BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1393—1398 (1969)

Solvent Effect in a Partial Asymmetric Synthesis. II[1]

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(Received September 27, 1968)

Further evidence for the unambiguous solvent polarity dependence of the stereochemistry in the base-catalyzed Michael type condensation was provided by the systems involving (—)-menthyl chloroacetate and methyl acrylate, and (—)-menthyl chloroacetate and (—)-menthyl acrylate with a modification of the work-up. The electrostatic control of the stereoselectivity was interpreted by the same theorem developed in the previous study and some novel features found for the present systems were discussed.

The first example of an olefin addition in which both the stereochemical outcome and optical yield are solvent polarity-dependent was presented in our earlier work[1a)] dealing with the base-catalyzed Michael type condensation of (—)-menthyl chloroacetate with ethyl acrylate to give optically active *trans*-cyclopropane-1,2-dicarboxylic acid plus a trace of the *cis*-acid after removal of the chiral center by

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[1] Previous papers of this series: a) Y. Inouye, S. Inamasu, M. Ohno and H. M. Walborsky, *J. Am. Chem. Soc.*, **83**, 2962 (1961); b) Y. Inouye, S. Inamasu and M. Horiike, *Chem. Ind.* (*London*), **1967**, 1293; c) Y. Inouye, S. Inamasu, M. Horiike and H. M. Walborsky, *Tetrahedron*, **24**, 2907 (1968).

alkaline hydrolysis. The stereochemistry of this asymmetric reaction depended markedly on the solvent: in toluene, the *trans*-diacid obtained was levorotatory whereas in dimethylformamide, this acid had the opposite configuration and the optical yield was higher.

In contrast to this finding, McCoy[2] argued that the actual asymmetric synthesis of the *trans*-diacid was unaffected by a change of solvent but that the change in configuration of the *trans*-acid was due to a possible asymmetric *cis*-to-*trans* isomerization of the diastereomeric (−)-menthyl ethyl *cis*-diesters which were formed in the initial kinetically controlled process. Recent results by the present authors,[1b,c] however, decidedly refuted McCoy's claim and established the solvent effect in the asymmetric synthesis of this type on a more sound basis of kinetic theory. The NaH-catalyzed condensation of (−)-menthyl α-chloropropionate with methyl methacrylate, in which the resulting *cis*- and *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylic acids carry no acidic α-hydrogen and the asymmetric isomerization by alkaline hydrolysis is excluded, was conducted in a binary solvent system of continuously varied dielectric constant. The *cis*/*trans* as well as *trans*-(−)-(R:R)/(+)-(S:S) ratios of the cyclopropane products unequivocally corroborated the dependence of stereoselectivity of the reaction on solvent polarity. That is, the *trans*-isomer predominated in more polar solvents whereas the *cis* in non-polar media and the *trans*-isomer produced in non-polar media exhibited levorotation whereas those in polar media were dextrorotatory. The solvent effect was accommodated fairly well in quantitative terms by the Kirkwood-Onsager theory as shown by the fine linearity of the plots of logarithms of *cis*/*trans* and (−)-(R:R)/(+)-(S:S) ratios against the Kirkwood-Onsager parameter of the reaction media. The stereochemical outcome was nicely explicable in terms of electrostatic stabilization and non-bonded interactions in the postulated transition state conformations which were stabilized by orbital overlap and charge delocalization at the rate-, and therefore, stereochemical-determining cyclization step.

In the present work, further evidence for the unambiguous operation of solvent effect is provided by both the earlier (−)-menthyl chloroacetate-methyl acrylate and the novel (−)-menthyl chloroacetate-(−)-menthyl acrylate systems with the work-up modified so that the final product ratio can represent the kinetically controlled results of the reaction. The conventional alkaline hydrolysis of the resulting diesters was replaced by lithium aluminum hydride reduction capable of converting the diesters into the corresponding stereomeric diols without thermodynamical equilibration and jeopardization of the absolute configurations of the reaction products.

Methods and Results

(−)-Menthyl chloroacetate was condensed with equimolar methyl acrylate or (−)-menthyl acrylate by means of sodium hydride at 25°C in binary solvent system of continuously varied dielectric constant, consisting of dimethylformamide and benzene in 10 : 0 through 0 : 10 by volume and covering the polarity range of ε 37.63 through 2.28. After 2 hr's reaction period, the resulting mixture was worked up as usual[1c] and the mixture of stereomeric cyclopropane-1,2-dicarboxylate esters was reduced with an excess of lithium aluminum hydride. Addition of acetic anhydride to the reaction mixture afforded *cis*-, and *trans*-1,2-bis-(acetoxymethyl)-cyclopropane, which was purified by distillation and separated pure by means of preparative vpc.

Results of the asymmetric reactions conducted in binary solvent system of continuously varied dielectric constant are summarized in Tables 1 and 2.

TABLE 1. ASYMMETRIC SYNTHESIS DATA IN METHYL ACRYLATE-(−)-MENTHYL CHLOROACETATE SYSTEM

Solvent ratio DMF : benzene	Dielectric constant (ε)	% Yield glycol-diacetate	*cis* : *trans* ratio	$[\alpha]^{25}_{D}$(EtOH) *trans*-diacetate	% Optical yield	RR : SS ratio
10 : 0	37.65	47.8	0.14	+1.75	9.85	0.82
9 : 1	19.87	43.6	0.15	+1.40	7.89	0.85
8 : 2	13.05	44.8	0.18	+1.38	7.77	0.90
7 : 3	9.45	51.8	0.19	+0.93	5.23	0.93
6 : 4	7.26	41.5	0.28	+0.52	2.92	0.94
5 : 5	5.77	40.4	0.34	+0.44	2.47	0.95
4 : 6	4.69	41.0	0.44	+0.10	0.53	0.98
3 : 7	3.87	44.3	0.53	+0.04	0	1
2 : 8	3.22	43.5	0.60	−0.29	1.63	1.03
1 : 9	2.66	45.2	1.11	−0.73	4.11	1.09
0 : 10	2.28	41.0	4.10	−1.36	7.66	1.16

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

TABLE 2. ASYMMETRIC SYNTHESIS DATA IN (−)-MENTHYL ACRYLATE-(−)-MENTHYL CHLOROACETATE SYSTEM

Solvent ratio DMF : benzene	Dielectric constant (ε)	% Yield glycol-diacetate	*cis* : *trans* ratio	$[\alpha]_D^{25}$ (EtOH) *trans*-diacetate	% Optical yield	RR : SS ratio
10 : 0	37.65	39.4	0.26	+0.82	4.62	0.91
9 : 1	19.87	37.8	0.31	+0.53	2.99	0.94
8 : 2	13.05	39.5	0.36	+0.27	1.52	0.97
7 : 3	9.45	36.1	0.46	0	0	1.0
6 : 4	7.26	35.8	0.48	−0.15	0.8	1.02
5 : 5	5.77	36.7	0.58	−0.54	3.04	1.06
4 : 6	4.69	35.1	0.66	−0.81	4.56	1.09
3 : 7	3.87	38.0	0.78	−1.07	6.03	1.13
2 : 8	3.22	37.2	0.88	−1.30	7.32	1.16
1 : 9	2.66	35.6	1.31	−1.63	9.18	1.19
0 : 10	2.28	34.0	6.24	−1.83	10.30	1.23

As can be seen from the data, the *cis/trans* ratio of the resulting glycol diacetates in these asymmetric reactions trends to increase as the solvent polarity decreases *i.e.* the *trans*-isomer predominated in more polar media rich in DMF, whereas the *cis* in less-polar media of more benzene composition.

The sign of rotation of the isolated *trans*-diacetates altered on changing the polarity of reaction media: the *trans*-diacetates obtained in less-polar media were found to be levorotatory, whereas those in more polar media were dextrorotatory. These findings, including the *cis*, *trans*-stereoselectivity, are completely consistent with those in the previous system and this fact, in the present systems where the thermodynamical equilibration of the asymmetric reaction product is excluded by the modification of work-up, furnished further cogent evidence for the unequivocal operation of solvent effect in the asymmetric cyclopropane synthesis.

Furthermore, when log (−)-(R:R)/(+)-(S:S) was plotted against the Kirkwood-Onsager parameter of the reaction media, a fine linearity was obtained in both systems (Figs. 1 and 2), as was also the case with log *cis/trans* *vs.* $(\varepsilon-1)/(2\varepsilon+1)$. A considerable deviation from the linearity of the regression lines of log *cis/trans* plots was observed also in the pure benzene runs of the present systems. This anomalous *cis*-formation in pure benzene may be accounted for by the same heterogeneity effect in this medium, as discussed in the previous paper.[1c)]

The linearity of the plots obviously shows the obedience of both *cis,trans*-stereoselectivity and asymmetric induction to the Kirkwood equation.

The absolute configuration and maximum rotation of the final product in the present asymmetric reaction, *trans*-1,2-bis(acetoxymethyl)-cyclopropane, were determined by the conversion of (−)-*trans*-cyclopropane-1,2-dicarboxylic acid of the well-

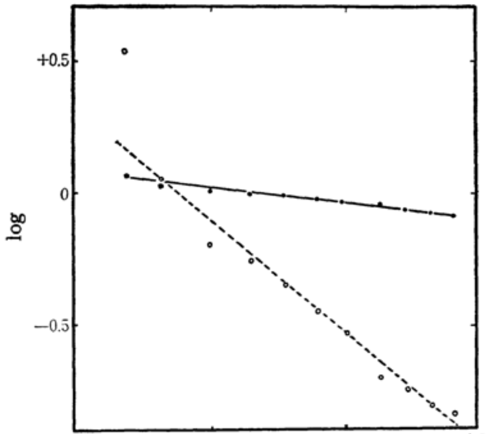

Fig. 1. The plots of log *cis/trans* (in dashed line) and log (−)-(R:R)/(+)-(S:S) (in solid line) *vs.* Kirkwood-Onsager parameter of media in methyl acrylate-(−)-menthyl chloroacetate system.

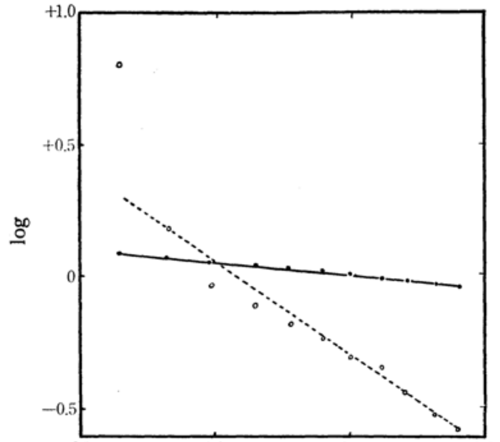

Fig. 2. The plots of log *cis/trans* (in dashed line) and log (−)-(R:R)/(+)-(S:S) ratio (in solid line) *vs.* Kirkwood-Onsager parameter of media in (−)-menthyl acrylate-(−)-menthyl chloroacetate system.

defined (R:R)-configuration[3] into (−)-*trans*-1,2-bis(acetoxymethyl)-cyclopropane. Since the starting (−)-(R:R)-acid, $[\alpha]_D^{25}$ −235°, was optically pure, the eventually derived (−)-diacetate, $[\alpha]_D^{25}$ −17.75°, should have the (R:R)-configuration and the rotation found should be maximal.

Discussion

The stereochemical outcome in the present systems is completely consistent with those in the previous system involving the base-catalyzed Michael type condensation of (−)-menthyl α-chloropropionate with methyl methacrylate (for convenience, designated as system A) and accordingly, can be successfully accounted for by the same theorem developed in the previous paper.[1c] Thus, the transition state of the intermediate carbanion is stabilized by orbital overlap and charge delocalization in the postulated sp^2-model conformation[1c] and, the steric factor being comparable in both competing transition state conformers as estimated by model inspection of the non-bonded interactions, then *ceteris paribus*, the electrostatic stabilization which varies depending on the solvent polarity becomes the controlling factor of the steric course of the reaction.

The carbanionic transition state *cis*-conformer with a reduced dipole moment (1.9 D) and a *cis*-compression relieved by the sodium cation chelation is electrostatically more favored in non-polar solvents than the *trans*-counterpart with a greater moment (2.75 D), and the situation is just reversed in polar and strongly solvating media. This naturally leads to the predominant formations of the *cis*-product in non-polar media, and of the *trans*-isomer in polar media. It is surprising to find that the regression line found for the log *cis*/*trans* plots in (−)-menthyl chloroacetate-(−)-menthyl acrylate system (designated as system C) is shifted towards the positive side as compared to that in (−)-menthyl chloroacetate-methyl acrylate (system B). *A priori*, the transition state *cis*-conformer in the system C may well be expected to experience a more serious *cis*-compression between two bulky carbomenthoxy groups than that between carbomenthoxy and carbomethoxy to be felt by the corresponding *cis*-conformer in the system B, and this should naturally disfavor the *cis*-formation in the system C. Despite this, the experiment actually showed that the system C is prone to produce more *cis* relative to *trans* than does the system B. A tentative interpretation of this stereochemical result is as follows. The microscopic dielectric constant (ε') of a cospherical region surrounding a carbanion is considered as being affected by the charge, steric shielding and local polarity of substituent groups of the carbanion, and is duly different from the macroscopic bulk dielectric constant (ε) outside this region. It is within this region that the reaction actually takes place. The polarization of solvent molecules within this region depends on ε' and thus, the degree and type of solvation of carbanion are also dependent on this parameter. The polarity (ε') of cybotactic region of the transition state *trans*-conformer in the system C would be lowered by the more steric shielding and the lower local polarity of the two carbomenthoxy groups than that of the corresponding *trans*-conformer in the system B which would be affected by a less bulky and more polar carbomethoxy and a carbomenthoxy group. The electrostatic stabilization of the *trans*-conformer in the system C by solvation is thus reduced by the lower polarity and steric shielding of its cybotactic region and this contributes more to the relative stability of the *cis*-counterpart with smaller moment in the unsolvated chelate form. The chemical consequence for this situation is the favored *cis*-formation in the double induction system. As a fair approximation, ε' should be a function of the bulk dielectric constant which is conveniently measured with pure solvent, so that the linearity of the log *cis*/*trans* *vs.* $(\varepsilon-1)/(2\varepsilon+1)$ plots in this case is reasonably borne out. For better understanding of this phenomenon, further investigations are needed and this will be the subject of furture publications.

A successful explanation of the solvent effect in the asymmetric synthesis of the *trans*-isomer in the present systems B and C can be made on the same theoretical basis as in the system A and/or the above-mentioned *cis*,*trans*-stereoselectivity. Of conceivable transition state conformations which fulfill the stereoelectronic requirements for orbital overlap and charge delocalization, the *trans*-conformer with a dipole moment of 2.75 D[1c] which, upon cyclization, would lead to the (R:R)-enantiomer, and the other with a slightly greater moment (3.05 D) leading to the (S:S)-product are chosen as sterically the most favored transition state conformer in each diastereomeric series, because of their minimized non-bonded repulsive interactions. Since the electrostatic stabilization of the carbanion by solvation is the controlling factor in the asymmetric induction too, the energy difference between these two transition states in solvents of varying polarity is reflected in the rate-, and consequently, the enantiomer-ratio of the *trans*-products. Reversal in sign and configuration of the *trans*-products was actually observed in the present systems B and C upon changing the solvent polarity. The fine linearity found for the log RR/SS plotted against the Kirkwood-Onsager parameter clearly shows the strict obedience of the asymmetric induction to the Kirkwood equation and provides cogent evidence based on kinetic

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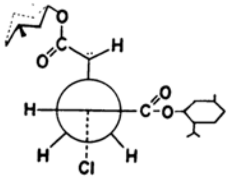
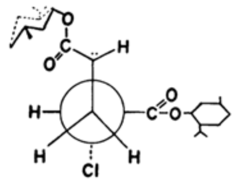
[3] Y. Inouye, T. Sugita and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).

theory for the solvent effect in the asymmetric induction of this type.

By superimposing the Figs. 1 and 2, one is aware of a slight shift of the log RR/SS plots in the double induction system C towards the positive side as compared to that in the system B. This implies that the levorotatory (R:R)-enantiomer is inclined to form to a more extent relative to the (S:S)-enantiomer in the double induction system than does in the system B. This may be rationalized by the steric advantage of the (R:R)-carbanion over the (S:S)-counterpart.



RR (2.75 D)



SS (3.05 D)

Model inspection reveals that the steric strain is comparable in the competing (R:R)- and (S:S)-transition state conformers in the system B (as was also the case in the system A), whereas in the double induction system C, the (R:R)-conformer (2.75 D) is sterically more favored than the (S:S)-counterpart (3.05 D). Upon intramolecular nucleophilic displacement, the latter carbanion has to experience more steric hindrance with the more bulky side (extended isopropyl branch) of (−)-menthyl grouping oriented towards the γ-carbon carrying the leaving chlorine atom, whilst in the former (R:R), this can be done with less hindered side of the menthyl. The (R:R)-conformer is thus sterically more favored than in the case of the system B, but this steric advantage *per se* is not great enough to control the steric course of the asymmetric induction and the electrostatic factor still remains dominant, so that the enantiomer ratio varies depending upon the solvent polarity and the sign of rotation of the products alters at ε 9.45. Although the point of the reversal of rotation was found at ε 3.87 for the system B and at ε *ca.* 2.4 for A, it is noteworthy that all the regression lines in the three asymmetric systems have nearly the same slope. In contrast to expectation, the optical yields in the double induction system C were not so high, as compared with those in the system B. This may well be understood by reasoning that the transition state in the double induction sees quite a different stereochemical environment from that in the individual asymmetric induction.

Experimental

The Asymmetric Synthesis of 1,2-Bis-(acetoxymethyl)-cyclopropane. The synthetic procedure is exemplified by a typical run of the (−)-menthyl chloroacetate-methyl acrylate system in a mixture of DMF and benzene (1 : 9 by volume). The reactions were repeated in exactly the same manner except the solvent composition. For the (−)-menthyl chloroacetate-(−)-menthyl acrylate system, the identical procedure was followed with one of the reactants changed.

Methyl acrylate (10.5 g; 0.12 mol) and (−)-menthyl chloroacetate (23.3 g; 0.1 mol) were condensed in the presence of sodium hydride (dispersed in a mineral oil from Metal Hydrides Inc., a commercial grade of 50% purity: 4.8 g; 0.1 mol) in 60 m*l* of the mixed solvent (DMF : benzene = 1 : 9 by volume) at 25°C for 2 hr with stirring. The reaction temperature was maintained constant throughout the reaction by cooling with ice-water if necessary. After the duration, a small amount of methanol (*ca.* 3 g) was added dropwise to the reaction mixture with stirring and cooling to decompose any residual hydride, and then sufficient water was added to dissolve sodium chloride. The organic layer was taken up in benzene, washed with saturated sodium chloride solution and dried by means of molecular sieves. Removal of solvent *in vacuo* yielded a mixture of crude, isomeric (−)-menthyl methyl cyclopropane-1,2-dicarboxylates, which weighed *ca.* 26 g. According to the Blomquist procedure,[4] the crude diester was reduced with lithium aluminum hydride (12 g; 0.3 mol) in absolute ether (300 m*l*). Acetic anhydride (100 m*l*) was added to the reaction mixture and ether was replaced with further anhydride to facilitate stirring and refluxing. After 10 hr, acetic acid, residual anhydride and (−)-menthyl acetate were driven in steam and the residue was extracted with ether. After drying, ether was removed to give crude, isomeric 1,2-bis-(acetoxymethyl)-cyclopropanes (*ca.* 9.5 g). This was distilled on a column packed with dixone to remove (−)-menthyl acetate and a fraction boiling at 108—125°C/17 mmHg was collected (*ca.* 8.4 g). Isomeric glycol diacetates were separated by means of preparative scale vpc (Wilkins Autoprep. 700) under the following conditions[*1]: column 3/8 in ×10 ft, Apiezon grease 30% impregnated Diasolid L, helium gas at the flow rate 200 m*l*/min, column temp. 180°C, detector temp. 220°C, injector temp. 210°C. The retention time found for the *cis*-diacetate was 11 min; for the *trans*, 10 min. *cis*-Diacetate, bp 125—126°C/22 mmHg, n_D^{20} 1.4456, 4.43 g (23.8%). (Found: C, 58.13; H, 7.46%. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58%). *trans*-Diacetate, bp 130—132°C/24 mmHg, n_D^{20} 1.4406, 3.98 g (21.4%). (Found: C, 58.27; H, 7.38%. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58%). $[\alpha]_D^{25}$ −0.73° (*c* 4.0, EtOH). The IR- and NMR-spectra of the *cis*- and *trans*-diacetates were identical in every respect with those of the authentic specimens.[4]

Resolution of *trans*-1,2-Cyclopropanediacarboxylic Acid. The racemic *trans*-acid, mp 174—175°C. (Found:C, 46.25; H, 4.59%. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65%). (60 g; 0.46 mol) was dissolved in

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4) A. T. Blomquist and D. T. Longone, *J. Am. Chem. Soc.*, **81**, 2012 (1959).

[*1] McCoy described in Ref. 2 that the *cis*-isomer peak appeared as an incompletely resolved small shoulder on the long retention time side of the *trans*-peak on his qualitative VPC column, but on our column under the conditions specified above, a clear-cut separation was obtained.

boiling water (3500 m*l*) and cinchonidine (136 g; 0.46 mol) was added and the mixture was allowed to stand still overnight at room temperature, when the cinchonidine salt crystallized out. After fractional triangular crystallization of the salt from 20% ethanol, the salt with a constant rotation was decomposed with dilute sulfuric acid to afford the optically active (−)-acid (6.9 g). Further recrystallization of the free acid from acetonitrile gave the optically pure acid, mp 171—173°C. (Found: C, 46.21; H, 4.53%. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65%). $[\alpha]_D^{25}$ −235° (*c* 2.0, water).

Conversion of (−)-*trans*-Cyclopropane-1,2-dicarboxylic Acid into (−)-*trans*-1,2-Bis-(acetoxymethyl)-cyclopropane. The (−)-acid (2.6 g) obtained by the resolution described above was converted by the standard method with diazomethane into the corresponding dimethyl ester. According to the Blomquist procedure,[4] the (−)-diester was transformed into (−)-*trans*-1,2-bis-(acetoxymethyl)-cyclopropane, bp 130—132°C/23 mmHg, n_D^{20} 1.4408. (Found: C, 58.06; H, 7.40%. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58%). $[\alpha]_D^{25}$ −17.75° (*c* 2.0, EtOH). The IR- and NMR-spectra were identical in every respect with those of the authentic racemic specimen.[4] 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 were given in the previous paper.[1c]

The authors are indebted to Drs. M. Ohno, M. Nakanishi and T. Mukai for their encouragement and interest in this work. Partial support of this study by grant D86547 from the Ministry of Education is gratefully acknowledged (Y. I.).