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The Decarboxylation of Phenylmalonamates and Phenylmalonilates

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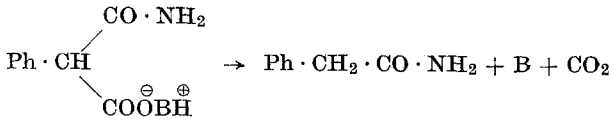
Whilst decarboxylation of dibasic acids and their derivatives under alkaline conditions and on heating at elevated temperatures is well established, the decarboxylation of the brucine salt of phenylmalonamic acid (brucine-2-carbamoyl-2-phenyl-ethanoate) unusually takes place rapidly in water at room temperature. The details of the kinetics are given.

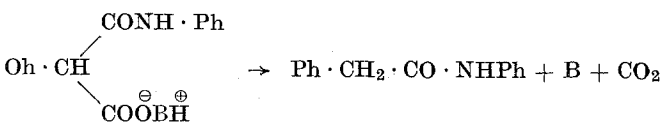
Die Decarboxylierung von Brucinsalzen von Phenyl-malonamidsäure und N-Phenyl-phenyl-malonamidsäure

Brucinsalze von Phenyl-malonamidsäure (Brucin-2-carbamoyl-2-phenyl-ethanoat) und *N*-Phenyl-phenyl-malonamidsäure (Brucin-*N*-phenyl-2-carbamoyl-2-phenyl-ethanoat) decarboxylieren in wäßriger Lösung bei Raumtemperatur sehr rasch. Details der Kinetik dieses Prozesses werden beschrieben.

Introduction

In the course of an investigation into asymmetric transformations in the malonamate and malonanilate series[1] curious results were obtained which could only be explained in terms of decarboxylation of





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the salts at room temperature to yield phenylacetamide and phenylacetanilide respectively.

In the preparation of the strychnine salt of phenylmalonamic acid from phenylmalonamic acid and strychnine in acetone, after the initial solution of the reagents in the acetone, strychnine started to precipitate out in about half an hour, giving finally an 87 % recovery, whilst from the filtrate, 79 % of phenylacetamide was obtained. In methanol-water solutions, on the other hand, the strychnine salt is obtained.

Phenylmalonamic acid [2-carbamoyl-2-phenyl-ethanoic acid (**1**)] with cinchonine and cinchonidine gives active salts by a second order asymmetric transformation, whilst with brucine, phenylacetamide is again formed but, unlike strychnine, the base itself stays in solution in acetone.

Phenylmalonanilic acid [*N*-phenyl-2-carbamoyl-2-phenyl-ethanoic acid (**2**)] gave analogous products to those obtained with phenylmalonamic acid, with both brucine and strychnine in acetone solution. The strychnine salt was not observed to decarboxylate in chloroform, dioxan and methanol, but a solution in methyl cyanide deposited strychnine.

Kinetics

Substitution for hydrogen atoms on the central methylene carbon atom of malonic acid may be expected to affect the rate of decarboxylation in accordance with the inductive and steric effects of the substituents[2].

In aqueous solutions of malonic, and of substituted malonic acids, undissociated acid, the mono-anion and the bi-anion will co-exist[3]. The rate of decarboxylation of these species has been studied[4] and for the parent acid it was shown that the rate of decarboxylation of the neutral molecule is ten times as great as that of the mono-anion. However, for certain substituted malonic acids, the mono-anion decarboxylates more rapidly than the undissociated species[5, 6]. The bi-anion was found to be stable in all the systems studied and its stability was attributed[6] to the high electron density in the C—C bonds and the difficulty in accommodating the negative charge in the fission process. A substituent with + I effect, adjacent to the C—C bond to be broken, leads to resonance stabilisation of the negative charge on the mono-anion, resulting in the increase of its relative reactivity as compared with the undissociated acid. Malonamic and malonanilic acids are the monoamide and monoanilide derivatives of malonic acid and, therefore, might be expected to behave in a rather similar manner, but see below.

Results and Discussion

The results are summarized in Tables 1 and 2.

Weak bases such as pyridine and quinoline, pK_a^{25} 5.21 and 4.81 respectively[7], are known to promote the decarboxylation of malonic

Table 1. *Rate of decarboxylation for brucine phenylmalonamate* (**1 a**) *and brucine phenylmalonanilate* (**2 a**)

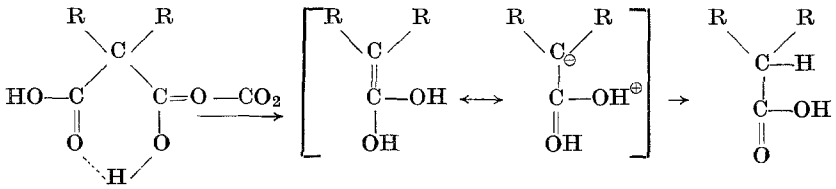
	T (K)	log T	k (s^{-1})	log k
1 a	293.3	2.4673	5.11×10^{-5}	—4.291
	303.2	2.4817	1.87×10^{-4}	—3.728
	310.2	2.4917	4.36×10^{-4}	—3.360
2 a	296.1	2.4714	8.15×10^{-5}	—4.088
	303.2	2.4817	2.11×10^{-4}	—3.676
	310.2	2.4917	5.49×10^{-4}	—3.261

Table 2. *Arrhenius parameters for the decarboxylation of* **1 a** *and* **2 a**

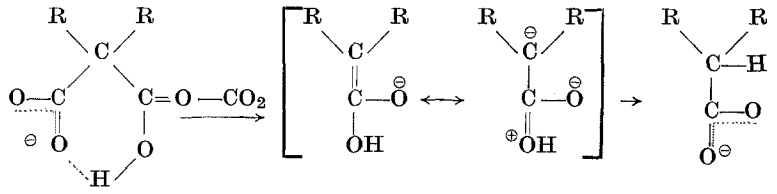
	ΔS^* ($J\,K^{-1}\,mol^{-1}$)	ΔH^* ($kJ\,mol^{-1}$)	ΔF^* ($kJ\,mol^{-1}$)
1 a	—28.0	88.3	95.8
2 a	+ 20,9	101.7	95.8

acid, although the acid is not appreciably dissociated in such weak bases[8]. To account for this it was suggested[9] that these bases enter into solvation of the carboxyl carbon of the malonic acid. Keeping this in view, a mechanism for the decarboxylation of malonic acid derivatives was proposed[6, 9] and its validity confirmed[10]:

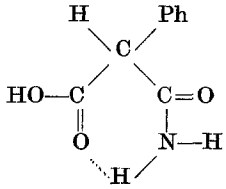
For the undissociated acid



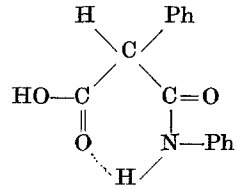
For the monoanion



The significant features of this mechanism are that: (i) it is the carboxylic group and *not* the carboxylate ion which is involved in the elimination process, (ii) a proton transfer occurs from the carboxylic group to be eliminated to the other, remaining, group; the intramolecular hydrogen bond assists this proton transfer, and (iii) the proton thus transferred is used in accommodating the negative charge, produced as a result of the C—C bond fission, by forming a new covalent bond.

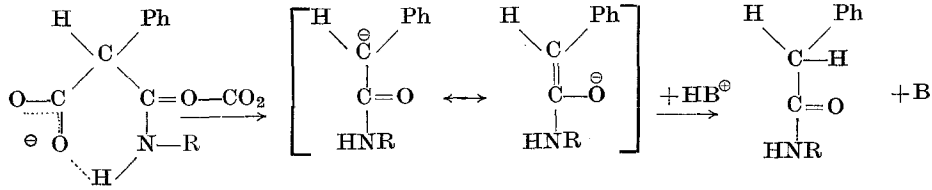


1

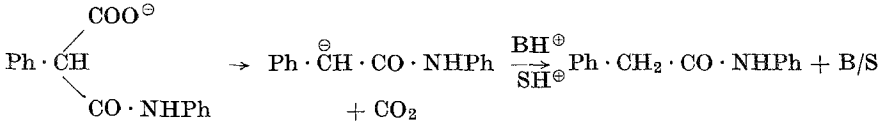


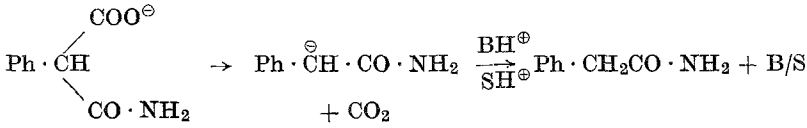
2

The above mechanism is quite satisfactory for the decarboxylation of malonic acids in weak bases but failed to explain the reaction in strong bases in which the acids are completely dissociated. This was first felt in the case of the malonanilic acid which is thought to decarboxylate in the form of its dissociated species[10]. Phenylmalonamic (**1**) and phenylmalonanilic (**2**) acids, the subject of the present study, also appear to decarboxylate as anions. These acids are dissociated in the presence of brucine, pK_a 8.25[11], a stronger base than pyridine, or quinoline and which forms stable salts with many organic acids. Since the reaction probably proceeds via the carboxylate ion, a proton must ultimately be supplied to give the final product. The only reasonable source for the proton is the conjugate acid of the base used in the reaction. A probable mechanism, therefore, would be:



In malonic acid the leaving group donates a proton to the carboxylate ion. If a similar mechanism were to obtain in this case, a complex rearrangement would have to follow the decarboxylation. The simpler hypothesis is that the decarboxylation proceeds in a manner similar to that suggested for most monocarboxylic acids, i.e. via the anion[12, 13].





Whilst it is noteworthy that substances such as quinaldinic acid decarboxylate via a zwitterion[14], such a mode is not available in phenylmalonamic and phenylmalonanilic acids under these conditions since they decarboxylate only as anions.

Strychnine also promotes the room temperature decarboxylation in acetone of the compounds studied and superficial observations indicate a similar rate and process to the brucine catalysed reaction. However, despite the optical activity of strychnine, kinetic studies with it could not be made owing to precipitation of the strychnine. As the decarboxylations proceeded the solution of the strychnine salt of these acids deposited crystals of the liberated base which made kinetic polarimetric readings impossible.

Experimental

Phenylmalonamic acid [2-carbamoyl-2-phenyl-ethanoic acid (**1**)] was prepared by the saponification of ethyl-α-amidophenylacetate, obtained by the method of *Wislicenus*[15], with 10% methanolic KOH (1:1 MeOH and H_2O). Recrystallised from $EtOH/H_2O$, mp 123-124°.

Phenylmalonanilic acid [*N*-phenyl-2-carbamoyl-2-phenyl-ethanoic acid (**2**)] was obtained by the method of *Redmon*[16] and recrystallised from $EtOH/H_2O$, mp 125-126°.

The acetone used in the experiments was the "ANALAR" grade reagent.

The brucine and strychnine were the commercially available alkaloids.

Decarboxylations and Identification of Products

a) To 4.5 g racemic **1** in acetone (1000 ml) was added 8.4 g strychnine. A solid began to separate within half an hour (identified by mp and mixed mp as strychnine). From the filtrate 2.7 g (79 %) phenylacetamide (mp and mixed mp with an authentic specimen 157°), was obtained.

b) To 3.2 g rac. **2** in acetone (100 ml) was added 4.29 g strychnine. The resulting solution was left overnight, depositing 3.5 g (83 %) strychnine (mp and mixed mp with authentic sample 286-288°). After filtration the mother liquor was concentrated to half bulk, then neutralised with 2 % sodium hydroxide solution and, finally, acidified with 4 N hydrochloric acid to yield phenylacetanilide, 1.8 g, 70 % (mp and mixed mp 117-118°).

c) To 3.2 g rac. **2** in acetone (500 ml) was added 4.9 g brucine. After standing overnight the solution was concentrated under reduced pressure to 100 ml, cooled, and treated with ice-cold hydrochloric acid; 2.1 g (76 %) phenylacetanilide, mp 116-118°, was precipitated from the solution (identified by a mixed mp with an authentic sample and by comparison of infrared spectra).

Kinetic Method

Equivalent quantities of brucine (0.098 g) and racemic **1** (0.045 g) or rac. **2** (0.064 g) were separately dissolved in 5 ml of acetone and left in a thermostat bath. After they had acquired the desired temperature the two solutions were mixed and filtered into a 1 dm water jacketed tube. The rotation of the solution was observed as soon as the temperature gradient in the tube had been eliminated. Further readings were taken at suitable intervals of time. The solution was left overnight to check the final reading.

The polarimetric readings were taken on a Bellingham and Stanley polarimeter and the temperature was controlled by a thermostat bath equipped with a Shandon Circotherm pump.

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