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 634 (1950).

(15) Prepared by reaction of 1,2-dibromethane and triethyl phosphite [G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **70**, 1971 (1948)] followed by treatment with phosphorus pentachloride and conversion of the resulting phosphonic dichloride to the dimethyl ester.