Solvent Effect in a Partial Asymmetric Synthesis. III

Kazuyoshi Nishiyama and Yuzo Inouye
Institute for Chemical Research, Kyoto University, Uji, Kyoto

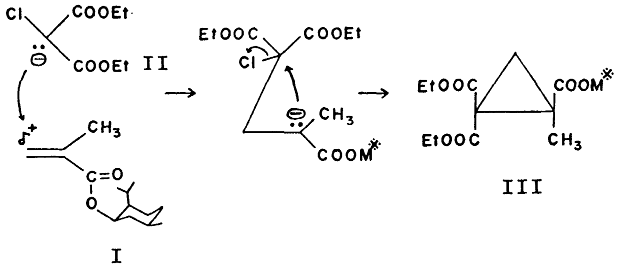
(Received April 22, 1971)

The solvent polarity-dependence of asymmetric stereochemistry was unambiguously corroborated in the Michael type cyclopropane formation in a system designed so as to proceed through the transition state conformations of an equal dipole moment not involving any geometrical isomerism: the NaH-catalyzed condensation of (—)-menthyl methacrylate with ethyl chloromalonate in solvent media of varying polarity resulted in the formation of (—)-1-methylcyclopropane-1,2,2-tricarboxylic acid having the same sign of rotation in all cases. The fit of the stereochemistry to the Kirkwood equation was borne out by the linearity found for the plots of log *R*/*S* against the Kirkwood-Onsager parameter. The *R*-configuration of (—)-1-methylcyclopropane-1,2,2-tricarboxylic acid was established by the correlation to (+)-2,2-diphenyl-1-methylcyclopropanecarboxylic acid of the well-defined (*R*)-configuration.

In previous papers,[1a–d] the solvent polarity-dependence of stereochemistry in the base-catalyzed Michael type cyclopropane formation was unequivocally established and a theory was advanced to rationalize the observed solvent effect. The theory asserts that both the *cis*, *trans*-stereochemistry and simultaneous asymmetric induction are the consequence of a delicate balance between the electrostatic and steric stabilities of the transition state conformations: *i.e.* where the electrostatic factor is dominant over the steric one, the transition state having the greater dipole moment is more stabilized by solvation in polar and strongly solvating media, while the situation is just reversed in non-polar media poor at solvation. This is naturally reflected in the rate of formation and leads to the stereochemical outcome that both *cis*/*trans* and *R*/*S* ratios in the cyclopropane products vary regularly depending upon the solvent polarity, and even a conspicuous reversal of the geometric isomer ratio and the sign of rotation of the cyclopropane products takes place at a given polarity of reaction media. The Kirkwood equation strictly holds for the stereochemistry in this type of reaction.

Gemoetrical isomerism necessarily intervened in all the systems investigated so far[1a–d], which sometime caused an argument[2] against our claim of the solvent effect in asymmetric synthesis. The solvent polarity-dependence of stereochemistry in the system designed so as to afford a single compound capable of existing only in enantiomeric forms would confirm the effect and would also enhance the validity of the theory.

For this purpose, we designed a system involving the NaH-catalyzed Michael type condensation of (—)-menthyl methacrylate (I) with diethyl chloromalonate (II) to give 1-methylcyclopropane-1,2,2-tricarboxylic acid ester (III). In contrast to the earlier systems, product (III) in the present system lacks *cis*, *trans*-isomerism by virtue of structural feature and the reaction gives rise to a single compound as mixture of enantiomers in unequal amounts. This not only simplifies the experimental procedure and makes easier the analysis of stereochemical results of the asymmetric reactions, but also suffices for testing the prediction based on the theory.



Scheme 1

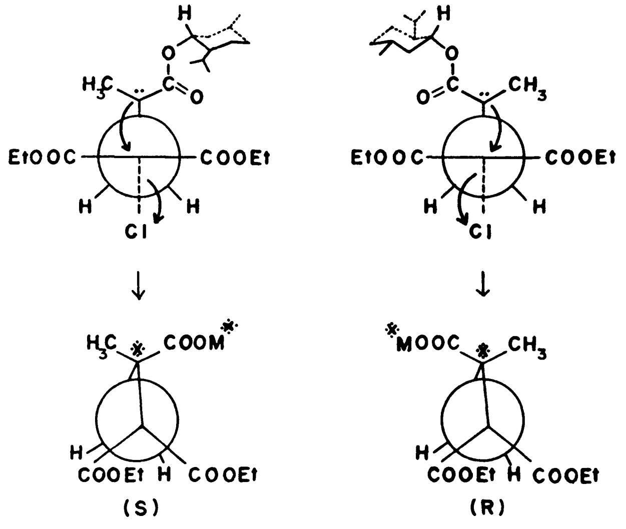


Fig. 1. Transition state conformations leading to *R*- and *S*-1-methylcyclopropane-1,2,2-tricarboxylic acid

Visualized in the Fig. 1 are the transition state conformations (sp^2-model)[1c] which fulfil the stereoelectronic requirements for maximum orbital overlap and charge delocalization and would eventually lead to the enantiomeric *R*- and *S*- products respectively. They have an equal dipole moment (3.2D)[3] and are thus electrostatically equalized to each other. However they differ in steric strain owing to different orientation of the chiral (—)-menthyl moiety.

---

[1] a) Y. Inouye, S. Inamasu, M. Ohno, and H. M. Walborsky, *J. Amer. Chem. Soc.*, **83**, 2962 (1961); b) Y. Inouye, S. Inamasu, and M. Horiike, *Chem. Ind.*, **1967**, 1293; c) Y. Inouye, S. Inamasu, M. Horiike, M. Ohno, and H. M. Walborsky, *Tetrahedron*, **24**, 2907 (1968); d) S. Inamasu, M. Horiike, and Y. Inouye, This Bulletin, **42**, 1393 (1969).

[2] L. L. McCoy, *J. Org. Chem.*, **29**, 240 (1964).

[3] For computation of dipole moment, see ref. 1c.

TABLE 1. ASYMMETRIC SYNTHESIS DATA IN (—)-MENTHYL METHACRYLATE-DIETHYL CHLOROMALONATE SYSTEM

Solvent ratio DMF:benzene	ε	%Yield trimethylester	$[\alpha]_D^{25}$(MeOH) (°)	%Optical yield[a]	R/S
10:0	37.63	7.8	−5.30	6.81	1.1461
9:1	19.87	6.5	−4.42	5.68	1.1204
8:2	13.05	6.9	−3.49	4.48	1.0938
7:3	9.45	7.3	−3.03	3.89	1.0809
6:4	7.26	5.6	−2.73	3.50	1.0725
5:5	5.77	6.5	−2.44	3.13	1.0646
4:6	4.69	6.0	−2.06	2.64	1.0542

a) Based on the maximum rotation $[\alpha]_D^{25}-77.78°$

It is seen that the *R*-transition state conformation is sterically more favored than the *S*-counterpart. It may therefore be safely predicted that inasmuch as the steric factor is the controlling factor, the product acid with the same sign[4] of rotation should result from the reactions. The experimental results are summarized in Table 1.

The yields of the cyclopropane product (III) in the present system were found to be rather poor[5], being accompanied by the formation of ethylenetetracarboxylic acid ester as has been observed in analogous non-dissymmetric reactions,[6] but sufficient for the determination of the sign and magnitude of rotation of the product cyclopropane acid which was isolated pure as trimethylester and fully characterized.

As can be seen from the data, the present asymmetric reaction afforded the cyclopropane acid ester (III-a) of levorotation within experimental errors over the range of polarity investigated (from ε 4.69 through 37.63). The plots of log *R*/*S* against the Kirkwood-Onsager parameter showed a satisfactory linearity (Fig. 2).

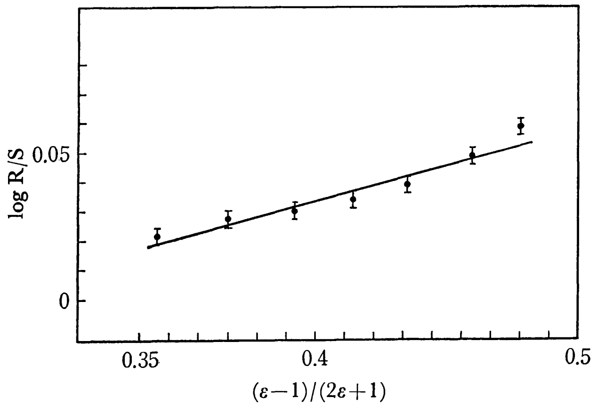
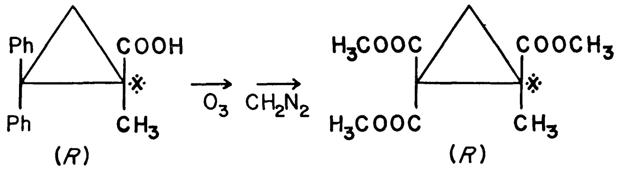


Fig. 2. The plots of log*R*/*S* *vs.*Kirkwood-Onsager parameter of reaction medium

A positive slope of the regression line was found for the plots in the present reactions in contrast to the negative ones in the previous systems. The Kirkwood equation, as applied to the present case (eq. 1) and coupled with the positive slope experimentally found, clearly shows $r_R^{\ddagger}<r_S^{\ddagger}$ (the radius of the transition state carbanion), since the dipole moment $\mu^{\ddagger}$ is equal to both transition state carbanions (Fig. 1). This is in good agreement with the qualitative prediction based on the mere visual inspection of the scale model that the *R*-transition state carbanion is sterically more favored, *i.e.* more compact, which would manifest itself in a smaller molecular radius or volume.

$$\ln R/S = C_0 - 1/\kappa T\cdot(\varepsilon-1)/(2\varepsilon+1)\cdot\mu^{\ddagger 2}\cdot(1/r_S^{\ddagger 3}-1/r_R^{\ddagger 3}) \quad (1)$$

The absolute configuration and the maximum rotation of the product acid ester (III-a), which are indispensable for analysis of the steric course as well as estimation of the extent of optical yields, were obtained by the ozonolysis of (+)-2,2-diphenyl-1-methylcyclopropanecarboxylic acid (IV) of the known *R*-configuration[7] leading to (—)-(III-a). The Brewster calculation of conformational asymmetry predicts [ϕ] —45° for (*R*)-(III-a), which shows an agreement with the observed value [ϕ] —138.6° in the sign of rotation, but not in the magnitude. Considering the empirical nature of the method and since the solvent interaction is not taken into consideration, the value may not be surprising.



Scheme 2

Experimental

General. Melting and boiling points were uncorrected. Rotations were taken on a Yanagimoto Model ORD-185A recording spectropolarimeter: NMR-spectra were on a Varian A-60.

---

[4] Accumulated knowledge of cyclopropane chirality suggests a levorotation for an *R*-configuration of cyclopropane ring carbon bearing polar groups. This rule of thumb is also in fair agreement with the Brewster conformational asymmetry calculation.

[5] This chemical situation may be well understood if one invokes the HSAB principle (R. G. Pearson, *Science*, **151**, 172 (1966) and references cited therein) to the present system: chloromalonate ester carbanion having a moderate base strength comparable to hydroxide anion reacts preferentially with chloromalonate which is harder than (—)-menthyl methacrylate. The self-condensation of chloromalonate thus proceeds *via* the consecutive S_N2 and E2 pathways to give ethylenetetracarboxylate in preponderance.

[6] R. Fraisse and R. Jacquier, *Bull. Soc. Chim. Fr.*, **24**, 986 (1957).

[7] H. M. Walborsky, L. Barash, A. E. Young, and F. J. Impastato, *J. Amer. Chem. Soc.*, **83**, 2517 (1961); C. Djerassi, K. Undheim, and A. Weidler, *Acta Chem. Scand.*, **16**, 1147 (1962).

Asymmetric Synthesis of 1-Methylcyclopropane-1,2,2-tricarboxylic acid ester (III). The synthetic procedure is exemplified by a typical run in a mixture of benzene and DMF (1:9 by volume ratio). The reaction was repeated in exactly the same manner except that the solvent composition was varied.

(−)-Menthyl methacrylate (22.4 g, 0.1 mol, bp 82°C/ 0.7 mmHg, n_D^{25} 1.4575) and diethyl chloromalonate (19.4 g, 0.1 mol) were allowed to react in the presence of sodium hydride (4.8 g, 0.1 mol; dispersed in oil from Metal Hydride Inc., 52.9% purity) in 150 m*l* of mixed solvent (benzene: DMF=1:9 by volume) at 25°C for 6 hr with stirring. The reaction temperature was maintained constant throughout the reaction by cooling with ice water when necessary. After the reaction period, sufficient water was added. The organic layer was extracted with ether and the combined extract, after removal of ether, was then hydrolyzed by refluxing with 8% potassium hydroxide in methanol (200 m*l*) for 40 hr. The hydrolyzate was concentrated by evaporation under reduced pressure and was dissolved in water and the liberated menthol was removed with ether. The aqueous layer was acidified with equivalent hydrochloric acid and the cyclopropane acid was thoroughly extracted with ether. The acid was esterified by the standard method with diazomethane, and the crude trimethylester was separated pure by means of preparative vpc (Varian Aerograph Autoprep 700) on a 10 mm×6 m column packed with Silicone SE 30 (15%) at 185°C using helium gas as carrier. *Trimethyl* 1-*methylcyclopropane*-1,2,2-*tricarboxylate* n_D^{25} 1.4511; Found: C, 51.95; H, 6.29%. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13%. NMR (CCl_4): τ 8.22 (d, J_{gem}=5.0 Hz, cyclopropane methylene 2H); τ 8.60 (s, C-1 methyl 3H); τ 6.26 (s, C-1 ester methyl 3H); τ 6.35 (s, C-2 ester methyl 6H). The IR-spectrum was identical with that of the authentic specimen derived from 1-methyl-2,2-diphenylcyclopropanecarboxylic acid *(vide infra)*. Yield 1.5 g (6.5%); $[\alpha]_D^{25}$ −4.42° (*c* 2.05, MeOH); optical yield 5.66% based on the maximum rotation $[\alpha]_D^{25}$ −77.78°.

Ozonolysis of R-*(+)-1-Methyl-2,2-diphenylcyclopropanecarboxylic acid.* (+)-*R*-1-Methyl-2,2-diphenylcyclopropanecarboxylic acid (mp 189°C, $[\alpha]_D^{25}$ +35° (chloroform); 700 mg), obtained by resolution *via* the brucine salt, was dissolved in acetic acid (100 m*l*). Crude ozone was passed through the solution at room temperature. After prolonged ozonolysis, hydrogen peroxide (30%, 20 m*l*) was added and the mixture was allowed to stand still overnight. Some palladium on carbon was added in order to decompose the remaining peroxide prior to evaporation of the mixture. After acetic acid was removed by evaporation at room temperature, diazomethane was added to the residue. The resulting trimethyl ester was separated pure by means of preparative vpc *(vide supra)*. The IR- and NMR-spectra fully substantiated the structure. Found: C, 52.11: H, 6.18%; Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13%. n_D^{25} 1.4518; $[\alpha]_D^{25}$ −77.78° (*c* 0.78, MeOH); yield 350 mg (54.8%); NMR (CCl_4): cyclopropane methylene protons τ8.22 (d, 2H, J_{gem}=5.0 Hz); C-1 methyl protons, τ 8.60 (s, 3H); ester methyl protons, τ 6.26 (s, 3H) and τ 6.35 (s, 6H).

The dielectric constants of the binary solvent system consisting of DMF and benzene in continuously varied volume ratios were computed by the mixing rule and the data given in a previous paper.[1c)]

The authors are indebted to Professor Walborsky at the Florida State University for the generous gift of samples and also to Professor Griffin at Louisiana State University for his kind suggestions.