

Michael Reaction, VI.
**Effect of Carbonyl Compounds on the Stereochemistry and
Mechanism of the Reaction**

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The equilibrium stereochemical result of the two-step *Michael* reaction between phenylacetic acid dialkylamides and methyl cinnamate or cinnamic acid dialkylamides is affected by the neutral carbonyl compounds taking part in the synthesis. This effect is explained by breakdown of the intramolecular chelate structure of the reaction adduct and appearance of an open metal form with isomeric partitioning close to that of the neutral adduct. This is further supported by the increased electroconductivity of the reaction mixtures. A chelate mechanism for the reaction in nonpolar medium is postulated which is in good agreement with the low stereoselectivity under kinetic conditions as well as with the effect of the polarity of the solvent on the kinetic stereochemical result.

(*Keywords: Mechanism; Michael reaction; Stereochemistry*)

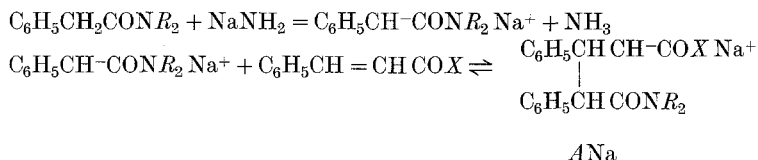
Zur Michael-Reaktion, 6. Mitt.: Der Einfluß von Carbonyl-Verbindungen auf die Stereochemie und den Mechanismus der Reaktion

Die Stereochemie einer zweistufigen Gleichgewichts-*Michael*-Reaktion zwischen Dialkylamiden der Phenylelessigsäure und Methylestern oder Dialkylamiden der Zimtsäure wird von den neutralen Carbonylverbindungen stark beeinflusst. Dieser Effekt kann mit der Zerstörung einer intramolekularen Chelatstruktur des Addukts und der darauffolgenden Bildung einer offenen Metallform mit einem dem neutralen Addukt ähnlichen *erythro-threo*-Verhältnis erklärt werden. Die Zunahme der elektrischen Leitfähigkeit des Reaktionsgemisches stützt diese Vorstellung.

Es wird ein über das Chelat verlaufender Mechanismus im nichtpolaren Medium postuliert. Dieser Mechanismus ist in guter Übereinstimmung sowohl mit der geringen Stereoselektivität (bei kinetischer Kontrolle) als auch mit dem Einfluß der Lösungsmittel auf die Stereochemie.

Introduction

In two previous papers of this series^{1,2} we studied the stereochemistry of the reaction between phenylacetic acid dialkylamides and methyl cinnamate or cinnamic acid dialkylamides, catalyzed by sodium amide under various conditions:



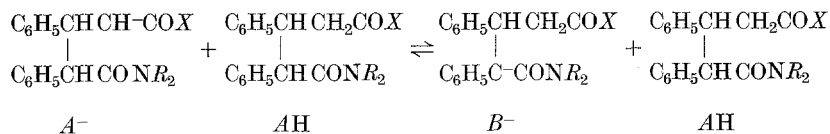
Conditions were defined where the reaction proceeded either under kinetic or thermodynamic control and possibilities to direct the stereochemical result were demonstrated. Two different equilibrium ratios (*erythro/threo*; *E/T*) were found. The first resulted from the one-step reaction procedure, (with catalytic amounts of sodium amide) and represents the relative stability of the neutral diastereomeric reaction products. The values of this ratio were found to depend on the solvent and are 60/40 in *THF* and 70/30 in *HMP*. The second ratio obtained between the metal forms of the reaction products in the two-step reaction was in all cases about 5/95. Studying the two-step reaction, however, a very interesting observation was made. Every time when metallation was not complete, the stereochemical result changed from 5/95 to 60/40 (*THF*).

The present paper reports the dependence of the stereochemistry of the two-step reaction upon the amount of the metal taking part in the reaction and discusses its mechanism.

Results and Discussion

If the *E/T* ratios between the neutral reaction products and the metal forms were independent the ratio observed should depend on the amount of the metal in the reaction (if it is less than equimolecular). Different amounts of sodium amide lead however to the same *E/T* ratios, as shown in Table 1.

This independence on the amount of sodium could be due to the formation of the carbanion *B*⁻ and epimerization at C-2 according to the following equilibrium:



This appeared a likely explanation, because the formation of such a carbanion had been already postulated or proven by other authors^{3,4}.

To our surprise, however, the hydrolysis of the equilibrium reaction mixture (obtained with 80% metal) with D₂O lead to the neutral product with deuterium at C-4 (*ANa* form). The possibility for epimerization even if the degree of formation of *B*⁻ is very low was

Table 1. *Syntheses with insufficient amounts of metal*^a

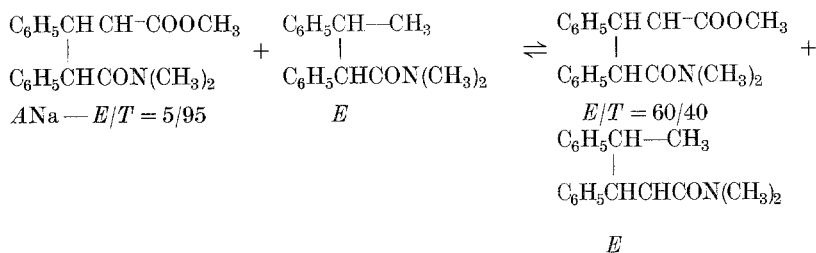
Compound	% Metal	Time, min	<i>E/T</i>
Dimethylamide	5	30	52/48
methyl ester	20-80	30	54/46 ^b
Dimethylamide	5	30	52/48
morpholide	20-80	60	20/80 ^c

^a 22° in *THF*.

^b If the stereochemistry depends on the amount of the metal when 20% metal is used the *E/T* ratio should be 49/51, and when this amount is 80% — 16/84.

^c Heterogenization of the mixture.

refuted by studying the following reaction where the dimethylamide of erythro-2,3-diphenylbutyric acid⁵ can isomerize only by epimerization at C-2:



No isomerization of the model compound was observed, but the ratio in the initial metal derivative was shifted to 60/40. This demonstrated the importance of neutral molecules in the formation of the ratio 60/40 for the case if the metal is less than one equivalent.

We studied the isomerization of *ANa* with various neutral molecules in *THF* at 22° (Tables 2-4). Isomerization can be provoked if donors (CH), acceptors and neutral adducts (*AH*) are used but only with at least one of the reacting molecule containing an ester group. If there is no such group the reaction mixture becomes heterogenous and no

Table 2. $ANa + CH \rightleftharpoons AH + CNa$

ANa	CH	Time, min	E/T
Dimethylamide methyl ester	$C_6H_5CH_2CON(CH_3)_2$	15	52/48
Dimethylamide morfolide	$C_6H_5CH_2CON(CH_3)_2$	60	10/90 ^a
	$C_6H_5CH_2COOCH_3$	15	52/48 57/43 ^b

^a Heterogeneous mixture.^b In the concurrently formed adduct.Table 3. $ANa + AH \rightleftharpoons AH + ANa$

ANa—5/95	AH	Time, min	ANa/AH	E/T^a	E/T^b	E/T^c
Dimethylamide methylester	Dimethylamide methylester- <i>erythro</i> - <i>threo</i>	30	1:1	50/50	57/43	—
		30	1:1	52/48	3/97	—
			1:5	58/42	2/98	—
		5:1	42/58	4/96	—	
	Dimethylamide morpholide- <i>threo</i>	30	1:1	57/43	—	52/48
Dimethylamide morpholide	Dimethylamide morpholide- <i>threo</i>	60	1:1	15/85	3/97	—
	Dimethylamide methylester- <i>threo</i>	30	1:1	55/45	—	45/55

^a In the reaction mixture.^b Calculated if the ratios in the metal and neutral form are independent.^c In the concurrently obtained adduct.

isomerization of ANa takes place. The isomerization does not depend on the amount or configuration of neutral adducts used. If the competitive reaction takes place the newly formed adduct has also an E/T ratio of 60/40.

Isomerization is induced even by compounds which are not CH-acids. Methyl cinnamate is used very often as an acceptor in the *Michael* reaction and it can also cause isomerization if its amount is relatively high. In general, the isomerization ability of this compound is similar to that of 18-crown-6 and *HMPT* which solvate well the metal cation.

Table 4. Other isomerization agents^a

<i>ANa</i> — 5/95	Isomerization agent	Ratio	<i>E/T</i>
Dimethylamide methyl ester	$C_6H_5CH=CH-COOCH_3$	1:1	58/42
		5:1	10/90
	$C_6H_5COOCH_3$	1:1	24/76
	$HCON(CH_3)_2$	1:1	54/46
	<i>HMPT</i>	1:1	40/60
Dimethylamide morpholide	18-Crown-6	10:1	60/40
	$C_6H_5COOCH_3$	1:1	52/48
	$CH_3COOC_2H_5$	1:1	51/49
	$CH_3COO-t-C_4H_9$	1:1	18/82
	18-Crown-6	10:1	50/50

^a At 22°, 15 min. in *THF*.

Comparing the isomerization ability of ethyl acetate and *tert*-butyl acetate it may be concluded that the action of the latter is sterically hindered.

Very likely the isomerization observed under the influence of neutral carbonyl compounds is due to the change in the state of the metal form *ANa* obtained during the two-step procedure. The literature data show, that with the concentrations used, in nonpolar aprotic solvents the contact ion pairs of ambident enolates are associated and are nonconducting^{6,7}. The addition of bipolar aprotic solvents leads to desaggregation (separation of the ions at this concentration is not possible) and to a change in the coordination of the metal, what makes the solution electroconducting⁸. The formation of stoichiometric solvates has been also postulated⁹.

Table 5 shows that all interactions mentioned above are accompanied by an increase of the electroconductivity whereas during the syntheses no significant change is observed. The conductivity increases rapidly and maximum values are observed after addition of half a mole of the neutral compound. The isomerization however is relatively slow (15-30 min) and the equilibrium *E/T* ratio does not depend on the amount of the isomerizing agents added. *HMPT* increases the conductivity continually probably due to dissociation of the metal enolate in this solvent. The decrease in the conductivity after the reaction mixture had become heterogeneous shows that the low degree of isomerization in these cases is really due to the separation of the solid metalated form. This is supported by the fact that dilution of the reaction mixture in such cases increases the degree of isomerization. It is not clear, however, why separation of the solid phase occurs only if no ester group in at least one of the reacting compounds is present.

Among all the possible changes in the metal form *ANa* the change of the intramolecular coordination of the metal can in our opinion explain

Table 5. *Change of the electroconductivity during the syntheses and isomerization*

System	Time, sec	Conducti- vity, μ s	E/T
$\text{NaNH}_2 + \text{THF}$	—	0,3	
$\text{NaNH}_2 + \text{THF} + \text{HMPT}$	—	0,4	
$\text{C}_6\text{H}_5\text{CH}^-\text{CON}(\text{CH}_3)_2 \text{Na}^+ - \text{DMANa}$	—	5,5	
$\text{DMANa} + \text{MC}$	2	2,5	5/95
$\text{DMANa} + \text{MC} + \text{AH}$	15	22,0	58/42
$\text{DMANa} + \text{MC} + 1/2 \text{AH}$	20	20,0	57/43
$\text{DMANa} + \text{CAMPH}$	2	2,7	5/95
$\text{DMANa} + \text{CAMPH} + \text{MB}$	20	16,0	50/50
$\text{DMANa} + \text{CAMPH} + 1/2 \text{MB}$	20	14,0	52/48
$\text{DMANa} + \text{CAMPH} + \text{AH}$	20	14,0	10/90 ^a
$\text{DMANa} + \text{CAMPH} + \text{HMPT}$		90,0 ^b	40/60

^a The mixture becomes heterogeneous and conductivity decreases to 3,0.

^b The conductivity increases with the amount of the solvent. *MC* — methyl cinnamate, *CAMPH* — cinnamic acid morpholide, *MB* — methyl benzoate.

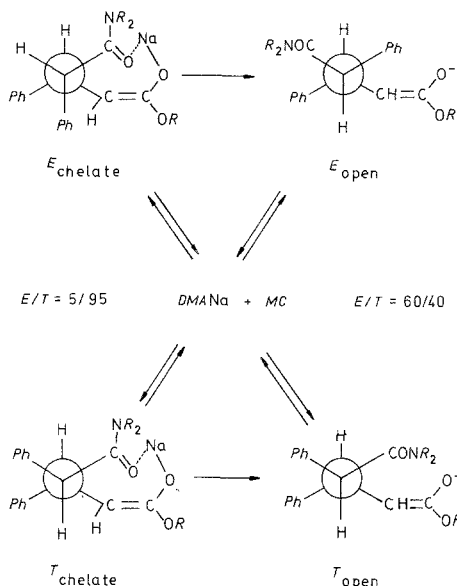
the observed equilibrium isomerization. Coordination in the *threo*-isomer can be realized in its preferred conformation and will contribute to further stabilization of the reaction product, whereas chelate formation in the *erythro*-isomer increases the sterical interactions and makes the difference in the stability of the reaction products more significant. The destruction of the chelate under the action of neutral carbonyl compounds leads to a new open form with other steric requirements similar to those in the neutral reaction products. A new equilibrium ratio corresponds to this new form and this is approximately the same as the ratio found between the neutral reaction products in the one-step reaction. Therefore the stereochemistry of the reaction does not depend on the amount of the metal added (Scheme 1).

Coordination in *HMPT* is obviously not possible and the result $E/T = 70/30$ reflects the equilibrium between the open forms.

It should be mentioned, that all factors which are able to destroy the chelate in question or to desaggregate the contact ion pairs cause isomerization similarly to the carbonyl compounds mentioned. These are either an increase of the temperature or a tenfold dilution of the reaction mixture. It is most likely that the aggregation and chelation are somehow connected.

The strong evidence for coordination in the reaction products allows the assumption that coordination takes place also in the transition state and to discuss a chelate mechanism for the reaction studied in aprotic nonpolar solvents. Such a mechanism has been postulated for many carbonyl reactions in poorly solvating solvents where the metal cation can be stabilized by coordina-

Scheme 1. Transformation of the metal form of the adduct and its effect on the stereochemistry



tion with methylene and carbonyl components¹⁰⁻¹². Reactions leading to diastereomeric products pass through two different transition states and at low temperature and short reaction times the stereochemistry is kinetically determined.

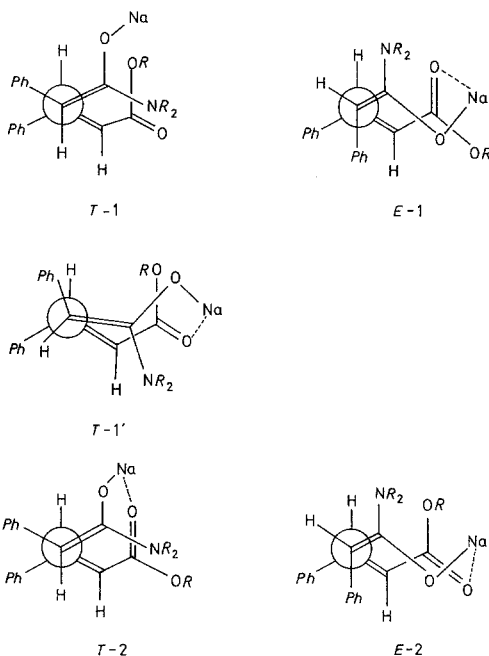
For 1,4-addition reactions such as the *Michael* reaction, such a mechanism has not yet been discussed. A cyclic transition state, however, has been postulated on the basis of kinetic data for some cases where the reaction products were not diastereomeric¹³.

In terms of the models developed for aldol reactions and the stereoelectronic requirements of addition¹⁴⁻¹⁶, one may discuss some transition conformations where a chelate formation is possible (Scheme 2, see p. 188).

The following prepositions were taken into consideration: (1) The enolate structure of the sodium reagent is proved by *Gaudemar et al.*^{17,18}. (2) *Z*-configuration of the enolate has been used to explain the stereochemistry of some 1,2-addition reactions¹⁹. (3) According to the ideas of *Seyden-Penne et al.* the transition state in our case is supposed to be more or less product-like²⁰.

The conformations *T*-2 and *E*-2 are unfavourable because of the NR_2/OCH_3 interactions (measurable steric effect of these groups was not observed). In the *threo* series the most stable conformation seems to be *T*-1 and in the *erythro* one

Scheme 2. Possible transition conformations

Table 6. Kinetic controlled *E/T* ratios²

Solvent	Dimethylamide methyl ester	Dicyclohexylamide methyl ester
Benzene	—	67/33
Ether	60/40	65/35
<i>THF</i>	40/60	50/50
<i>HMPT</i>		12/88 ^a

^a Obtained at the beginning of the one-step reaction at 64° (see Ref.¹).

E-1. The latter is on the other hand more hindered than *T-1* because of the $C_6H_5/CH-gauche$ interaction. This should lead to the significant predomination of the *threo*-isomer under kinetic conditions. The chelate formation in *T-1*, however, requires transformation in *T-1'* where the phenyl groups and protons are partially eclipsed. This equilibrates the energies of both *erythro* and *threo* transition states and is a good explanation for the low stereoselectivity under kinetic control. The decrease in the fraction of the *threo*-isomer if the polarity of the solvent changes in the order *THF* > ether > benzene (Table 6) could be explained with the increase in the energy of *T-1* because of more tight coordination.

In more polar medium (*HMP*T) the metal cation is well solvated and the transition state is open. In such a transition state according to *Heublein*²¹ the stereochemistry determining factor is the correspondence between the polarity of both medium and transition state* and one has to compare transition conformations *T*-1 and *E*-1 to explain the stereochemistry.

The observed highly variable stereochemistry suggests the necessity of very careful interpretation of experimental data for this kind of reactions. We believe that the mechanism discussed and the observed effect of carbonyl compounds on the stereochemistry are valid for the more general case of nucleophilic 1,4-addition reactions. Investigations in this respect are in progress.

Experimental

All results were obtained in dry peroxide free *THF* at 22 °C under dry nitrogen. The reaction mixtures was worked up as described before. The diastereomers were isolated by *TLC* and the *E/T* ratios were determined by NMR spectroscopy (see Ref.^{1,2}).

Two-step reaction with defined unsufficiency of metal

The corresponding mole fraction of the sodium derivative of the donor was obtained and the rest of the donor as well as the whole equimolecular amount of the acceptor were added.

Absence of epimerization at C-2

The reaction mixture obtained with 80% metal as described above was decomposed with D₂O. The NMR spectrum of the isolated diastereomer shows a 40% decreased intensity of the CH₂ protons at 2,63-3,11 ppm.

Isomerization of ANa

To the reaction mixture obtained by the two-step procedure at 22° the corresponding amount of the neutral carbonyl compound or other reagent dissolved in *THF* (4 ml for each 1.25 mmol) was added. The reaction time, the ratio between *ANa* and the added reagent and the *E/T* ratios are presented in the Tables. The interaction with dimethylamide of *erythro*-2,3-diphenylbutiric acid was carried out analogously.

Electroconductivity

The measurements were performed in a 10 ml reaction cell with standard platinum electrodes on the Conductivity meter type OK-102 (Radelkis, Hungary).

* At the root of this postulate is *Kirkwood's* theory²² for the effect of the medium on the free energy of polar molecules and *Ingold's* idea²³ for better solvation of a more polar transition state from a more polar solvent.

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