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Enantioselective Catalysis, C [1]. Decarboxylation of Malonic Acids in the Presence of Copper(I) Compounds – Not a Copper(I) Catalysis but a Base Effect[#]

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Summary. The catalytic decarboxylation of malonic acids, claimed to be catalyzed by copper(I) compounds, has been investigated. Decarboxylation of different malonic acid derivatives (**1–5**) in acetonitrile was far more effective with Cu_2O than with CuCl. Thus, the decarboxylation is obviously influenced by the basicity of the anion. In the decarboxylation of phenylmalonic acid (**3**), *bis*(tricyclohexylphosphane)copper(I) hydrogenphenylmalonate (**6**) and potassium hydrogenphenylmalonate (**7**) show nearly identical rate constants. It is concluded that the monoanions of the malonic acid derivatives are the reactive species undergoing decarboxylation. Further experiments are presented which demonstrate that everything that increases the concentration of the monoanions also increases the rate of decarboxylation. In the enantioselective decarboxylation of the monoethyl ester of methylphenylmalonic acid (**2**), the enantiomeric excess of (*S*)-(+)-ethyl 2-phenylpropionate could be raised to 34.5% *ee* using the alkaloid cinchonine.

Keywords. Malonic acids; Decarboxylation; Enantioselectivity; Mechanism.

Enantioselektive Katalyse, 100. Mitt. [1]. Decarboxylierung von Malonsäuren in Gegenwart von Kupfer(I)-Komplexen – keine Kupfer(I)-Katalyse, sondern ein Baseneffekt

Zusammenfassung. Die katalytische Decarboxylierung von Malonsäuren, von der behauptet wird, daß sie von Kupfer(I)-Komplexen katalysiert wird, wurde untersucht. Die Decarboxylierung verschiedener Malonsäurederivate (**1–5**) verlief mit Cu_2O wesentlich effektiver als mit CuCl. Die Decarboxylierung wird also durch die Basizität des Anions beeinflußt. In der Decarboxylierung von Phenylmalonsäure (**3**) zeigen *Bis*(tricyclohexylphosphan)kupfer(I)-hydrogenphenylmalonat (**6**) und Kaliumhydrogenphenylmalonat (**7**) nahezu identische Geschwindigkeitskonstanten. Daraus ergibt sich, daß die Monoanionen der Malonsäurederivate die reaktiven Spezies sind, die der Decarboxylierung unterliegen. Weitere Experimente werden präsentiert, die zeigen, daß alles, was die Konzentration der Monoanionen erhöht, auch die Geschwindigkeit der Decarboxylierung ansteigen läßt. Bei der enantioselektiven Decarboxylierung des Monoethylesters von Methylphenylmalonsäure (**2**) konnte der Enantiomerenüberschuß von (*S*)-(+)-Ethyl-2-phenylpropionat bei Einsatz des Alkaloids Cinchonin auf 34,5% *ee* gesteigert werden.

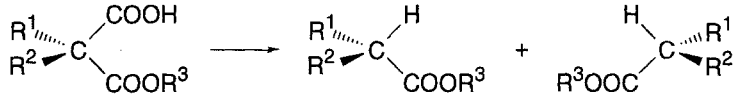
[#] Dedicated to Prof. Dr. *J. Müller* on the occasion of his 60th birthday.

Introduction

The synthesis of enantiomerically pure 2-aryl-substituted propionic acids is an important problem in organic chemistry. Many pharmaceuticals, including naproxen, contain this structural element. A preparative approach to compounds of this type is the enantioselective decarboxylation of arylmethylmalonic acids.

In 1986, *Toussaint et al.* reported the decarboxylation of malonic acids using copper compounds such as Cu_2O. Monocarboxylic acids were obtained in nearly quantitative yields [2]. Using a combination of CuCl with cinchona alkaloids, optical inductions in the resulting mono-carboxylic acids were found. The highest enantiomeric excess of 27% in the decarboxylation of methylphenylmalonic acid (**1**) was obtained with a molar ratio substrate:cinchonine:CuCl = 1.4:2:1 [3]. A catalytic cycle based on copper(I) derivatives of the malonic acid derivatives was postulated [2, 3]. Later on it was shown that in the decarboxylation of the same substrate the amount of the CuCl catalyst could be reduced (molar ratio substrate:cinchonine:CuCl = 38:58:1) while increasing the optical induction to 36% *ee* [4].

In 1993, *Darensbourg et al.* isolated complexes with a novel monodentate coordination between copper(I) and hydrogenmalonates. The compounds *bis*(tricyclohexylphosphane)- and *bis*(triphenylphosphane)copper(I) hydrogenphenylmalonate were proposed to be intermediates in the catalytic process and effective catalysts for the decarboxylation of malonic acids [5]. In a recent paper, *Darensbourg et al.* further investigated the mechanism of the influence of copper(I) and zinc(II) on the decarboxylation of malonic acid derivatives [6]. A novel catalytic cycle was postulated, minimizing the role of copper(I) in the decarboxylation process [6].



1–5

	1	2	3	4	5
R^1	Me	Me	H	H	H
R^2	Ph	Ph	Ph	H	H
R^3	H	Et	H	Et	H

Scheme 1

In the present paper, we report on our studies concerning the decarboxylation of malonic acid derivatives **1–5** [7, 8]. It is demonstrated that the idea of copper(I) catalysis of the decarboxylation which has haunted the literature for about ten years should be abandoned.

Results and Discussion

Decarboxylation of 1–5 in the Presence of Cu_2O and CuCl

We investigated the decarboxylation of malonic acid derivatives **1–3** (Scheme 1) with Cu_2O and CuCl (molar ratio substrate:copper(I) = 10:1) in acetonitrile.

Table 1. Conversion (%) in the decarboxylation of malonic acid derivatives **1–5** in the presence of Cu_2O and CuCl; 1.0 mmol of **1–5**, 0.05 mmol of Cu_2O or 0.1 mmol of CuCl, 1.0 ml of acetonitrile, 1.5 h, 65 °C

substrate	Cu_2O	CuCl	—[a]	Cu_2O	CuCl	—[a]
	analyzed by ^1H NMR			analyzed by gas buret		
methylphenylmalonic acid (**1**)	100	13	10	100	13.5	11
monoethyl ester of methylphenylmalonic acid (**2**)	100	19.5	16	100	20.5	17.5
phenylmalonic acid (**3**)	100	26.5	23	100	25.5	19.5
monoethyl ester of malonic acid (**4**)	4.7	1.2	1.0	5.1	1.4	1.0
malonic acid (**5**)	–	–	–	4.5	1.0	0.8

[a] Thermally induced reaction without any copper(I) compound

CuCl was readily soluble in acetonitrile, whereas Cu_2O only dissolved after addition of the malonic acid derivative. In all cases, clear solutions were obtained which were heated to 65 °C for 1.5 hours. After removal of the acetonitrile, the copper salts were hydrolyzed with 2 *N* hydrochloric acid, and the organic compounds (starting material and product) were extracted with ether. The ratio starting material/product was determined by ^1H NMR spectroscopy. In later experiments, the ^1H NMR analysis was complemented by a volumetric analysis (*vide infra*).

If the reaction was actually catalyzed by copper(I), the acceleration of the decarboxylation by a given amount of copper(I) should be independent of its counter ion. As shown in Table 1, the results for Cu_2O and CuCl differ enormously. In the reaction of the derivatives **1–3** with Cu_2O, total decarboxylation occurred after 1.5 hours, whereas the decarboxylations with CuCl reached only 13, 19.5 and 26.5% conversion for **1**, **2**, and **3**, respectively, over the same time period. Under the same conditions the extent of decarboxylation without any copper(I) additive was 10, 16 and 23% for **1**, **2**, and **3** (Table 1). Thus, the decarboxylation of malonic acid derivatives **1–3** in the presence of Cu_2O turned out to be extremely fast, whereas in the presence of CuCl it proceeded only slightly faster than in the absence of copper(I). These results indicate that the decarboxylation of **1–3** is not sensitive to copper(I), but to another property of the additives.

Under the same reaction conditions, the unsubstituted malonic acid derivatives **4** and **5** are relatively unreactive towards decarboxylation. In the presence of Cu_2O, only 4.7% (5.1%) of the *hemi* ester **4** and 4.5% of the malonic acid **5** decarboxylated within 1.5 hours. The decarboxylation of **4** and **5** in the presence of CuCl and in the absence of copper(I) amounted to only about 1% (Table 1).

In the experiments with monoethyl malonate (**4**, Scheme 1), workup and ^1H NMR analysis were different from **1–3**. Because of its high volatility, the product ethyl acetate was removed with the solvent. Ether was added to the residue, and the anions of the copper salts were transformed to the free acids with an acidic ion exchange resin (DOWEX 50 X 8) added to the mixture. A definite amount of the

Table 2. Conversion (%) in the decarboxylation of methylphenylmalonic acid (**1**) in the presence of CuCl/cinchonine and cinchonine; 1.50 mmol of **1**, 2.30 mmol of cinchonine, 70 ml of acetonitrile, 60 °C; ( ) = number of experiments

time (min)	conversion (%) (with 1.05 mmol CuCl)	conversion (%) (without CuCl)
10	11, 13(2)	13, 15(2)
25	22, 25(2)	26, 29(2)
50	30, 34(2)	42, 45(2)
75	43, 46(2)	50, 53(2)
100	51, 56(2)	63, 63(2)
135	64, 66(2)	72, 75(2)

standard toluene was added to the remaining monoethyl malonate to allow the determination of its quantity by ^{1}H NMR spectroscopy.

The decarboxylation of malonic acid **5** (Scheme 1) could not be worked up and analyzed as described above (the starting material is soluble in water, and the product (acetic acid) is highly volatile). Therefore, these experiments were analyzed by measuring the volume of evolved carbon dioxide with a gas buret [9]. In addition, the conversion rate in the decarboxylation of derivatives **1–4** was determined by the same volumetric technique. The results are given in Table 1. Obviously, the different methodologies of workup and analysis lead to comparable results.

*Decarboxylation of **1** in the Presence of Cinchonine and CuCl*

Since for the enantioselective decarboxylation of malonic acids optically active bases are required, we investigated the influence of CuCl/cinchonine and of cinchonine alone on the decarboxylation of **1** in acetonitrile at 60 °C (Table 2). The second column of Table 2 shows the conversion in two parallel experiments for a ratio substrate:base:CuCl = 2.9:4.4:2 as a function of time. Column 3 contains the results of the same experiments without CuCl. Obviously, in the presence of excess cinchonine, the addition of comparable amounts of CuCl decreases the conversion in the decarboxylation of **1**. Runs in which small amounts of CuCl are added cannot be differentiated from experiments without CuCl [7].

To study the thermal decarboxylation of methylphenylmalonic acid (**1**) in acetonitrile, the temperature had to be raised to 80 °C. Then, without CuCl and alkaloid, the decarboxylation gave 49% conversion after 135 minutes. The expected dependence of the decarboxylation rate on the temperature could be established. Upon lowering the temperature from 60 °C to 40 °C, the decarboxylation rate of **1** (ratio copper(I):cinchonine:**1** = 1:7.5:7.5) dropped from 70% after 135 minutes to 30% after 120 minutes. At a temperature of 21 °C, the conversion over a period of 10 hours was reduced to about 5%.

Decarboxylation of **3** *in the Presence of Bis(tricyclohexylphosphane)copper(I) Hydrogenphenylmalonate* (**6**) *and Potassium Hydrogenphenylmalonate* (**7**)

In the course of our present investigations we also examined the copper(I) complex *bis*(tricyclohexylphosphane)copper(I) hydrogenphenylmalonate (**6**) which had previously been used as a catalyst in the decarboxylation of malonic acid derivatives [5]. To demonstrate that the copper(I) ion is not the decisive factor for the decarboxylation, we have synthesized potassium hydrogenphenylmalonate (**7**) and shown that **7** has about the same activity in the decarboxylation of malonic acid derivatives as **6**.

7 was prepared from potassium hydride and an excess of phenylmalonic acid (**3**) in *THF*. If copper(I) is the catalyst in the decarboxylation of malonic acid derivatives, the potassium salt **7** should not undergo decarboxylation at the same rate under the same reaction conditions.

In a series of kinetic studies, phenylmalonic acid (**3**) was decarboxylated in the presence of **6** in *THF* at 55 °C. After given time intervals, samples were taken from the mixture. Analysis was carried out by ^{1}H NMR spectroscopy in acetone-d_6. A plot of ln(*conversion*) *vs.* time was linear indicating first-order behavior in **6**. The same kinetic sudies were carried out with **7**. To dissolve **7** in *THF* it was necessary to add 18-crown-6. Surprisingly, here also a first-order behavior in the potassium salt **7** could be established. The rate constants for the decarboxylation with **6** ($1.30 \cdot 10^{-3}\,s^{-1}$) and with **7**/18-crown-6 ($1.35 \cdot 10^{-3}\,s^{-1}$) are nearly identical (Fig. 1). Thus, both additives behave similarly. Addition of 18-crown-6 to solutions of **3** in acetonitrile gave a slight increase in decarboxylation compared to the uncatalyzed thermal reaction (Table 1).

In order to obtain additional information concerning the mechanistic aspects of decarboxylation, we investigated the dependence of the decarboxylation of **3** on the concentration of additives **6** and **7**. A stock solution containing the potassium salt

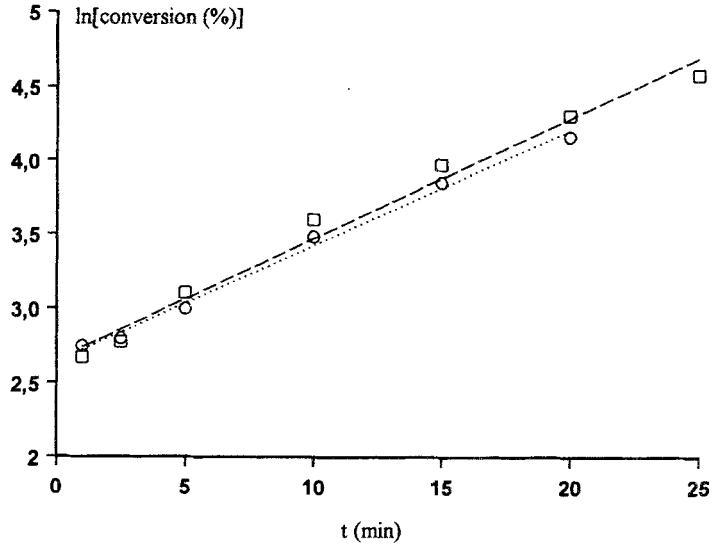


Fig. 1. Kinetics of the decarboxylation of **3** in *THF* at 55 °C in the presence of **6** (○, dotted line) and **7** (□, dashed line), respectively

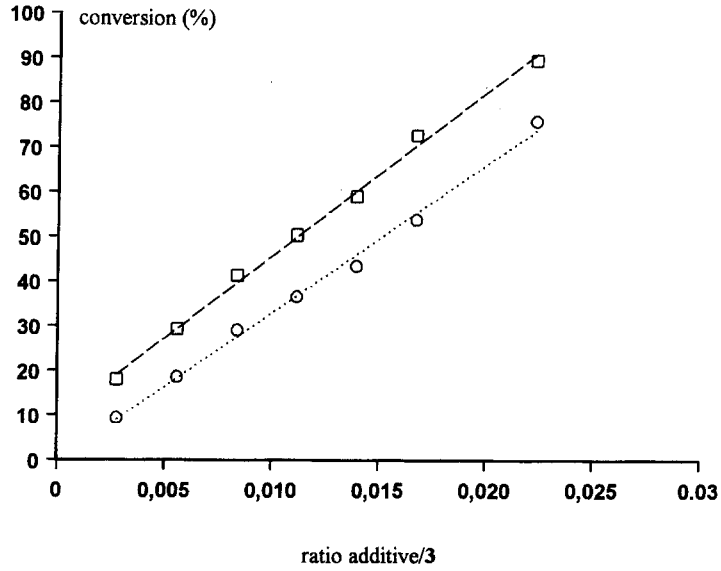


Fig. 2. Dependence of the decarboxylation of **3** in *THF* at 55 °C on the concentration of **6** (○, dotted line) and **7** (□, dashed line), respectively (reaction time: 20 min)

7 and 18-crown-6 in *THF* was prepared. The various concentrations were obtained by adding different amounts of stock solution to the same quantities of phenylmalonic acid (**3**) with subsequent filling up with absolute *THF*. After heating to 55 °C for 20 minutes, workup and analysis in acetone-d_6 by ^{1}H NMR spectroscopy were carried out as described above.

A plot of the extent of decarboxylation (in %) *vs.* concentration in the presence of **7**/18-crown-6 was linear indicating zero-order behavior in the additive (Fig. 2). A slope of $3.67 \cdot 10^{-3}$ (correlation coefficient: 0.997) was obtained. Similar studies were performed with **6** under the same conditions. As for **7**, a linear relationship between decarboxylation rate and concentration was observed. The slope of the plot of decarboxylation *vs.* concentration (Fig. 2) was $3.32 \cdot 10^{-3}$ (correlation coefficient: 0.998).

In addition, the decarboxylation of the copper(I) complex **6** was investigated without any other substrate. By heating **6** to 55 °C in *THF* for 15 minutes, total decarboxylation occurred. In contrast, no decarboxylation took place in boiling CH_2Cl_2. The rate of decarboxylation of **3** in *THF* is not changed on addition of tricyclohexylphosphane. Also, tricyclohexylphosphane has no influence on the decarboxylation of **3** in the presence of **7**/18-crown-6.

Decarboxylation of **3** *in the Presence of Other Additives*

Different metal and ammonium oxides and chlorides were tested as additives in the decarboxylation of phenylmalonic acid (**3**) in acetonitrile to further evaluate the role of copper(I) as a specific decarboxylation catalyst. In the presence of **3**, Ag_2O in acetonitrile formed a homogeneous solution. The decarboxylation of **3** under addition of Ag_2O was carried out as described above (molar ratio 10:1, 65 °C, 1.5 h). Total decarboxylation occurred.

Table 3. Decarboxylation of phenylmalonic acid (**3**) in the presence of different chlorides; 0.75 mmol of **3**, 0.25 mmol of chloride, 7.0 ml of acetonitrile, 2.0 h, 70 °C

chloride	**3**:chloride[a]	conversion
CuCl	3:1	79.5%
bis(2-chloroethyl)ammonium chloride	3:1	83.5%
triethylbenzylammonium chloride	3:1	89%
without any additive[b]	–	39%
$CuCl_2$	3:1	12%
$CuCl_2$	6:1	14.5%
$CuCl_2$	15:1	18%
$ZnCl_2$	3:1	21.5%
$ZnCl_2$	6:1	26.5%

[a] Molar ratio; [b] thermally induced reaction

For other chlorides tested in the decarboxylation of **3**, a reaction time of 2.0 hours, a temperature of 70 °C, and a molar ratio of substrate:additive up to 3:1 was chosen. Under these conditions, CuCl reached 79.5% decarboxylation (Table 3). The two soluble ammonium chlorides *bis*(2-chloroethyl)ammonium chloride and benzyltriethylammonium chloride gave 83.5% and 89% decarboxylation, respectively (Table 3). In the presence of other ammonium chlorides such as dimethyl- and triethylammonium chloride, **3** was totally decarboxylated in 2 hours, a behavior which could be due to the hygroscopic nature of these ammonium chlorides. This explanation was corroborated by the fact that adding small amounts of water in experiments with CuCl increased the extent of decarboxylation.

$CuCl_2$ and $ZnCl_2$ were also tested in the decarboxylation of **3** under the conditions given in Table 3. $CuCl_2$, added in a molar ratio **3**:$CuCl_2$ = 3:1, reached only 12% decarboxylation. Surprisingly, the higher the amount of $CuCl_2$, the lower was the conversion of **3** (Table 3). The same tendency was found in the decarboxylation of **3** in the presence of $ZnCl_2$ (Table 3). Addition of $[Pd(PPh_3)_2Cl_2]$, a potential catalyst, had no effect on the decarboxylation of **2** in *THF* because it is not involved in the protonation/deprotonation equilibria.

Enantioselective Decarboxylation of **2**

As the present study showed that the decarboxylation of malonic acids is not catalyzed by copper(I) but induced by basic compounds, the enantioselective decarboxylation of the monoethyl ester of methylphenylmalonic acid (**2**) by chiral bases was studied. The effect of different bases on yield and enantioselectivity is reported in Table 4. After 20 hours, the decarboxylation was complete in all cases (confirmed by ^1H NMR). For workup, the solvent was removed, and the residue was treated with ether and hydrochloric acid. The organic phase was washed with water and dried over Na_2SO_4. The resulting oily residue was distilled. The enantiomer analysis was carried out by polarimetric measurements [4, 10].

Table 4. Enantioselective decarboxylation of the monoethyl ester of methylphenylmalonic acid (**2**) to give ethyl 2-phenylpropionate; 1.50 mmol of **2**, 0.15 mmol of base, 30 ml of *THF*, 20 h, room temperature; ( ) = number of experiments

chiral base	yield (%)	% *ee*
cinchonine	85–93 (3)	33.8–34.5 (*S*)
cinchonidine	82–89 (3)	16.0–16.4 (*R*)
quinine	86–89 (3)	12.4–12.7 (*R*)
quinidine	90–91 (3)	13.5–13.6 (*S*)
2,4-*bis*[(cinchonine)carbamyl]toluene	92 (1)	10.3 (*R*)
N-phenyl(cinchonine)carbamate	92–94 (3)	11.5–12.8 (*S*)
N-*tert*-butyl(cinchonine)carbamate	88–90 (3)	27.6–28.3 (*S*)
di(quinine)carbonate	83–87 (3)	26.6–26.9 (*R*)

The highest levels of enantiocontrol were obtained with the cinchona alkaloids and their derivatives (Table 4). Cinchonine itself afforded the highest *ee* with 34.5% (*S*)-(+)-ethyl 2-phenylpropionate. The corresponding diastereomer cinchonidine achieved only 16.4% *ee*, giving (*R*)-(−)-ethyl 2-phenylpropionate. With the other pair of alkaloids, quinine and quinidine, similar results were obtained. Interestingly, use of quinidine which, compared to cinchonine, has an additional methoxy group at the quinoline system, provided an *ee* value of only 13.6%. In addition, cinchona alkaloids, modified at the hydroxy group of C-9, were used in the enantioselective decarboxylation of the monoethyl ester of **2** (Table 4). Different carbamates of cinchonine were less effective (10.3%–28.3% *ee*) than the alkaloid itself. The carbonate derivate of quinine, however, increased appreciably the optical induction in comparison to quinine (Table 4). The carbonates of the other cinchona alkaloids and other chiral bases, such as (*S*)-(−)-1-phenylethylamine or (1*R*,2*S*)-ephedrine, afforded only low *ees* [7].

Historical Development

In the literature there are scattered reports on the decarboxylation of copper(I) carboxylates, *e.g.* copper(I) nitrobenzoate [11, 12]. About 10 years ago, *Toussaint et al.* published that the Cu_2O catalyzed decarboxylation of malonic acid derivatives afforded the corresponding monocarboxylic acids in nearly quantitative yield (molar ratio substrate:copper(I) = 10:1) [2, 3]. A catalytic cycle based on copper(I) was postulated [2]. Later, an optical induction of 27% *ee* in the decarboxylation of methylphenylmalonic acid (**1**) was obtained using the catalyst CuCl/cinchonine (molar ratio substrate:cinchonine:CuCl = 1.4:2:1) [3]. In a study of the same reaction from our laboratory, the amount of CuCl could be reduced to a molar ratio of substrate:cinchonine:CuCl = 38:58:1; the optical induction was increased to 36% *ee* [4]. In 1993, *Darensbourg et al.* isolated copper(I) complexes with a novel monodentate coordination between copper(I) and hydrogenmalonates. Compounds such as *bis*(tricyclohexylphosphane)copper(I) hydrogenphenylmalonate (**6**) were used as

effective catalysts in the decarboxylation of malonic acid derivatives [5]. Thus, copper(I) catalysis in the decarboxylation of malonic acid derivatives seemed to be well documented in the literature. In a recent study, discussed below in more detail, *Darensbourg et al.* reexamined the role of copper(I) in the decarboxylation of malonic acid derivatives [6]. Evidence was presented which minimized the role of copper(I).

Present View of the Decarboxylation

In the present paper we have demonstrated that copper(I) does not act as a catalyst in the decarboxylation of malonic acid derivatives. We propose, instead, that catalysis is due to the basic properties associated with the anions of the copper(I) salts used. We consider the monoanion $R^3OOC\text{-}CR^1R^2\text{-}COO^-$ to be the reactive species in the decarboxylation of malonic acid derivatives. Loss of CO_2 leads to the enolate $R^3OOC\text{-}CR^1R^{2-}$ which is protonated to give the final product $R^3OOC\text{-}CHR^1R^2$. Everything which increases the concentration of the monoanion increases the rate of decarboxylation and *vice versa.*

Role of Cu_2O and CuCl in the Decarboxylation of **1–5**

In the decarboxylation of malonic acid derivatives **1–3** with Cu_2O and CuCl under analogous condition, enormous differences were observed (Table 1). If the reaction was really catalyzed by copper(I), the rates of decarboxylation should be nearly identical, independent of the source of copper(I). Obviously, however, Cu_2O is a much more effective additive in the decarboxylation of malonic acid derivatives than CuCl. Thus, catalysis is not due to copper(I) but to the basicity of the corresponding anions.

Cu_2O which is insoluble in acetonitrile dissolves in the presence of malonic acid derivatives **1–5**. In this process, the malonic acid derivatives present in a ten-fold excess are partially converted to the corresponding monoanions. A high concentration of monoanions results, and fast decarboxylation occurs.

The thermally induced decarboxylation of **1–3** is appreciably slower (Table 1). The reason for the thermal reaction could be the autoprotolysis of the malonic acids in which monoanions are formed which decarboxylate. As is to be expected, decarboxylations in the presence of CuCl which does not contain a strongly basic anion is only insignificantly different from the thermal-only reactions (Table 1).

Another experiment supports our assumption that those factors which decrease the concentration of the monoanion $R^3OOC\text{-}CR^1R^2\text{-}COO^-$ retard the decarboxylation. If HCl gas was passed through the solution of CuCl and **3** in acetonitrile, the extent of decarboxylation fell from 79.5% for CuCl alone to 21.5% (experimental conditions as in Table 3), indicating that part of the monoanions present in the system CuCl/**3** were protonated by HCl.

The influence of substituents on the decarboxylation of malonic acid derivatives **1–5** is reflected by the conversions shown in Table 1. The decarboxylation rate of methylphenylmalonic acid (**1**) is much lower than that of phenylmalonic acid (**3**). This is due to the electron-donating effect of the methyl group which increases the negative charge of the carbanion in the transition state. The reason for the

extremely low conversions in the decarboxylation of the unsubstituted malonic acid **5** and its *hemi*ester **4** is the lack of the phenyl substituent which stabilizes the carbanion.

Role of Bases and CuCl in the Decarboxylation of **1**

In the preceding section it was shown that the oxide ion in Cu_2O deprotonates malonic acid derivatives, increasing the concentration of the monoanions and the rate of decarboxylation. If this explanation is true, the addition of other bases should have the same effect. Indeed, bases such as triethylamine give increased decarboxylation rates [7].

According to previous reports, the enantioselective variant of the decarboxylation of methylphenylmalonic acid (**1**) requires the presence of systems such as CuCl/cinchona alkaloid [3, 4]. Therefore, we investigated the influence of CuCl/cinchonine and of cinchonine alone on the decarboxylation of **1** in acetonitrile at 60 °C (Table 2). Surprisingly, for a given cinchonine concentration, addition of CuCl leads to a decrease in the extent of decarboxylation (Table 2). This can be explained by the formation of complexes between copper(I) and cinchonine which reduce the base concentration. Thus, addition of CuCl in the presence of a base slightly decreases the extent of decarboxylation, whereas, as shown above, addition of CuCl in the absence of a base increases the extent of decarboxylation (which can be reduced by passing HCl through the solution).

Role of Bis(tricyclohexylphosphane)copper(I) Hydrogenphenylmalonate (**6**) *and Potassium Hydrogenphenylmalonate* (**7**) *in the Decarboxylation of* **3**

The copper(I) complex **6** is proposed to be an intermediate and an effective catalyst in the decarboxylation of dicarboxylic acids by *Darensbourg* [5]. For comparison, we synthesized potassium hydrogenphenylmalonate (**7**) and carried out experiments on the decarboxylation of **3** with both **6** and **7**. According to *Toussaint*'s theory of the copper(I) catalyzed decarboxylation, **7** should not accelerate the reaction [3]. To dissolve **7** in *THF* it was necessary to add 18-crown-6. Interestingly, the conversion with the potassium salt **7** (together with the crown ether) was slightly higher throughout the reaction that with the copper(I) complex **6**. However, in kinetic studies both the copper(I) complex **6** [4] and **7**/18-crown-6 exhibited first-order kinetics (Fig. 1) and, even more surprisingly, with nearly identical rate constants. Obviously, it is not the copper(I) ion which is responsible for the decarboxylation but the monoanion $HOOC—CHPh—COO^-$ present in both **6** and **7**. Furthermore, in the decarboxylation of **3**, different catalyst concentrations of **6** and **7**/18-crown-6 were used. Plots of conversion in % *vs.* the concentrations of the additives **6** and **7** demonstrate similar slopes, indicating zero-order behaviour in the additives (Fig. 2). Heating **6** in boiling anhydrous *THF* gave total decarboxylation within 15 minutes. In contrast, no decarboxylation of **6** could be detected under same conditions in boiling CH_2Cl_2. These results are consistent with *THF* acting as a ligand which solvates and separates the cation and anion of **6**. Then, the "free" anion decarboxylates. In CH_2Cl_2, cation and anion of **6** stay together, and there is no decarboxylation.

Role of Other Additives in the Decarboxylation of **3**

In addition to Cu_2O and CuCl, other metal and ammonium oxides and chlorides not involving copper(I) were tested. Ag_2O was found to be soluble in an acetonitrile solution of **3**. Total decarboxylation of **3** in the presence of Ag_2O occurred similar to the reaction with Cu_2O.

For testing the less reactive chlorides in the decarboxylation of **3** in acetonitrile, we increased reaction time, temperature, and concentration of the additives compared to the experiments with Cu_2O and CuCl shown in Table 1. Under these conditions, 79.5% decarboxylation was obtained in the reaction of **3** with CuCl (Table 3). Because of their solubility in acetonitrile, ammonium chlorides were chosen as additives. *Bis*(2-chloroethyl)ammonium chloride and benzyltriethylammonium chloride gave 83.5% and 89% decarboxylation, respectively (Table 3), values slightly higher than that with CuCl. Other ammonium chlorides, such as dimethyl- and triethylammonium chloride, showed total decarboxylation of **3** within 2 hours (Table 3). An explanation for this result could be the hygroscopic nature of these ammonium chlorides. In agreement with this, the addition of small amounts of water to the system CuCl/**3** also showed an increase of the rate of decarboxylation. It can be assumed that the presence of water affects the autoprotolysis equilibrium of the system, increasing the concentration of the monoanion. *Bis*(2-chloroethyl)ammonium chloride is non-hygroscopic. Therefore, the decarboxylation of **3** in the presence of *bis*(2-chloroethyl)ammonium chloride (83.5%) is similar to that in the presence of CuCl (79.5%).

All experiments with copper(I) compounds were carried out under an inert atmosphere to prevent oxidation of copper(I). In another series, copper(II) chloride was used as an additive in the decarboxylation of **3** under the same conditions (Table 3). Interestingly, the conversion of 12% with $CuCl_2$ was much smaller than the 39% of the thermally induced reaction. Thus, whereas an addition of CuCl increased the extent of decarboxylation of **3**, an addition of $CuCl_2$ decreased it. This decrease must be due to the copper(II) ion. Copper(II) forms stable complexes for which the negatively charged monoanions of malonic acid derivatives are better ligands than the neutral species. Upon coordination of the monoanions, the remaining proton becomes more acidic. It protonates other monoanions present in the solution and responsible for the decarboxylation, thus reducing their concentration. The same explanation holds for the decarboxylation of **3** in the presence of $ZnCl_2$ (Table 3).

Recent Results and Suggestions

In a recent study, *Darensbourg et al.* examined the role of copper(I) and zinc(II) in the decarboxylation of malonic acid derivatives [6]. It was shown that the decarboxylation in the presence of copper(I) and zinc(II) carboxylates occurred *via* a predissociation involving metal-carboxylate bond rupture. Salts such as $[(C_2H_5)_4N][HOOC—CH_2—COO]$ and [Na(Kryptofix-221)][HOOC—CH_2—COO] containing noninteracting cations were more effective catalysts in the decarboxylation of **3** than the corresponding copper(I) and zinc(II) compounds; this is in accordance with the requirement of a preequilibrium affording the monoanions from the copper(I) and zinc(II) malonate derivatives. Addition of 2 equiv. of the

ligand (and base) neocuproine to the catalyst copper(I) butyrate in the decarboxylation of **3** increased the rate of decarboxylation compared to addition of only 1 equiv. of neocuproine [6]. According to *Darensbourg et al.*, the increase is caused by the complexation of copper(I) by 2 equiv. of neocuproine releasing free butyrate [6]. On the other hand, neocuproine is a base which deprotonates malonic acids increasing the concentration of the monoanion which is the reactive species.

Zinc(II) acetate is only an effective catalyst in the decarboxylation of phenylmalonic acid monobenzylester if 1,10-phenanthroline is present [6]. In addition to the above explanation, *Darensbourg et al.* proposed a zinc(II) complex consisting of a 1,10-phenanthroline ligand, an anion of benzyl phenylmalonate weakly bound to the metal center by the carboxylate group, and a second benzyl phenylmalonate coordinated to the metal by the ketonic oxygen of the ester function. The electron-attracting effect of the metal center on the ketonic oxygen is thought to support the decarboxylation by electrophilic assistance. However, such processes in the solvents used are difficult to assess. Thus, the (minor) participation of pathways such as the electrophilic assistance mentioned above should only be discussed when unambiguous proof is available.

Enantioselective Decarboxylation of **2**

As it became obvious during the present study that the decarboxylation of malonic acid derivatives is not a copper(I) catalyzed reaction, it was necessary to examine the enantioselective decarboxylation in the absence of copper(I). The best results were obtained with the cinchona alkaloids and their derivatives (Table 4). Cinchonine afforded the highest enantiomeric excess with 34.5% (*S*)-(+)-ethyl 2-phenylpropionate. The base-only results were compared with those obtained by the base/copper(I) combination used in literature procedures [3, 4]. As expected, the enantiomeric excess obtained in the decarboxylation of methylphenylmalonic acid (**1**) was the same with and without copper(I) [7].

Experimental

Materials and Methods

All manipulations were carried out under an inert atmosphere unless otherwise stated. The solvents were freshly distilled prior to use. Malonic acid (**5**) and phenylmalonic acid (**3**) were purchased from Acros Chimica. Methylphenylmalonic acid (**1**) and the ethyl ester of methylphenylmalonic acid (**2**) were prepared according to published procedures [4] starting from the diethyl ester of phenylmalonic acid which was purchased from Acros Chimica. Monoethyl malonate (**4**) was prepared from diethyl malonate. CuCl and Cu_2O were purchased from Aldrich and tricyclohexylphosphane from Fluka. *Bis*(tricyclohexylphosphane)copper(I) hydrogenphenylmalonate (**6**) was synthesized according to the published procedure [5]. Potassium hydrogenphenylmalonate (**7**) was prepared from potassium hydride and an excess of phenylmalonic acid (**3**) in *THF* [8] (purity checked by C, H, and K analysis). The cinchona alkaloids (purity >99%) were purchased from Merck.

^{1}H NMR spectra were recorded on a Bruker ARX 400 spectrometer with tetramethylsilane as internal standard. Enantiomeric excesses were determined using a Perkin-Elmer polarimeter 241. Elemental analyses were performed by the microanalytical laboratory of the University of Regensburg.

Decarboxylation of the Malonic Acid Derivatives **1–4** *in the Presence of Cu_2O and CuCl Monitored by ^1H NMR Spectroscopy*

In the standard procedure, each of the malonic acids **1–4** (1.0 mmol) was heated in acetonitrile (1 ml) with Cu_2O (7.2 mg, 0.1 mmol Cu^I) and CuCl (9.9 mg, 0.1 mmol Cu^I), respectively, to 65 °C with stirring for 1.5 h.

In the experiments with the derivates **1–3**, the solvent was removed in vacuum, ether (20 ml) was added to the residue, and the copper salts were hydrolyzed with 2 *N* hydrochloric acid (1 ml). The organic compounds (starting material and product, depending on the extent of decarboxylation) were extracted with ether (2 × 25 ml). The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The ratio of starting material to product was determined by ^1H NMR spectroscopy. For integration, the following signals (starting material/product) were used **1**, 1.85/1.42 ppm (*DMSO*-d_6); **2**, 1.95/1.46 ppm ($CDCl_3$); **3**, 4.66/3.61 ppm (*DMSO*-d_6).

In the experiments with monoethyl malonate (**4**), the workup was different. Because of its high volatility, the product ethyl acetate was removed with the solvent. Ether (20 ml) was added to the residue. The anions of the copper salts were transferred to the free acids by adding an acidic ion exchanger (DOWEX 50 X 8) to the mixture. Then, the ion exchanger was filtered off and washed with ether. After removal of the solvent, a definite amount of the standard toluene (*ca.* 270 mg) was added to the remaining monoethyl malonate **4** to allow the determination of its quantity by ^1H NMR spectroscopy (neat). The signals at 3.48 ppm for **4** and 2.32 ppm for the standard toluene were used for integration.

In another series of experiments, the malonic acid derivatives **1–4** (1.0 mmol) were heated to 65 °C in acetonitrile (1 ml) without the presence of any copper(I) compound to obtain information about the thermal instability of the acids. After the solvent was evaporated, the residue was dissolved in acetone-d_6 and used directly for the measurement of the ^1H NMR spectrum.

Decarboxylation of the Malonic Acid Derivatives **1–5** *in the Presence of Cu_2O and CuCl Monitored by Volumetry*

The decarboxylation of malonic acids **1–5** was monitored by volumetry. As above, a molar ratio substrate:copper(I) = 10:1 was used, the reaction time was 1.5 h, and the temperature 65 °C. The progress of the reaction was followed by measuring the volume of carbon dioxide with a gas buret similar to that described by *Fraenkel et al.* [9]. The amount of conversion was calclated by the *van der Waals* equation.

Decarboxylation of Methylphenylmalonic Acid (**1**) *in the Presence of Cinchonine and CuCl*

Methylphenylmalonic acid (**1**, 291.3 mg, 1.50 mmol) was heated in acetonitrile (70 ml) with cinchonine (677.1 mg, 2.30 mmol) or cinchonine (677.1 mg, 2.30 mmol) together with CuCl (104.0 mg, 1.05 mmol), respectively, to 60 °C. After given time intervals, samples (10 ml) were withdrawn with a syringe. The workup of each sample was carried out as described above using more ether (30 ml) and 2 *N* hydrochloric acid (20 ml). The ratio starting material:product was determined by ^1H NMR spectroscopy in acetone-d_6.

Decarboxylation of Phenylmalonic Acid (**6**) in the Presence of *$(Cy_3P)_2CuOOC$-CHPh-COOH* (**6**) and KOOC-CHPh-COOH (**7**)

Phenylmalonic acid (**3**, 0.8 g, 4.4 mmol) was heated in *THF* (50 ml) with **6** (75 mg, 0.1 mmol) or alternatively with **7** (21 mg, 0.1 mmol) and 18-crown-6 (38 mg, 0.15 mmol) to 55 °C. After given time intervals, samples of 5 ml were taken from the reaction mixture. After workup as described above, small amounts of 18-crown-6 were present in the isolated mixture of starting material/product which

obscured the methylene signal of the product phenylacetic acid. Therefore, the ratio phenylmalonic acid/phenylacetic acid was determined by integration of the phenyl signal (both compounds) and the methine signal (only phenylmalonic acid) in acetone-d_6.

To determine the dependence of the decarboxylation of phenylmalonic acid (**3**) on the concentration of the additives **6** and **7** (+18-crown-6), respectively, stock solutions of **6** and **7** together with 18-crown-6 in *THF* were prepared. The different concentrations were obtained by adding the corresponding volumes of the stock solutions to **3** (135 mg, 0.75 mmol) and subsequent filling up to 6 ml with anhydrous *THF*.

Decarboxylation of Phenylmalonic Acid (3) in the Presence of CuCl, $[NR_4]Cl$, $CuCl_2$, and $ZnCl_2$

To phenylmalonic acid (**3**, 135 mg, 0.75 mmol), the respective chloride was added in the ratios given in Table 3. The mixtures were heated in acetonitrile (7 ml) to 70 °C with stirring for 2 h. Workup and analysis proceeded as described above.

Enantioselective Decarboxylation of the Monoethyl ester of Methylphenylmalonic Acid (**2**)

The monoethyl ester of methylphenylmalonic acid (**2**, 333 mg, 1.50 mmol) and an optically active base (0.15 mmol) were stirred in *THF* (30 ml) under a nitrogen atmosphere for 20 h at room temperature. After removal of the solvent, the residue was dissolved in ether (20 ml) and the base was separated by shaking with 2 *N* hydrochloric acid (20 ml). The organic phase was washed with water (3 × 10 ml) and dried over Na_2SO_4. The solution was filtered and concentrated. The oily product was purified by bulb-to-bulb distillation (b.p.: 108–109 °C, 3 torr). The chemical yield ranged from 80–95% (by weight). ^{1}H NMR and microanalytical data of ethyl 2-phenylpropionate are given in Ref. 4. For determination of the enantiomeric excess, the optical rotation of the product was compared with the value of (*S*)-(+)-ethyl 2-phenylpropionate: $[\alpha]_D^{24} = +72.0°$ ($c = 10$, toluene) [10].

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