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SOLVENT EFFECT IN A PARTIAL ASYMMETRIC SYNTHESIS—I[1,*]

Y. INOUYE,[2] S. INAMASU, M. HORIIKE and M. OHNO
Institute for Chemical Research, Kyoto University, Takatsuki, Japan

and

H. M. WALBORSKY
The Department of Chemistry, Florida State University, Tallahassee, Florida, U.S.A.

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Abstract The *cis/trans* ratio as well as *trans*-(−)-(*R*:*R*)/(+)-(*S*:*S*) ratio of cyclopropane products in the NaH-catalyzed Michael type condensations of (−)-menthyl chloropropionate with methyl methacrylate, conducted in media of varying dielectric constant, unequivocally showed the dependence of stereoselectivity of the reaction on solvent polarity. The stereochemical results were explicable in terms of electrostatic stabilization and non-bonded interactions in the postulated transition state conformations stabilized by orbital overlap in the rate- and therefore, stereochemistry-determining cyclization step. The solvent effect was also correlated fairly well in quantitative terms by the Kirkwood–Onsager theory.

IN AN earlier paper[3] dealing with the base-catalyzed condensation of (−)-menthyl chloroacetate and ethyl acrylate, it was shown that solvent polarity has a marked effect on the stereoselectivity in the partial asymmetric synthesis. That is, changing the solvent medium from toluene to N,N-dimethylformamide or to nitrobenzene results in a complete reversal of sign of rotation in the resulting optically active *trans*-cyclopropane-1, 2-dicarboxylic acid. In support of this finding, the solvent polarity dependence of stereoselectivity was subsequently observed by Pracejus[4] in two partial asymmetric amide syntheses and more recently by Sauer[5] in a partial asymmetric Diels–Alder reaction.

In contrast, McCoy[6] modified an earlier experiment[3] using the (−)-menthyl chloroacetate-methyl acrylate system and concluded that there was not any solvent effect in the asymmetric steric course of the reaction. This was based on his finding that the *cis*-isomer was always produced to more or less extent depending on the solvent polarity along with the *trans*-isomer and that the former was isomerized during alkaline hydrolysis into the thermodynamically more stable *trans*-isomer.

He suggested the difference in ease with which carbomethoxy and carbomenthoxy groups in the diastereomeric (−)-menthyl methyl *cis*-cyclopropane-1,2-dicarboxylate, formed in the kinetically controlled process, were hydrolyzed and isomerized to enantiomeric *trans*-acids and that this asymmetric isomerization of the *cis*-diester, together with the difference in *cis/trans* product ratio in solvents of different polarity, operates so as to make the optical yield in benzene smaller than that in DMF. Although his argument may be reasonable so far as his experiment is concerned, he did not measure the rotation of his products. The present authors were still confident of the

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probable solvent effect in the asymmetric synthesis because Inouye has obtained a more pronounced solvent effect[*] in an asymmetric synthesis which involved (−)-menthyl chloroacetate and (−)-menthyl acrylate where the asymmetric transformation of the *cis*-diester can be safely excluded.

In order to prove the unambiguous operation of a solvent effect in partial asymmetric cyclopropane synthesis of this type, the following system was devised:

The asymmetric isomerization of the products may be circumvented by using a system in which the reaction products are not thermodynamically controlled in the conventional alkaline hydrolysis: i.e. methacrylate-chloropropionate system can meet the above requirement, since in this system, the resulting 1,2-dimethylcyclopropane-1,2-dicarboxylic acid carries no acidic α-hydrogen and the alkaline hydrolysis of isomeric diesters would not be affected by a thermodynamical equilibration. The final product ratios would therefore represent the kinetically controlled results of the asymmetric reaction.

METHODS AND RESULTS

(−)-Menthyl α-chloropropionate and methyl methacrylate were condensed at 25° by means of sodium hydride in a binary solvent system of varying dielectric constant, consisting of DMF and benzene in 10:0 through 0:10 by volume and covering the range of ε 37·63 through 2·28. After 2 hr reaction period, the reaction mixture was worked up as usual[3,8] and the resulting isomeric 1,2-dimethylcyclopropane-1,2-dicarboxylate esters were subjected to hydrolysis with potassium hydroxide in boiling methanol for 45 hours. The acid mixture collected was esterified with diazomethane into the corresponding dimethyl esters, which were separated pure by means of preparative VPC.

Results of the asymmetric reactions conducted in binary solvent system of varying dielectric constant are summarized in Table 1.

TABLE 1. ASYMMETRIC SYNTHESIS DATA IN (−)-MENTHYL CHLOROPROPIONATE–METHYL METHACRYLATE SYSTEM

Solvent ratio DMF:benzene	Dielectric constant (ε)	% Yield dimethylester	*cis*/*trans* ratio	$[\alpha]_D^{25}$ ° *trans*-ester	% Optical yield[*]	*RR*/*SS* ratio
10:0	37·63	41	0·43	+30·80	17·6	0·70
9:1	19·87	46	0·45	+38·18	21·8	0·64
8:2	13·05	48	0·49	+36·60	20·9	0·65
7:3	9·45	39	0·50	+29·49	16·0	0·71
6:4	7·26	45	0·49	+27·80	15·9	0·72
5:5	5·77	43	0·60	+29·63	16·9	0·71
4:6	4·69	35	0·62	+11·93	6·8	0·87
3:7	3·87	34	1·41	+10·11	5·8	0·89
2:8	3·22	35	2·28	+ 6·26	3·6	0·93
1:9	2·66	27	4·58	+ 3·78	2·2	0·96
0:10	2·28	44	ca. 100	− 1·91	−1·1	1·02

[*] Based on the maximum rotation $[\alpha]_D^{25}$ 175°

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[*] *trans*-Cyclopropane-1,2-dicarboxylic acid $[\alpha]_D$ −8·0° in toluene run and $[\alpha]_D$ +5·7° in DMF run.[7]

As can be seen from the data, the *cis*/*trans* ratio of the resulting dimethyl esters in this asymmetric reaction increases with decreasing solvent polarity, i.e. the *trans*-isomer predominated in more polar media rich in DMF, whereas the *cis* in less polar media of more benzene composition. This is consistent with previous findings in non-dissymmetric reactions of this type by other workers.[9–12]

Polarimetric measurement of rotation of the isolated *trans*-esters corroborated the unequivocal operation of solvent effect in the partial asymmetric synthesis: the *trans*-ester formed in benzene was found to be levorotatory, whereas in a more polar media rich in DMF, it was dextrorotatory. This observation, in a system where the thermodynamical control of the asymmetric reaction product is precluded, decidely refutes McCoy's claim.

Furthermore, when log $(-)(R:R)/(+)(S:S)$ was plotted against $(\varepsilon - 1)/(2\varepsilon + 1)$, a good linearity was obtained, as was also the case with log *cis*/*trans* *vs.* $(\varepsilon - 1)/(2\varepsilon + 1)$, although a considerable deviation was observed in the low-dielectric region in the latter case.* The linear relationships between logarithm of the product ratio and the Kirkwood–Onsager parameter of the reaction media, clearly show that the Kirkwood equation is obeyed. Accordingly, the solvent polarity dependence of stereoselectivity of the reaction is evidenced on a more sound basis of kinetic theory. Since both *cis*,*trans*-stereochemistry and the asymmetric induction of the *trans*-isomer in this reaction obey the same rate law, any mechanistic argument should possess a common theoretical basis which enables one to interpret both concomitant steric courses from the identical reactants.

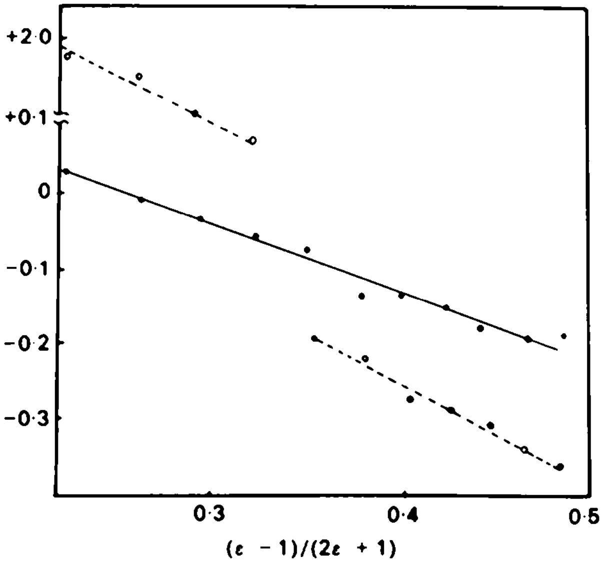

FIG. 1 The plots of log *cis*/*trans* (in dashed line) and log $(-)(R:R)/(+)(S:S)$ (in solid line) *vs.* Kirkwood–Onsager parameter of medium.

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* This deviation may be attributed to the preferential solvation and concentration effect, which will be discussed in footnote at the end of the discussion.

Table 2 summarized data of non-dissymmetric reactions of the same type and will be called upon later in discussing the mechanism.

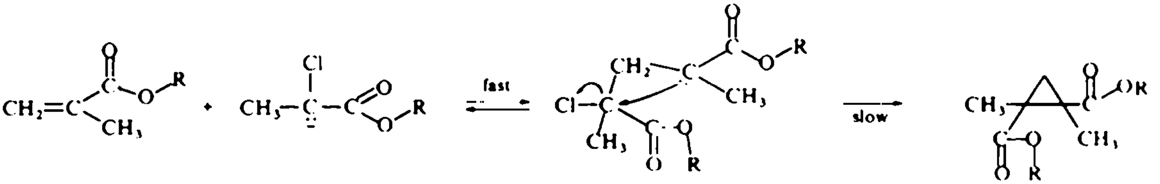
TABLE 2. NON-DISSYMMETRIC REACTIONS OF METHYL CHLOROPROPIONATE WITH METHYL METHACRYLATE UNDER DIFFERENT CONDITIONS (0·1 MOLE SCALE)

Solvent	Volume of medium	Base	*cis*/*trans* ratio of product
DMF	60 ml	NaH	0·41
DMF	60	LiH	0·97
DMF : Benzene (3 : 7)	60	NaH	1·05
DMF : Benzene (3 : 7)	300	NaH	0·79

Informations about the absolute configuration of *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylic acid were obtained by means of ORD of the N-methylthionamide of the optically active acid. The dextrorotatory acid was assigned the (*S* : *S*)-configuration on the basis of the configurational formulation previously reported by us.[13] An identical conclusion may be reached by the Brewster Conformational Asymmetry calculation ($[\phi]_D$ calc $-75°$; $[\phi]_D$ obs $-305°$).

DISCUSSION

The general feature of this reaction is that the thermodynamically less stable *cis*-isomer predominates in the cyclopropane products. This is in contrast to other methods of preparation in which the more stable *trans*-isomer is usually the major product. Attempts have been made to elucidate the *cis,trans*-stereochemistry of this reaction and a tentative interpretation has been proposed by McCoy.[10]



The reaction proceeds through a Michael type addition of α-haloester carbanion to the polarized double bond of acrylate, followed by an intramolecular S_{N_2} cyclization of the adduct carbanion to form a cyclopropane product. As has been known, the initial Michael addition is a fast equilibrated reversible step and the subsequent intramolecular nucleophilic displacement of the intermediate carbanion with Walden inversion is the slow and irreversible i.e. the rate- and therefore stereochemistry-determining step. It is not surprising, therefore, that the electrostatic analysis of conformation of α-haloester carbanion failed in explaining the solvent effect in the earlier asymmetric syntheses.[7, 14]

For an interpretation of the solvent effect in this asymmetric synthesis, one has to consider both electrostatic and steric factors affecting the relative stability of carbanionic transition conformations leading to *cis* or *trans* as well as to *RR* or *SS* cyclopropane products.

It is attractive to postulate a transition intermediate model stabilized by p-orbital overlap for the present system. Dewar[15] advanced a theory for a facile bimolecular nucleophilic displacement of halogen α to a keto group and his theory states that the transition state is stabilized by overlap and conjugation of the C═O π-orbital with the orbitals of the bonds being formed and broken at α-carbon atom. This concept was successfully applied by Zimmerman[16] for stereochemical interpretation of the Darzens reaction, in which the stereochemical preference in epoxide product was overlap-controlled in the rate-determining cyclization step. The overlap stabilization concept can reasonably be applied to the transition state in the present system. The Michael adduct carbanion first formed in the reversible step assumes an sp^3-configuration and as such can not, of course, meet the stereoelectronic requirements for orbital overlap stabilizations.

When this carbanion reaches the transition state for cyclization, the rehybridization of orbitals takes place via sp^2 into sp.[4, 12] Thus, the proposed sp^2-transition model can fulfil the stereoelectronic requirements for orbital overlap stabilizations (Fig. 2).*

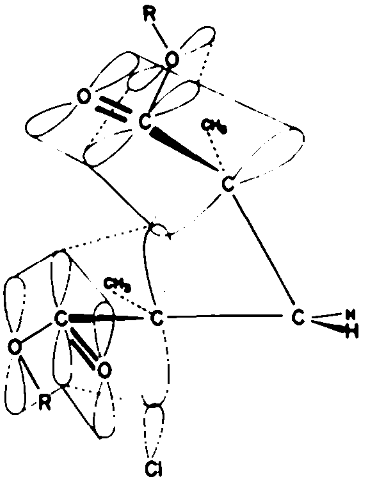


FIG. 2 Side view perspective of the postulated transition conformation model.

In this way, the transition state of intermediate carbanion may be stabilized by orbital overlap and charge delocalization. This transition model permits both *cis* and *trans* geometries due to the relative arrangement of methyl and carbalkoxy groups in the present system and furthermore, because of free rotation around the two single bonds connecting carbalkoxy groups with carbons α and γ, 4 rotomeric conformations with different spatial orientation of carbalkoxy groups are conceivable for each *cis* and *trans* series as depicted in Fig. 3 (only one enantiomer being drawn in head-on view).

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* The picture is too idealized. Clearly a certain amount of rehybridization towards sp,[4, 12] in particular with C_β has taken place by the time the transition state has been reached.

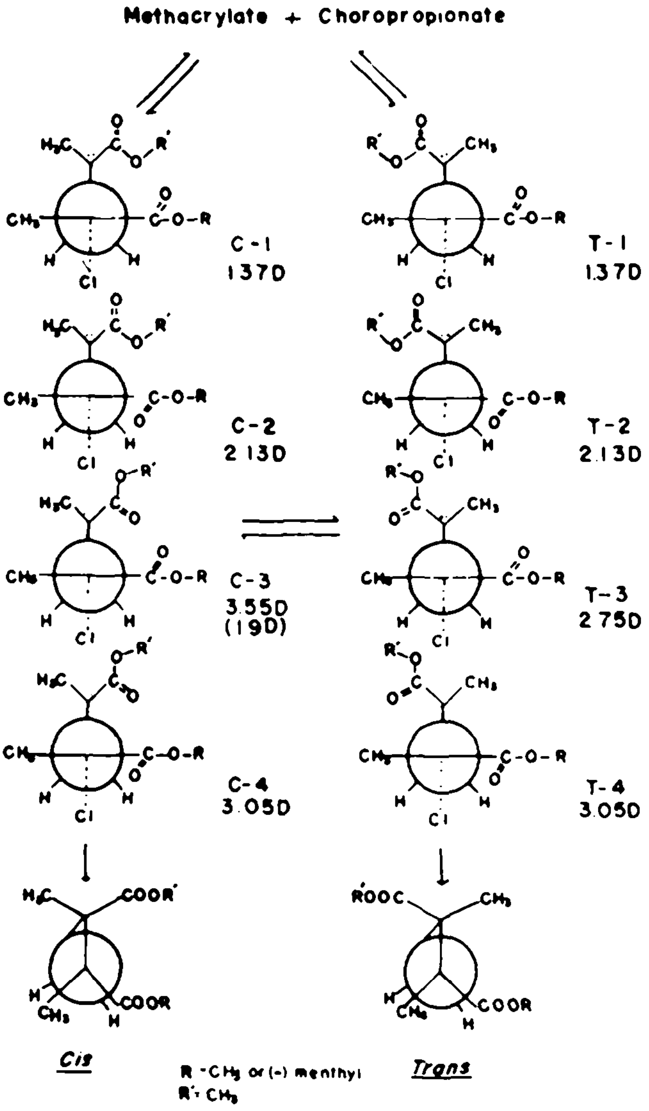
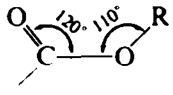


FIG. 3 Transition state conformations leading to *cis*-, and *trans*-cyclopropane products.

Net dipole moments were computed for each of the transition conformations with the postulated transition geometry, by using adequate bond moment values and internuclear angles.

C—O 1·2 D: $C=O$ 2·7 D: C— Cl 1·9 D*

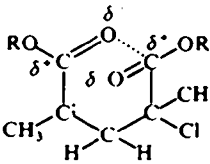


cis

$\angle sp^2\, C_\alpha - C_\beta - sp^2\, C_\gamma = 60°$

A priori the prime consideration being that all non-bonded interactions in the transition state carbanion should be minimized, the transition conformation C-3 may be preferred as the most probable and most populated one of the 4 conceivable *cis*-conformations, and the T-3 in the *trans*-series. There remain two transition conformations, C-3 and T-3, which on cyclization would lead to *cis* or *trans* product respectively. Should the transition intermediate exist as free carbanion, apparently T-3 would be sterically more favored than C-3 with its serious *cis*-compression. Despite this, the *cis*-product is found to predominate, particularly in less polar media.

McCoy[9] explained the preferred stabilization of the *cis*-intermediate carbanion by postulating an "attraction-interaction" due to the close proximity of the two carbalkoxy groups in a conformation which would permit distribution of the negative charge on both ends. This intermediate could yield the *cis*-product by a small and almost unhindered rotation of the leaving group, whereas the rotation necessary for the formation of the *trans*-isomer is considerably more hindered.



Such an attraction due to internal solvation, however, does not account for the formation of considerable amount of *cis*-isomer even in highly polar and strongly solvating media. The charge delocalization may be more reasonably attained by the above-mentioned orbital-overlap. An attractive possibility is chelate formation of metal cation in the C-3 conformation. Fortuitously, the basic ester carbonyl oxygens of the C-3 conformation which was chosen as the most probable one of *cis*-series, in view of minimization of van der Waals repulsions, are so disposed as to enable a metal cation to chelate. As is discernible in Fig. 3, this is not the case in the other C-1,

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* This value of C—Cl σ-bond moment of aliphatic chloride is obviously inadequate for the bond being broken at a transition. Since it is not clear what value one should choose for this, the normal σ-bond moment value was used here. In the absence of any precise information regarding the electrostatic influence of delocalized negative charge on dipole moment, the negative charge was also neglected in computation. These approximations employed here may eventually incur crudity of the over-all moment, which nevertheless seems appropriate for the present purpose of comparison of the relative magnitude of dipole moment of transition conformations.[17]

C-2 and C-4 conformations where the two oxygen atoms are too remote to attain such an effective metal-chelation without violating the stereoelectronic requirement for maximum orbital overlap stabilization. Chelation of this type not only compensates for the otherwise intolerable *cis*-compression but also reduces the component dipole moment of the two carbalkoxy groups. In such a chelate form, the C-3 transition conformation would now have a steric strain comparable to the T-3 in a form of carbanion (or loose ion-pair), and furthermore, would possess an additional electrostatic advantage of smaller moment of residual C-Cl alone (1·9 D).

In support of this view of chelate *cis*-stabilization, the *cis/trans* ratio of the product in a non-dissymmetric reaction in DMF, good at solvation, was found to be much higher with LiH (0·97) than that (0·41) with NaH (Table 2). This demonstrates that reactivity of the carbanionic intermediate is influenced by the nature of the cation in the medium and the increased *cis/trans* ratio in LiH run is brought about by lithium cation forming a more tightly associated chelate than sodium.[18a–c]

In order to see how solvent polarity affects stabilization or destabilization of dipolar species, some pertinent data can be cited. Mizushima[19] and Powling[20] observed that the equilibrium between polar gauche and non-polar anti forms of 1,2-dichloroethane was greatly affected by solvent polarity: the gauche isomer of greater dipole moment predominated in more dielectric media. Wada[21] successfully interpreted this phenomenon caused by energy difference between gauche and anti rotamers in various solutions by assuming spheroidal cavity of the solute molecules and regarding the dipole moment as constituting two point dipoles at the foci of the cavity.

Similar interpretations have been made with conformationally mobile substituted α-halocyclohexanones in various solvents.[22–24] The polarity dependence of conformational mobility was exemplified by (+)-2-chloro-5-methylcyclohexanone which exhibits a positive Cotton effect in methanol whereas a negative one in octane. In light of the Octant Rule, this implies that in methanol, the molecule exists largely in a chair conformation with the α-chlorine disposed in an equatorial position whereas in octane, it is in an axial position. In the former, the C=O and C—Cl are disposed *cis* to each other and the net moment is expected to be greater than that in octane, where the component dipoles point roughly opposite directions (*trans*) and therefore smaller moment. At any rate, it may suffice here qualitatively to state that the more dielectric the medium, electrostatically the more favored is the conformation of greater dipole moment. Returning to the present system, the polarity dependence of conformational equilibrium is invoked to account for the relative electrostatic stabilization of C-3 and T-3 transition conformations of comparable steric strain.

In low-dielectric solvent poor at solvation, electrostatically more favored is the C-3 in a form of tight chelate with smaller dipole moment (1·9 D) and the lower activation energy of C-3 transition conformation should lead to an enhanced rate of cyclization, resulting in the predominant formation of the *cis*-isomer in product. The situation is just reversed in highly dielectric media, where the more polar carbanion T-3 (2·75 D) in the form of solvated free ion (or loose ion-pair) is electrostatically more favored and the lower activation energy of T-3 would lead to an accumulation of the *trans* in preponderance over the *cis*-isomer in the cyclization product.

The *cis,trans*-stereochemistry in this reaction receives an alternative rationale in terms of the Kirkwood theory[25] for the influence of the medium on the free energy of polar molecules.

The Kirkwood equation states the following relation:

$$\ln k = k_0 - 1/\kappa T \cdot (\varepsilon - 1)/(2\varepsilon + 1) \cdot (\mu_A^2/r_A^3 + \mu_B^2/r_B^3 - \mu^{\ddagger 2}/r^{\ddagger 3}) \qquad (1)$$

where k is the rate constant in the medium of dielectric constant ε, and k_0 the rate constant in condensed medium of dielectric constant unity: μ_A, μ_B and $\mu^{\ddagger}$ the dipole moment of the reactants A, B and the transition state: r the radius respectively: κ the Boltzman constant.

The application of Eq. 1 to the present system leads to Eq. 2:

$$\ln k_C/k_T = c_0 - 1/\kappa \mathrm{T} \cdot (\varepsilon - 1)/(2\varepsilon + 1) \cdot (\mu_T^{\ddagger 2}/r_T^{\ddagger 3} - \mu_C^{\ddagger 2}/r_C^{\ddagger 3}) \qquad (2)$$

As was mentioned above, a straight line with a negative slope was obtained by plotting log *cis/trans* of runs in binary system of varying dielectric constant against the Kirkwood–Onsager parameter $(\varepsilon - 1)/(2\varepsilon + 1)$. The product ratio obtained under conditions that ensure kinetic control is equal to the ratio of the specific rate coefficient, *cis/trans* $= k_C/k_T$. In order to show that the Kirkwood equation is obeyed by the present stereochemistry, it suffices to verify that the term $(\mu_T^{\ddagger 2}/r_T^{\ddagger 3} - \mu_C^{\ddagger 2}/r_C^{\ddagger 3})$ is positive with the competing transition conformations C-3 and T-3. This is substantiated by the net dipole moment values computed for the respective conformation: $\mu_T^{\ddagger} = 2{\cdot}75$ D and $\mu_C^{\ddagger} = 1{\cdot}9$ D and as a first approximation $r_T^{\ddagger} \doteqdot r_C^{\ddagger}$.

A reasonable explanation of the solvent effect in the asymmetric synthesis of the *trans*-isomer in the present system can be made on the same theoretical basis. Eight conceivable transition conformations which fulfil the stereoelectronic requirement for orbital overlap in two diastereomeric series are depicted in Fig. 4, together with the respective net dipole moment computed. All these diastereomeric conformations are in the form of solvated free carbanion or loose ion-pair. Again, the principle of minimization of non-bonded interactions, which would be dominant over electrostatic factor, is applied to these conformations, this time taking into consideration the steric influence of the asymmetric moiety of (−)-menthyl grouping. Then, the diastereomeric pair of transition conformations,* R-3 and S-3, which would lead, upon cyclization, to (−)-(*R*:*R*)-, and (+)-(*S*:*S*)-esters respectively, are chosen as the sterically most favored ones, since the methyl group attached to the α-carbon faces the less bulky side of (−)-menthyl group. Model inspection reveals that the steric strain is comparable in R-3 and S-3. The solvent polarity dependence of the competition between R-3 and S-3 transition conformations comparable in steric strain but different in dipole moment, is self-explanatory: in polar media, S-3 of greater moment (3·05 D) is electrostatically more favored whereas the counterpart R-3 of smaller dipole (2·75 D) is favored in non-polar media. The energy difference between the transition states in solvent of varied dielectric constant is reflected in the rate-, and consequently, the enantiomer-ratio of the *trans*-products.

Further substantiation of this explanation for the solvent effect in the asymmetric synthesis is also provided by the Kirkwood treatment. The fine linearity of the plot of log (−)-(*R*:*R*)/(+)-(*S*:*S*) *vs.* $(\varepsilon - 1)/(2\varepsilon + 1)$ was already mentioned and the application of Eq. 1 for the present case results in Eq. 3.

$$\ln k_R/k_S = c_0 - 1\ \kappa \mathrm{T} \cdot (\varepsilon - 1)/(2\varepsilon + 1) \cdot (\mu_S^{\ddagger 2}/r_S^{\ddagger 3} - \mu_R^{\ddagger 2}/r_R^{\ddagger 3}) \qquad (3)$$

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* The energetics of diastereomeric transition states leading to asymmetric synthesis has been systematically described.[26]

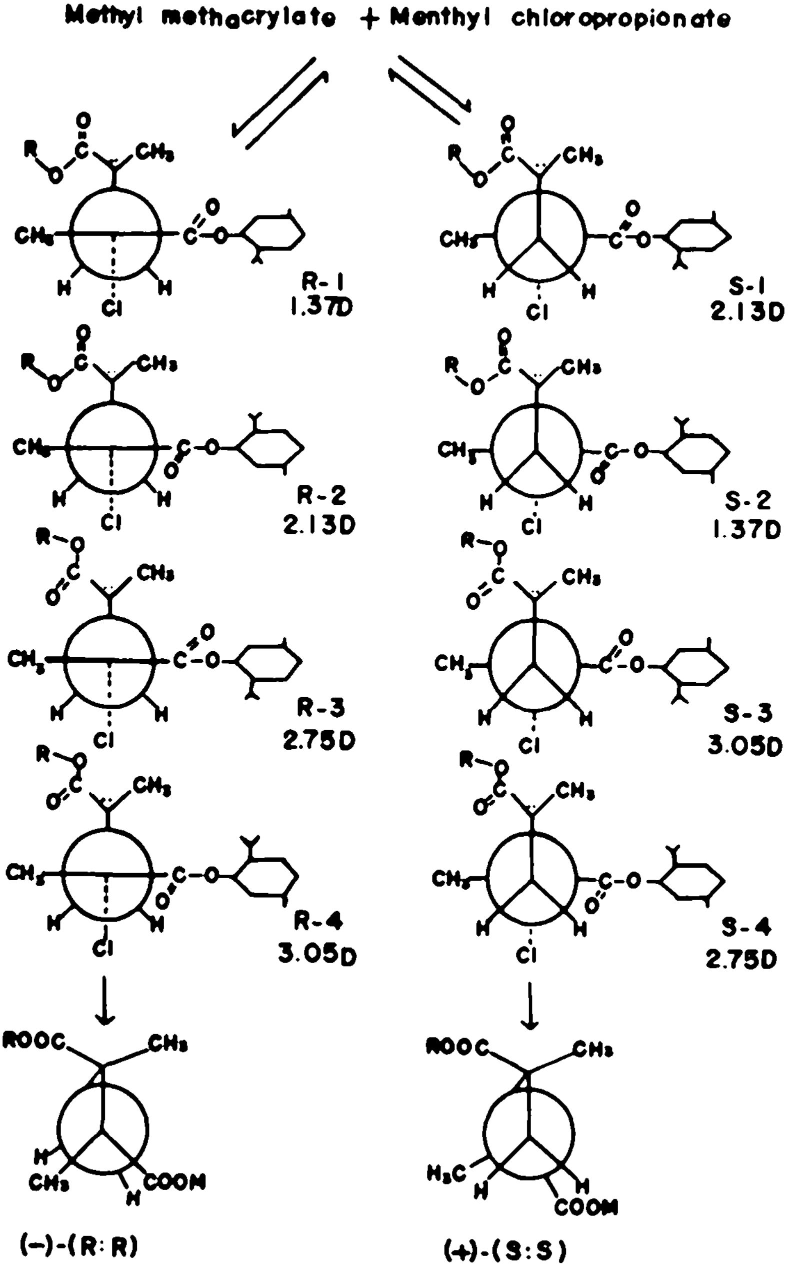

FIG. 4 Transition state conformations leading to (–)-(*R*:*R*) and (+)-(*S*:*S*) products.

Here again, $k_R/k_S = (-)\text{-}(R:R)/(+)\text{-}(S:S)$, and in order that this asymmetric induction obeys the Kirkwood equation, the term $(\mu^{\ddagger 2}_S/r^{\ddagger 3}_S - \mu^{\ddagger 2}_R/r^{\ddagger 3}_R)$ in Eq. 3 has to be positive. On the basis of a reasonable approximation of $r^{\ddagger}_S \doteqdot r^{\ddagger}_R$ and the net dipole-moments $\mu^{\ddagger}_S = 3{\cdot}05$ D and $\mu^{\ddagger}_R = 2{\cdot}75$ D, the unequality $\mu^{\ddagger}_S/r^{\ddagger 3}_S > \mu^{\ddagger 2}_R/r^{\ddagger 3}_R$ obtains. Thus, the enantiomer ratio varies regularly depending on the polarity of medium and this is just what was found experimentally.[*]

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[*] It naturally follows that the plot of log *cis/trans* or log RR/SS against $1/\varepsilon$ or against molar fraction of either component solvent also shows good linearity, since the Kirkwood–Onsager term is proportional to the reciprocal of ε (above 7) and is related by $1/\varepsilon = 0{\cdot}359 - 0{\cdot}72(\varepsilon - 1)/(2\varepsilon + 1)$: and since the molar fraction of component solvents is involved in the Mixing Rule with which the Kirkwood term of the mixed solvent was computed. The latter finding seems to permit one to assume, in an alternative interpretation of the solvent effect, that microscopically the two solvents act independently, and the abruptly rising curve of the plot of log *cis/trans* in the region of higher mole fraction of benzene (ca. 0·7) may well be attributed to preferential solvation of the transition state carbanion (*trans*-conformation) by the higher dielectric and strongly solvating component (DMF). This deviation was amplified by the concentration effect. Actually, each 0·1 mole of the reactants was condensed in 60 ml of the mixed solvent. For example, DMF present in the reaction medium consisting of benzene and DMF in 7:3 by volume is just 0·23 mole, which is probably insufficient to be available for solvation of the intermediate carbanion and sodium cation, and also to permit an unrestricted equilibrium between the chelated and the solvated carbanionic intermediate conformations. The equilibrium is therefore shifted largely toward the chelated side (C-3). Consistently, the *cis/trans* ratio found in a non-dissymmetric reaction of methyl methacrylate with methyl chloropropionate (0·1 mole scale) in 300 ml of the mixed solvent (benzene:DMF = 7:3) was 0·79, which is much lower than the ratio of 1·05 found in 60 ml of the same medium (Table 2). And the ratio (0·79) in complete solution effected by the dilution is just that required by the regression line in the higher dielectric region.

The ground state reactants leading to the pair of diastereomeric transition state (*R*-3 and *S*-3) are identical, so that log k_R/k_S or log $(-)\text{-}(R:R)/(+)\text{-}(S:S)$ is directly proportional to the free energy difference between the two transition states.

$$\log k_R/k_S = \log(-)\text{-}(R:R)/(+)\text{-}(S:S) = \Delta\Delta F^{\ddagger}_{S-R}/2{\cdot}3\,RT = (\Delta F^{\ddagger}_S - \Delta F^{\ddagger}_R)/2{\cdot}3\,RT \qquad \text{(i)}$$

In principle, the activation energy at the transition state may be bisected into electrostatic (el) and steric (st) contributions in origin.

$$\Delta F^{\ddagger}_S - \Delta F^{\ddagger}_R = (\Delta F^{\ddagger}_{S\,el} + \Delta F^{\ddagger}_{S\,st}) - (\Delta F^{\ddagger}_{R\,el} + \Delta F^{\ddagger}_{R\,st})$$
$$= (\Delta F^{\ddagger}_{S\,el} - \Delta F^{\ddagger}_{R\,el}) + (\Delta F^{\ddagger}_{S\,st} - \Delta F^{\ddagger}_{R\,st}) \qquad \text{(ii)}$$

It was assumed that the steric strain in both R-3 and S-3 transition conformations is comparable and therefore, the last term in (ii) is negligible. It then follows:

$$\Delta\Delta F^{\ddagger}_{S-R} = (\Delta F^{\ddagger}_{S\,el} - \Delta F^{\ddagger}_{R\,el}) \qquad \text{(iii)}$$

and since experiments showed the following:

$$\log(-)\text{-}(R:R)/(+)\text{-}(S:S) > 0 \quad \text{in benzene}$$

and

$$\log(-)\text{-}(R:R)/(+)\text{-}(S:S) < 0 \quad \text{in DMF},$$

the energetic requirements for the reversal of rotation of the *trans*-product in the present system of asymmetric synthesis are

$$(\Delta F^{\ddagger}_{S\,el} - \Delta F^{\ddagger}_{R\,el})\ \text{benzene} > 0$$
$$(\Delta F^{\ddagger}_{S\,el} - \Delta F^{\ddagger}_{R\,el})\ \text{DMF} < 0$$

or in a more general form,

$$(\Delta F^{\ddagger}_{S\,el} - \Delta F^{\ddagger}_{R\,el})\ \text{non-polar} > (\Delta F^{\ddagger}_{R\,st} - \Delta F^{\ddagger}_{S\,st})$$
$$(\Delta F_{S\,el} - \Delta F_{R\,el})\ \text{polar} < (\Delta F^{\ddagger}_{R\,st} - \Delta F^{\ddagger}_{S\,st})$$

According to the analysis, the present enantiomer ratio is the consequence of a delicate balance between two factors electrostatic and steric in origin, resonance factor being equal in both transition states.

Similar energetics should naturally hold for the *cis,trans*-stereochemistry in the present system as well.

The steeper slope of the plot of log *cis*/*trans* ratio *vs.* Kirkwood parameter than that of the plot of log (−)-(*R*:*R*)/(+)-(*S*:*S*) against the same parameter is also reasonably accounted for by the relative magnitude of the term of slope in Eqs. 2 and 3.

$$(\mu_T^{\ddagger 2}/r_T^{\ddagger 3} - \mu_C^{\ddagger 2}/r_C^{\ddagger 3}) > (\mu_S^{\ddagger 2}/r_S^{\ddagger 3} - \mu_R^{\ddagger 2}/r_R^{\ddagger 3})$$

EXPERIMENTAL

The asymmetric synthesis of 1,2-dimethylcyclopropane-1,2-dicarboxylic acid. The synthetic procedure is exemplified by a typical run in a mixture of benzene and DMF (2:8 by volume). The reactions were repeated exactly in the same manner except the solvent composition was varied.

Methyl methacrylate (10 g, 0·1 mole) and (−)-menthyl α-chloropropionate (b.p. 138–8·5°/13 mm, n_D^{25} 1·4582: $[\alpha]_D^{25}$ −59·61° (c, 19·2, 1 dm, EtOH): 24·75 g, 0·1 mole) were reacted in the presence of NaH (dispersed in oil from Metal Hydrides, Inc.: 52·9% purity: 4·56 g, 0·1 mole) in 60 ml of the mixed solvent (benzene: DMF = 2:8 by volume) at 25° for 2 hr with stirring. The reaction temp was maintained constant throughout the reaction by cooling with ice–water bath if necessary. After the duration, a small amount of MeOH was added dropwise with stirring to decompose any residual NaH, and sufficient water to dissolve NaCl was added. The organic layer was extracted with ether, washed with sat. NaClaq and then was hydrolyzed by refluxing with a 50% excess of 10% KOHaq in MeOH (200 ml) for 45 hr. The completion of hydrolysis was checked by the disappearance of ester CO band in IR spectrum of the neutral fraction drawn from the reaction mixture. The hydrolyzate was concentrated under reduced press. and the residue was dissolved in water and extracted with ether to remove liberated menthol. The aqueous soln was acidified with 10N H_2SO_4 and was thoroughly extracted with ether. After drying over $MgSO_4$, the ethereal extract was evaporated to give a crude acid mixture. By the standard method with diazomethan, the acid mixture was converted into dimethyl esters; after removal of ether, residual oil was distilled to give a mixture of dimethyl ester of isomeric 1,2-dimethylcyclopropane-1,2-dicarboxylic acids; b.p. 107–118°/20 mm, n_D^{25} 1·4468, yield 8·93 g (48%).

Isomeric diesters were separated by means of preparative VPC (Yanagimoto Model GSC 100) on a column of P.E.G. 20M, 10 mm × 3 m, at 170–178° using He as carrier gas at the flow rate of 400 ml/min. Retention time for the *trans*-ester, 11 min and for the *cis*, 16 min, dimethyl *cis*-1,2-dimethylcyclopropane-1,2-dicarboxylate, b.p. 114–116°/23 mm, n_D^{25} 1·4482, yield 2·94 g: dimethyl *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylate, m.p. 38–39° (after standing in refrigerator), n_D^{25} 1·4465, yield 5·99 g.

The IR spectra of these esters were identical in every respect with those of the authentic specimen, respectively.

The rotation was taken on an Eiko Polarimeter. For the *trans*-ester isolated $[\alpha]_D^{25}$ +36·6° (*c*, 2·52, 1 dm, EtOH): optical yield 20·9% based on the maximum rotation $[\alpha]_D^{25}$ +175°.

Resolution of trans-*1,2-dimethylcyclopropane-1,2-dicarboxylic acid.*

The racemic *trans*-acid was prepared according to McCoy procedure,[8] m.p. 230–231°. (Found: C, 53·18; H, 6·43. Calc. for $C_7H_{10}O_4$: C, 53·16; H, 6·33%).

To a hot soln of the racemic acid (20·16 g, 0·13 mole) in 600 ml water, was added a soln of quinine (42·17 g, 0·13 mole) in 200 ml MeOH, and the resulting soln was boiled to remove excess of MeOH and allowed to stand overnight at room temp, when the quinine salt crystallized out. After triangular fractional crystallization from aqueous MeOH (30%), the quinine salt was decomposed with dil HCl to afford the optically active acid of the constant rotation $[\alpha]_D^{25}$ −193° (*c*, 0·87, 1 dm, EtOH), m.p. 154°, yield 1·1 g; dimethylester b.p. 102°/23 mm, n_D^{25} 1·4438; $[\alpha]_D^{25}$ −175° (*c*, 0·63, 1 dm, EtOH).

Configurational correlation of trans-*1,2-dimethylcyclopropane-1,2-dicarboxylic acid.* According to the procedure of Sawada,[13] the optically active (+)-*trans*-1,2-dimethylcyclopropane-1,2-dicarboxylic acid was converted via dimethylamide into the corresponding N,N-dimethylthionamide, m.p. 183° dec. (Found: C, 53·98; H, 8·46; N, 11·23. Calc. for $C_{11}H_{20}N_2S_2$: C, 54·10; H, 8·20; N, 11·48%).

The IR spectrum of the thionamide exhibited the characteristic bands at 1056, 1455 and 1385 cm^{-1} and the UV (EtOH) absorption max 352 mμ (ε 88·2).

N,N-dimethylthionamide showed a positive Cotton curve in MeOH.

1st extremum $[\phi]$ $+20{\cdot}97 \times 10^2$ at 384 mμ
2nd extremem $[\phi]$ $-24{\cdot}56 \times 10^2$ at 326 mμ
molar amplitude (*a*) 45·53

Calculation of the dielectric constants of mixed solvents.

The dielectric constants of the binary system consisting of benzene and DMF in continuously varied volume ratios were computed by means of the Mixing rule[27] for the molar polarizability.

$$\frac{(\varepsilon_{12}-1)}{(\varepsilon_{12}+2)}\cdot\frac{M_{12}}{\rho_{12}} = \frac{(\varepsilon_1-1)}{(\varepsilon_1+2)}\cdot\frac{M_1}{\rho_1}\cdot C_1 + \frac{(\varepsilon_2-1)}{(\varepsilon_2+2)}\cdot\frac{M_2}{\rho_2}\cdot C_2$$

where ε: dielectric constant
M: molecular weight
ρ: density
C: molar fraction

subscripts 1,2 and 12 indicating the components and the mixed solvent of the binary system.

By substituting the known dielectric constants, 2·28 D for benzene and 37·6 D for DMF and the observed densities of the mixed solvents, the ε and then the Kirkwood Onsager parameter values were obtained, which was collected in Table 3.

TABLE 3. CALCULATIONS OF DIELECTRIC CONSTANT AND KIRKWOOD–ONSAGER PARAMATER OF DMF-BENZENE MIXTURE

DMF : Benzene (by volume)	$\rho_{obs.}$ (25°C)	$\frac{(\varepsilon-1)}{(\varepsilon+2)}$	ε	$\frac{(\varepsilon-1)}{(2\varepsilon+1)}$
10:0	0·9440	0·9242	37·63	0·4803
9:1	0·9379	0·8626	19·87	0·4631
8:2	0·9315	0·8006	13·05	0·4461
7:3	0·9252	0·7386	9·45	0·4246
6:4	0·9185	0·6762	7·26	0·4034
5:5	0·9120	0·6140	5·77	0·3804
4:6	0·9049	0·5514	4·69	0·3555
3:7	0·8977	0·4885	3·87	0·3284
2:8	0·8901	0·4254	3·22	0·2984
1:9	0·8820	0·3624	2·66	0·2627
0:10	0·8730	0·2991	2·28	0·2302

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