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THE CHEMISTRY OF PHTHALIDE-3-CARBOXYLIC ACID - I
DECARBOXYLATION IN THE PRESENCE OF ALDEHYDES

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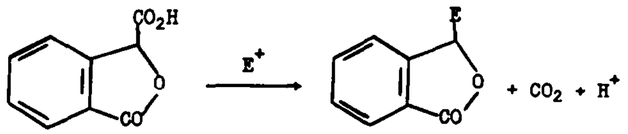
Abstract - The decarboxylation of phthalide-3-carboxylic acid (3-oxo-1,3-dihydroisobenzofuran-1-carboxylic acid) has been studied in the melt, in dimethylsulfoxide, and in the presence of aromatic aldehydes. The latter are efficiently trapped to produce mixtures of 3-arylidenephthalides and 3-(arylhydroxymethyl)phthalides. Kinetic and other evidence supports the proposal that this reaction occurs in a tight cyclic transition state.

INTRODUCTION

The thermal decarboxylation of carboxylic acids has been known and used synthetically since the beginning of organic chemistry, but in spite of this, considerable interest continues to be shown in clarifying the mechanism of this reaction.[1] Reaction pathways involving both the ionised and the unionised form of the carboxyl group have been identified,[2] but in general the reaction proceeds more readily through dissociated ions. Thus Hunter et al.[3] have correlated the pKa of the resulting hydrocarbon with the rate of decarboxylation of its acid, and suggest the practical limit for decarboxylation is approximately pKa 32. A thorough study of the effect of solvent[4] and of crown ethers[1] has led to a fairly clear understanding of this reaction.

The pKa of phthalide is probably near the limit suggested by Hunter et al.,[3] and phthalide-3-carboxylic acids have been known to decarboxylate readily near their melting points since 1855,[5,6] and although nothing of the mechanism of this reaction is known, we were intrigued by the possibility of capturing an intermediate with suitable electrophiles, as shown in Scheme 1.

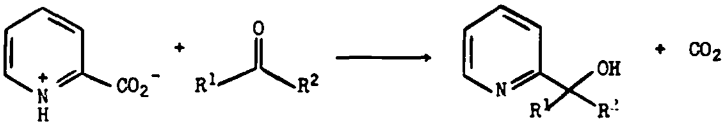


(1)

Scheme 1

There are several reports of the successful capture of decarboxylation intermediates with electrophiles, the best known being the Hammick reaction, the reaction of aldehydes and ketones with some heterocyclic carboxylic acids (eq. 1).[7,9] More recently, the decarboxylation of acetoacetic, malonic and cyanoacetic acids in the presence of α,β-unsaturated ketones and nitriles has been studied,[10] yielding conjugate addition products in good yields. It is interesting to note that in many cases the presence of pyridine has been synthetically useful, and tertiary bases have been shown to lower the activation energy of malonate decarboxylations,[11] presumably by addition to the carbonyl group, thereby changing it from sp^2 to sp^3 hybridised, and making it easier to break the carbon-carbon bond in the transition state (eq. 2).

In this communication we detail our investigation of the decarboxylation of phthalide-3-carboxylic acid in the presence of aromatic aldehydes.



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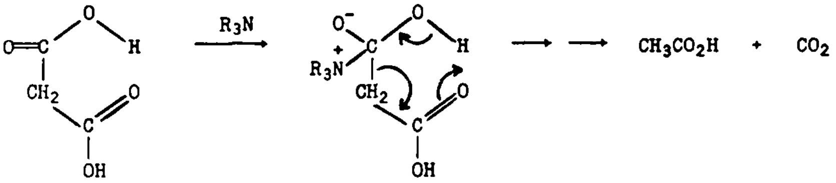
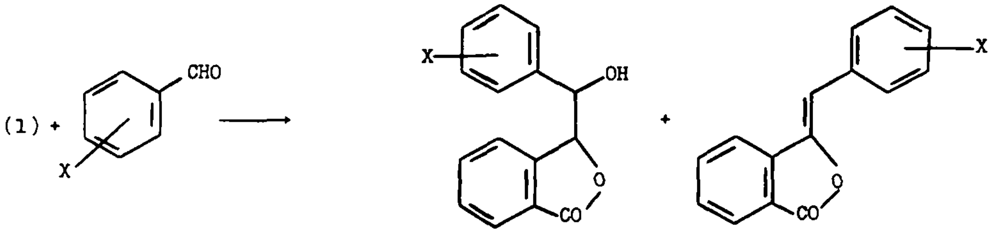


(2)

RESULTS AND DISCUSSION

By analogy with the conditions of the Hammick reaction,[12] phthalide-3-carboxylic acid (1) was heated to 145° in an excess of several aromatic aldehydes, and in all cases examined the product in good yield was a mixture of the corresponding diastereoisomeric 3-(hydroxyarylmethyl)phthalides (2) and their dehydration product, the 3-arylidenephthalide (3). Even with only two equivalents of the aldehyde (Table 1) reaction was efficient, in contrast to the Hammick reaction, and with one equivalent the reaction remained synthetically useful.



(4) (2) (3)

Table 1. Decarboxylation of phthalide-3-carboxylic acid (1) in the presence of aldehydes (4)*

X in (4)	Ratio (4):(1)	Yield Product (2)+(3)
4-NO_2	2	90
	1	88
4-CN	2	88
	1	83
4-Cl	2	75
	1	67
H	2	75
	1	57
4-CH_3	2	66
	1	47
3,4-OCH_2O	2	80
	1	53
4-OCH_3	2	87
	1	64
4-NMe_2	2	60
	1	64

* 145°, neat, 1.5 to 3 h

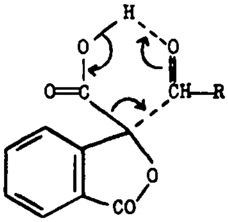
The ratio of products depended on the time of reaction and the temperature. Electron-donating groups in (4) usually gave only the dehydration product (3), suggesting that (3) arose from (2) by an acid-catalysed E-1 reaction. The reactions above were carried out essentially in the melt, and the effect of various solvents was now examined. Cantwell and Brown[13] have shown that the Hammick reaction proceeded best in non polar solvents such as *p*-cymene, although in general an ionising aprotic solvent such as dimethylsulfoxide is considered to be best for decarboxylations,[4] and recently Gold has shown[14] that trichloroacetic acid decarboxylates at room temperature in dimethylsulfoxide, and the intermediate trichloromethyl anion may be trapped with various nitroarenes. We were surprised to find that decarboxylation of (1) essentially failed to occur in non polar solvents at 140°, and in dimethylsulfoxide the intermediate was generally only poorly trapped by the aldehyde. Thus 4-methoxybenzaldehyde (6 equivalents) gave only 14% of the corresponding alcohol (2), and 4-nitrobenzaldehyde 75% of the alcohol (2) when two equivalents were used, and 100% when four were used. Dehydration of (2) to (3) did not occur appreciably in dimethylsulfoxide. The reaction described herein thus appeared to be quite different in character from other decarboxylation reactions in the literature. A simple observation gave a clue to the nature of this difference.

At 140° (1) loses carbon dioxide quite slowly, but in the presence of an aldehyde, decarboxylation occurs about four times faster, the rate depending on the nature of the aldehyde. This observation clearly implies that the aldehyde is assisting the acid to decarboxylate in a specific way. Again, this is in contrast with the measured rates of decarboxylation of other acids in the presence of electrophiles,[15-17] where the rate determining step is independent of the electrophile, and preceeds reaction with it. To put this on a quantitative basis, the rate of decarboxylation of (1) has been measured at various temperatures alone, and in the presence of 4-cyanobenzaldehyde. The rate constants, and the derived enthalpy and entropy of activation for the two reactions are shown in Table 2.

Table 2. Rate constants, enthalpy and entropy of activation for decarboxylation of (1) alone and in the presence of 4-cyanobenzaldehyde.

(1) Neat				(1) + 4-cyanobenzaldehyde			
Temp (°K)	k_1 (sec^{-1} x 10^4)	$\Delta H^\ddagger$ (kJ)	$\Delta S^\ddagger$ (448K)	Temp (°K)	k_2 ($l\ mol^{-1}\ sec^{-1}$ x 10^4)	$\Delta H^\ddagger$ (kJ)	$\Delta S^\ddagger$ (406K)
438	0.73 ± .2			406	2.73 ± .1		
448	3.42 ± .1			410	4.90 ± .1		
467	16.0 ± 1.5			416	5.40 ± 1.7		
		175 ± 20	+69 ± 7	422	8.97 ± .8		
						95.6 ± 2.7	-90.7 ± 2.7

It can be seen that the aldehyde considerably decreases the enthalpy of activation for decarboxylation, and has a marked effect on the entropy of activation. The reaction in the presence of aldehydes is second order, and clearly involves a highly ordered transition state. In contrast, the decarboxylation of acid (1) alone involves a similar enthalpy of activation to that of malonic acid under similar conditions,[18] but the entropy change is even more positive, implying a relatively open transition state. We suggest the transition state (5) is consistent with the above evidences.



(5)

The complex above must have quite a high dissociation constant, consistent with the marked decrease in yield of (2) and (3) in the presence of polar solvents which complex more readily with the acid. By competitive reactions we have been able to determine the relative rates of decarboxylation in the presence of substituted benzaldehydes, and find there is a correlation with the Hammett σ value (Fig. 1), the ρ value being 0.60, suggesting a small build up of negative charge on the aldehyde carbonyl group in the transition state, and consistent with an essentially concerted electron re-distribution.

Under identical conditions to those used with the aldehydes, the ketones acetophenone, cyclohexanone and hexachloroacetone failed to react with phthalide carboxylic acid, nor was there any reaction other than decarboxylation in the presence of excess of ketone at 145°.

EXPERIMENTAL

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. N.m.r. spectra were obtained on a Jeol PMX-60 spectrometer in deuterochloroform and chemical shifts (δ) are presented in p.p.m. downfield from TMS. Infra-red spectra were measured on a Jasco IRA-1 spectrometer. Mass spectra were recorded using an AEI MS 30 mass spectrometer. Microanalyses were determined by AMDEL, Melbourne.

Reaction of 3-oxo-1,3-dihydroisobenzofuran-1-carboxylic acid with substituted benzaldehydes.

3-Oxo-1,3-dihydroisobenzofuran-1-carboxylic acid[19,20] and the aldehyde were mixed in a test tube under nitrogen, and the mixture heated at 145° until no further decarboxylation was apparent. Reactions with excess of aldehyde were usually complete in an hour, while equimolar reactions required up to four hours. Yields of products were determined directly by ^{1}H n.m.r. spectroscopy, and the products were then isolated either by crystallisation of the product, or by preparative t.l.c. The benzylidene isobenzofuran-1(3H)-ones were compared directly with authentic samples.[21-24] Z-3-(4-dimethylaminophenyl)-methyleneisobenzofuran-1(3H)-one was obtained as fluorescent yellow plates from ethyl acetate/light petroleum, m.p. 191-2°. (Found: C, 76.86; H, 5.90; M^+ 265.1104. $C_{17}H_{15}NO_2$ requires C, 76.96: H, 5.70%; M^+ 265.1107), ν_{max} 1760, 1630 cm^{-1}; δ 7.32-8.00 (6H, m, ArH); 6.72 (2H, d, J 9 Hz, H-3'); 6.35 (1H, s, ArCH); 3.03 (6H, s, $N(CH_3)_2$).

Z-4-[(3-oxoisobenzofuran-1-ylidene)methyl]-benzonitrile was isolated as a pale yellow solid, m.p. 200-201° from ethyl acetate/ether. (Found: M^+ 247.0637. $C_{16}H_9NO_2$ requires M^+ 247.0633), ν_{max} (CH_2Cl_2/DMSO) 2310, 1790 cm^{-1}; δ 7.35-8.03 (8H, m, ArH); 6.43 (1H, s, ArCH).

The 3-(arylhydroxymethyl)isobenzofuran-1(3H)-ones were generally *ca.* 1:1 mixture of diastereoisomers, and were identified by comparison with authentic samples.[25]

Kinetic determinations

Duplicate samples of a mixture of 3-oxo-1,3-dihydroisobenzofuran-1-carboxylic acid (40 mg; 225 μmol) and 4-cyanobenzaldehyde (11 mg; 84 μmol) were heated at the temperatures recorded in Table 2 under nitrogen. Ampoules were examined, periodically by ^{1}H n.m.r. spectroscopy, which allowed the determination of aldehyde and addition product concentrations. Initial concentrations were determined by accurate determination of the density of the melts. The reactions obeyed pseudo first order kinetics.

Relative rates for the data in Figure 1 were obtained by following the decarboxylation in the melt in pairs of aldehydes, each present in threefold excess, by n.m.r. spectroscopy. Triplicate determinations were made for each pair, and each aldehyde was compared with at least two others. The Hammett rho value was obtained by linear least squares regression analysis.

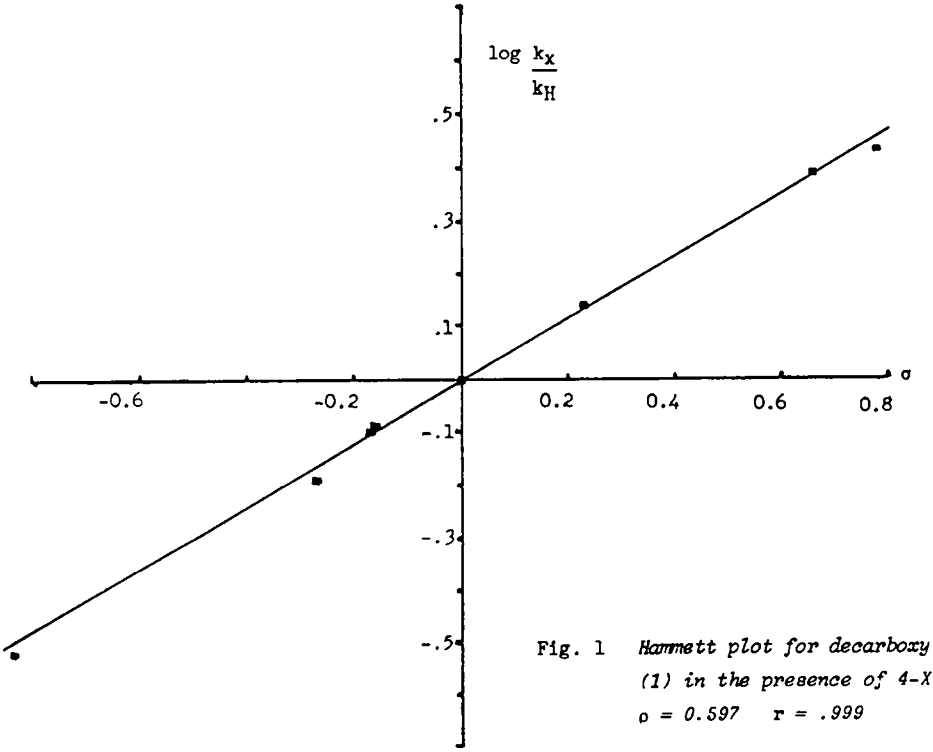


Fig. 1 *Hammett plot for decarboxylation of (1) in the presence of 4-X-benzaldehydes.* $\rho = 0.597$ r = .999

ACKNOWLEDGEMENTS

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