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# Epimerization and Kinetic Protonation as Factors Determining the Stereochemistry of the Michael Reaction

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**Summary.** Model compounds in which the only possibility for isomerization is epimerization were synthesized. They undergo isomerization under the conditions widely used in the Michael addition. Conclusions are drawn as to the possibilities for epimerization or kinetic protonation in the actual Michael adducts.

**Keywords.** Michael reaction; Stereochemistry; Epimerization; Kinetic protonation.

**Epimerisierung und kinetische Protonierung als Faktoren der Stereochemie der Michael-Reaktion**

**Zusammenfassung.** Modellverbindungen, bei denen nur eine C-2 Epimerisierung möglich ist, wurden synthetisiert und einer Isomerisierung bei verschiedenen Reaktionsbedingungen unterworfen. Die Epimerisierung und kinetische Protonierung der Michaeladdukte wird diskutiert.

## Introduction

The stereochemical equilibrium is a general question of interest to investigators of the stereochemistry of the classical (one stage) Michael reaction resulting in an adduct with two vicinal asymmetric carbon atoms. This result can be brought about either by retroaldolization of the adduct or by direct isomerization (epimerization) at the C-2 acid center or in both. Different approaches have been used in solving the problem in different cases, but no definite answer has been given yet [1–5].

## Results and Discussion

The object of this work is a new approach for solving the problem. We have investigated the isomerization of model compounde of the type:

$$\begin{array}{l} C_6H_5-CH-CH_3 \\ \quad\quad\quad | \\ C_6H_5-CH-X \end{array}$$

**Table 1.** Syntheses of **1** and **3**

| Compound | Solvent | T°C | Time, min | Yield, % | Erythro/Threo |
|---|---|---|---|---|---|
| **1** | *HMPT* | 22 | 3 | 79 | 45/55 |
| | *THF* | 22 | 3 | 84 | 60/40 |
| | Ether | 22 | 5 | 68 | 63/37 |
| | Benzene | 22 | 5 | 72 | 70/30 |
| **3** | *THF* | 64 | 15 | 86 | 62/38 |

**Table 2.** $CH_3$ signals of the diastereomeric compounds **1–4**

| Compound | Configuration | Chemical shifts (δ, ppm) | | |
|---|---|---|---|---|
| | | $CH_3$ | $COOCH_3$ | $CON(CH_3)_2$ |
| **1** | erythro | 0.83 0.96 | | 2.60 2.90 |
| | threo | 1.30 1.40 | | 2.93 2.96 |
| **2** | erythro | 0.85 1.03 | 3.32 | |
| | threo | 1.32 1.40 | 2.92 2.97 | |
| **3** | erythro | 0.96 1.07 | | |
| | threo | 1.30 1.40 | | |
| **4** | erythro | 1.26 1.37 | | |
| | threo* | 1.40 1.50 | | |

* Not isolated

where $X = CON(CH_3)_2$ **1**, $COOCH_3$ **2**, $COC_6H_5$ **3**, CN **4**, where the only possibility for changing the configuration is the isomerization at C-2.

The isomerization conditions used correspond to conditions already employed previously [2–4].

*Syntheses and Relative Configuration of* **1–4**

**1** and **3** were obtained by alkylation of the sodium N,N-dimethylphenylacetamide and deoxybenzoine enolates with 1-phenylethylbromide:

$$C_6H_5-CH^{-1}-X\,Na^+ + C_6H_5-\underset{\displaystyle Br}{\underset{|}{CH}}-CH_3 \rightarrow C_6H_5-\underset{\displaystyle C_6H_5-CH-X}{\underset{|}{CH}}-CH_3 .$$

Where $X = CON(CH_3)_2$ or $COC_6H_5$

Table 1 shows the decrease of the diastereosalectivity of the alkylation with increasing polarity of the medium.

The isomers of **2** were obtained from the corresponding 2,3-diphenylbutyric acis [6] with diazomethane.

**Table 3.** Isomerization of erythro **1–4**

| Compound | Solvent | Isomerizing agent | T°C | Time, min | Erythro/Threo |
|---|---|---|---|---|---|
| **1** | *THF* | $NaNH_2$ | 64 | 300 | 90/10 |
| | | *ANa* | 22 | 60 | 100/0 |
| | *HMPT* | $NaNH_2$ | 22 | 60 | 100/0 |
| **2** | *THF* | $NaNH_2$ | 64 | 150 | 67/33 |
| | | *ANa* | 22 | 60 | 62/38 |
| **3** | *THF* | $NaNH_2$ | 22 | 60 | 100/0 |
| | | | 64 | 60 | 40/60 |
| | | *ANa* | 22 | 60 | 52/48 |
| | *HMPT* | $NaNH_2$ | 22 | 60 | 60/40 |
| | $CH_3OH$ | KOH | 22 | 3000 | 100/0 |
| | $CHCl_3$ | HCl | 22 | 3000 | 100/0 |
| **4** | *THF* | $NaNH_2$ | 22 | 15 | 57/43 |
| | $C_2H_5OH$ | $C_2H_5ONa$ | 0 | 60 | 100/0 |
| | | | 22 | 30 | 60/40 |

The preparation of erythro-**4** has been described in Ref [7].
The configurations of **1** and **2** were correlated with the corresponding erythro-acid [6].

The signals of the $CH_3$ protons in the erythro-isomers appear at higher fields (Table 2), which was used determining the configurations of **3**.

The differences in the position of the $COOCH_3$ and $CON(CH_3)_2$ signals can also be used for the configurational assignments [8].

*Isomerization*

The isomerization conditions and isomerizing agents are shown in Table 3. In all cases erythro isomers have been used because of their accessibility. Erythro/threo ratios were determined using the above mentioned NMR differences. A very suitable isomerizing agent (because of its solubility) is the sodium derivative of the adduct of the reaction between sodium N,N-dimetyhlphenylacetamide enolate and methyl cinnamate [9] (*ANa* in Table 3).

$$\begin{array}{l} C_6H_5-CH-CH^- -COOCH_3 \quad Na^+ \\ \quad\quad\quad | \\ C_6H_5-CH-CON(CH_3)_2 \\ \quad\quad\quad ANa \end{array}$$

The isomerization of **1** does not occur under a wide range of conditions. **2** undergoes isomerization in boiling *THF* or when *ANa* is used. The isomerization of **3** is easier and in the case of **4** isomerization does not occur only at low temperature.

Obviously the isomerization is parallel to the CH-activity. The $pK_A$ values for

the corresponding phenylacetic acid derivatives [10] and for deoxybenzoine [11] indicate the following sequence of decreasing CH-activity:

$$CN > COC_6H_5 > COOCH_3 > CON(CH_3)_2$$

On the other hand the isomerization is related to the rate of metalation; the degree of the latter was monitored by the shifting of the CO or CN absorbtion bands in the IR spectrum. In all cases, shown in Table 3, where isomerization is recorded, metalation is complete. Thus, the stereochemistry is determined by the protonation of the prochiral carbanion but not by the epimerization itself.

The ratio erythro/threo = 67/33 for **2** with catalytic amounts of $NaNH_2$ seems to be a result of metal exchange (epimerization). As expected, one can observe the epimerization only when catalytic amounts of metal are used. It is worth noting that both asymmetric protonation and epimerization lead to the same stereochemical result.

With actual Michael adducts having two CH-acid centres (at C-2 and C-4), the possibilities of direct isomerization (epimerization) with unsufficient amounts of catalysts will additionally depend on the difference in the acidity of these two centres – a necessary condition for C-2 carbanion formation. This more or less trivial conclusion allows one to predict that when dialkylamides or esters are used as donors in the Michael addition, most probably the erythro/threo ratio at equilibrium is a result of the "retroaldol" decompozition (metal at C-4). In the case of nitriles one may expect a direct isomerization (epimerization at C-2) with a wide range of acceptors and experimental conditions. When donors like deoxybenzoin are used, the stereochemistry will depend more strongly on the second component of the reaction, and conclusions concerning the origin of the equilibrium stereochemistry should be drawn with caution. Thus Baradel [2] considers the equilibrium stereochemistry of the reaction between deoxybenzoin and chalcone to be a result of epimerization. An argument for that is the isomerization of the adduct by KOH in methanol and HCl in $CHCl_3$: Table 3 shows that under these conditions **3** does not undergo isomerization. We think that in the case described only "retroaldol" decomposition is responsible for the isomerization.

The results obtained suggest a low diastereoselectivity for those cases where epimerization or protonation take place.

## Experimental

*Dimethyl Amides of the Diastereomeric 2,3-Diphenylbutyric Acids* (**1**)

0.185 g (1 mmol) of 1-phenylethylbromide in 2 ml of *THF* were added under stirring at room temperature to 1 mmol of sodium N,N-dimethylphenylacetamidoenolate obtained in 2 ml of *THF* [9]. After separation of sodium bromide (2 min) 1 ml of water was added, the solvent evaporated under vacuum and the residue extracted with chloroform. The mixture of the diastereomeric **1** was separated by TLC (Kieselgel 60 $PF_{254}$ "Merck", ether/petroleum ether). Two recrystalization from benzene/hexane lead to 0.07 g (26%) of erythro-**1** with m.p. 144–145°, $R_f = 0.5$. IR ($c = 1$, $CHCl_3$): 1 636 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 0.83$ and 0.96 (d, 3H, $CH_3$), 2.60 and 2.90 [d, 6H, $N(CH_3)_2$], 3.30–3.76 (m, 1H, H-3), 3.80 and 4.00 (d, 1H, H-2, $J = 11$ Hz), 7.00–7.56 (m, 10H, $2C_6H_5$) ppm. $C_{18}H_{21}NO$ (267.4). Calc. N 5.24; found N 5.40.

Threo-**1** was isolated from the mother liquor after recrystalization from hexane. Yield 0.03 g (11%), m.p. 139–141°, $R_f = 0.47$. IR ($c = 1$, $CHCl_3$): 1 636 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 1.30$ and

1.40 (d, 3H, $CH_3$), 2.93 and 2.97 [d, 6H, $N(CH_3)_2$], 3.16–3.66 (m, 1H, H-3), 3.66 and 3.83 (d, 1H, H-2, $J = 9$ Hz), 6.76–7.26 (m, 10H, $2C_6H_5$) ppm. $C_{18}H_{21}NO$ (267.4). Calc. N 5.24; found N 5.17.

*Methyl Esters of the Diastereomeric 2,3-Diphenylbutyric Acids* (**2**)

Ether solution of diazomethane was added to a solution of 0.240 g (1 mmol) of the corresponding acid [6] until the reading permanent yellow color of the mixture was reached.

Erythro-**2**. M.p. 114–115° (ethanol), $R_f = 0.82$ (ether/petroleum either 2 : 1). IR ($c = 1$, $CHCl_3$): 1726 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 0.95 and 1.03 (d, 3H, $CH_3$), 3.32 (s, 3H, $COOCH_3$), 3.37–3.67 (m, 1H, H-3), 3.67 and 3.80 (d, 1H, H-2, $J = 11$ Hz), 7.12–7.62 (m, 10H, $2C_6H_5$) ppm. $C_{17}H_{18}O_2$ (254.3). Calc. C 79.07, H 7.03; found C 79.09, H 6.82.

Threo-**2**. M.p. 55–58° (ethanol/water), $R_f = 0.82$. IR ($c = 1$, $CHCl_3$): 1726 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.32 and 1.40 (d, 3H, $CH_3$), 2.92 and 2.97 (d, 3H, $COOCH_3$), 3.30–3.70 (m, 1H, H-3), 3.75 and 3.97 (d, 1H, H-2, $J = 10$ Hz), 6.87–7.12 (m, 10H, $2C_6H_5$) ppm. $C_{17}H_{18}O_2$ (254.3). Calc. C 79.07, H 7.03; found C 79.09, H 6.92.

*Diastereometric 3-Benzoyl-2,3-diphenylpropane* **3**

After addition of 1 mmol of 1-phenylethylbromide in 2 ml of *THF* to 1 mmol of the sodium reagent of deoxybenzoin obtained with $NaNH_2$ in 2 ml of *THF* and stirring 15 min under reflux, 1 ml of water was added and worked up as described for **1**. The mixture of the diastereomeric products was separated by TLC (ether/petroleum ether 1 : 1).

Recrystalization from ethanol leads to pure erythro-**3**. Yield 0.055 g (18.3%), m.p. 189–190°, $R_f = 0.67$. IR ($c = 1$, $CHCl_3$): 1678 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 0.96 and 1.07 (d, 3H, $CH_3$), 3.30–4.00 (m, 1H, H-3), 4,70 and 4.86 (d, 1H, H-2, $J = 11$ Hz), 7.00–8.00 (m, 15H, $3C_6H_5$) ppm. $C_{22}H_{20}O$ (300.4). Calc. C 88.00, H 6.67; found C 87.93, H 6.67.

Threo-**3** was not isolated.

$^1H$ NMR ($CDCl_3$, data are taken from the spectrum of the mixture): $\delta$ = 1.30 and 1.40 (d, 3H, $CH_3$), 3.50–3.95 (m, 1H, H-3), 4.60 and 4.77 (d, 1H, H-2, $J = 11$ Hz) ppm.

*Isomerization of* **1–4**

*General procedure.* To 1 mmol of the corresponding erythro isomer dissolved in the solvent, 1 mmol of the isomerizing reagent was added and the mixture stirred under the conditions shown in Table 3. After addition of 1 ml of water, the mixture was worked up and the crude product isolated was analysed by $^1H$ NMR spectroscopy.

When *ANa* was used, 0.5 mmol of the erythro isomer was added to the reaction mixture obtained from 1 mmol of sodium N,N-dimethylphenylacetamidoenolate and methyl cinnamate in 2 ml of *THF* at room temperature. After stirring at the temperature indicated, the mixture was hydrolyzed by HCl (1 : 1). The solvent was evaporated and the $CHCl_3$ extract separated by TLC (ether/petroelum ether).

The isomerization with HCl was conducted in $CHCl_3$ (0.6 mmol erythro-**2** in 3 ml) with addition of several drops of HCl. After washing with water the solution was analyzed (NMR).

When KOH was used 0.6 mmol of erythro-**2** in 12 ml of dried methanol was treated with 1 ml of 2*N* KOH. After acidification with HCl, the mixture was worked up as described before.

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