

# The Relative Importance of Ground-state Conformation and Orbital Orientation in Intramolecular Catalysis: Hydrolysis of Aryl Hydrogen Biphenyl-2,2'-dicarboxylates

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The pH-rate profile for the hydrolysis of 4-nitrophenyl hydrogen biphenyl-2,2'-dicarboxylate (diphenate) shows a pH-independent region in the pH range 5–9, and obeys rate law (i). Compared with 4-nitro-

$$k_{\text{obs}} = k_a \frac{a_{\text{H}}}{K_a + a_{\text{H}}} + \frac{K_w}{a_{\text{H}}} \cdot k_{\text{OH}} + k_b \frac{K_a}{K_a + a_{\text{H}}} \quad (\text{i})$$

phenyl benzoate, the hydrolysis of 4-nitrophenyl hydrogen diphenate proceeds 800 times faster at pH 6.0. This is explained by invoking intramolecular nucleophilic catalysis by the neighbouring carboxylate ion. The negligible solvent isotope effect at pH 6.0 ( $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$  1.22) and the low negative entropy of activation ( $-7.2 \text{ cal K}^{-1} \text{ mol}^{-1}$ ), the high value of the Hammett reaction constant ( $\rho$  2.19) and Brønsted constant ( $\beta$   $-0.95$ ) for variations in the leaving group provide evidence for nucleophilic catalysis. The effective molarity for the intramolecular cyclisation of 4-nitrophenyl hydrogen diphenate has been calculated to be *ca.* 200, which is close to that observed for this phenomenon in glutarates and quite low in comparison with that obtained for succinates. This has been taken to indicate that the reactivity of diphenic acid esters is governed more by steric factors which affect the proper orientation of the orbitals than the ground-state conformation arising out of restriction of rotamer distribution.

Intramolecular catalysis by the carboxy-group has attracted particular attention in recent times since such reactions form simple chemical models for enzyme reactions.<sup>1</sup> Based on the rates of intramolecular cyclisations of the monoaryl esters of the dicarboxylic acids, Bruice and his co-workers<sup>1b,2</sup> have shown that the efficiency of intramolecular catalysis is governed by the favourable ground-state conformation due to restriction of the rotamer distribution. This point has been well contested by Koshland<sup>3</sup> on the basis of the rates of lactonisation reactions and he concluded that the proper orientation of the orbitals is of vital importance in deciding the efficiency of intramolecular catalysis. The relative importance of the ground-state conformation *versus* the orbital orientation could be ascertained by studying a system in which partial rotation is possible but which could be affected and even frozen by substituents. One such model system is that of biphenyl derivatives with substituents in the 2,2'- and 6,6'-positions. It was, therefore, considered of interest to study the intramolecular catalysis by the carboxy-group in biphenyl-2,2'-dicarboxylic (diphenic) acid derivatives. We report here the results of a kinetic study of the hydrolysis of monoaryl esters of diphenic acid which suggest a greater role for the orbital orientation effect than for the ground-state conformation.

## Experimental

**Aryl Hydrogen Diphenates.**—The monoaryl esters of diphenic acid were prepared by the method of Novikov<sup>4</sup> and recrystallised from chloroform–hexane: [aryl group, m.p. (°C), lit. value<sup>4</sup>] phenyl, 157–159; *p*-chlorophenyl, 157–159, 159; *p*-methylphenyl, 163–164, 162; *m*-nitrophenyl, 139, 141; *p*-nitrophenyl, 208–209, 209. The purity of the esters was checked by t.l.c. and by the absorbance of the phenol released on complete hydrolysis.

The buffer solutions were made from reagent grade chemicals. Water used in all experiments was twice distilled from all-glass apparatus and was boiled before use.

**Methods.**—The rate of hydrolysis of the esters was measured spectrophotometrically by monitoring the release of the phenol

at suitable wavelengths (Table 1) using a Carl Zeiss VSU2-P spectrophotometer. In a typical run ester (50  $\mu\text{l}$ ) of the appropriate concentration in acetonitrile as solvent was injected into the buffer (2.45  $\mu\text{l}$ ; 0.1N ionic strength), kept thermostatted in the cell compartment, and the absorbance measured at regular time intervals. The first-order rate constants were evaluated by least-squares analysis of  $\log(A_\infty - A_t)$  *versus* time using a Hindustan MICRO 2200 programmable calculator. The results are reproducible to within  $\pm 3\%$  error. pH Values were measured with a digital pH meter (0.01 accuracy; Bhagyanagar Instruments, India). pD Values were calculated from the pH measurements after the usual correction (0.41).<sup>5</sup> The  $\text{p}K_a$  of the ester was determined by the potentiometric method.<sup>6</sup>

**Trapping Experiments.**—To the buffer (100 ml; pH 5.0; [aniline]  $10^{-3}\text{M}$ ) containing 20% acetonitrile as co-solvent was injected the ester (2 ml; 0.01M) and after two half-lives the solution was extracted with ether, dried ( $\text{Na}_2\text{SO}_4$ ), and solvent evaporated. The product was identified as *NN'*-diphenylbiphenyl-2,2'-carboxamide by comparative t.l.c. with an authentic sample.

## Results

The rate of release of the phenol is exponential with time, indicating first-order dependence of the rate on [ester]. The reactions conducted at various buffer concentrations at constant pH indicate the absence of buffer catalysis (Table 1). Rate measurements over the pH range 2–11 have been cast into a  $\log k_{\text{obs}}$  *versus* pH plot (Figure) (Table 2). The points in the Figure are experimental and the line theoretical, derived from the empirical rate expression (1) where  $k_a = 1.26 \times$

$$\text{rate} = k_a \frac{a_{\text{H}}}{K_a + a_{\text{H}}} + k_b \frac{K_a}{K_a + a_{\text{H}}} + k_{\text{OH}} \frac{K_w}{a_{\text{H}}} \quad (1)$$

$10^{-5} \text{ l mol}^{-1} \text{ s}^{-1}$ ,  $k_b = 3.51 \times 10^{-4} \text{ l mol}^{-1} \text{ s}^{-1}$ ,  $k_{\text{OH}} = 1.72 \text{ l mol}^{-1} \text{ s}^{-1}$ , and  $K_a = 1.25 \times 10^{-4}$ .  $k_a$  is the rate coefficient for the hydrolysis of the un-ionised ester,  $k_b$  the rate coefficient

**Table 1.** Rate dependence on buffer concentration <sup>a</sup>

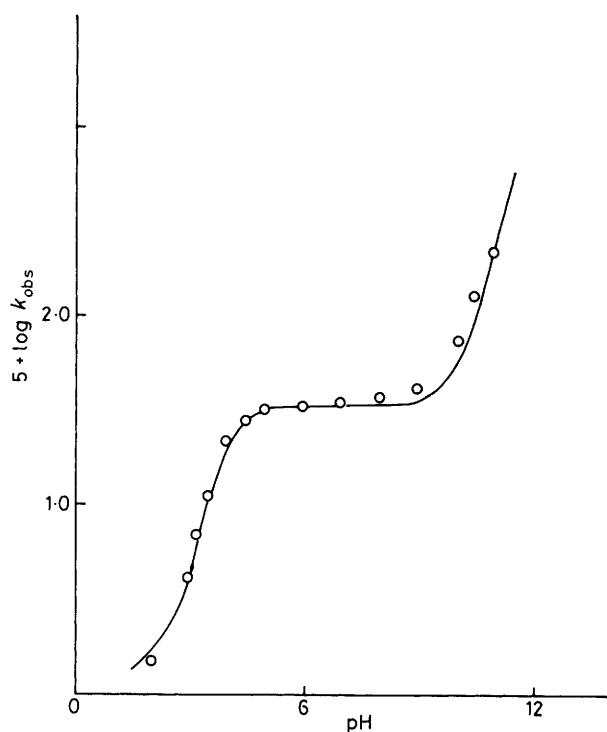
[NaH <sub>2</sub> PO <sub>4</sub> ]/M	10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>
0.02	3.31
0.05	3.27
0.08	3.25
0.10	3.39

<sup>a</sup> [4-Nitrophenyl hydrogen diphenate] 2 × 10<sup>-5</sup>M; pH 6.0; μ 1.0M (KCl); 30 °C.

**Table 2.** Dependence of rate of hydrolysis on pH <sup>a</sup>

pH	Buffer used	10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>
2.0	KCl-HCl	0.140
2.5	Acid phthalate-HCl	0.250
3.0	Acid phthalate-HCl	0.401
3.2	Acid phthalate-HCl	0.705
3.5	Acid phthalate-HCl	1.09
4.0	Acid phthalate-HCl	2.25
4.5	Acid phthalate-OH <sup>-</sup>	2.75
5.0	Acid phthalate-OH <sup>-</sup>	3.26
6.0	Dihydrogen phosphate-OH <sup>-</sup>	3.30
7.0	Tris-HCl	3.35
8.0	Borate-HCl	3.46
9.0	Borate-HCl	3.56
10.0	CO <sub>3</sub> <sup>2-</sup> -HCO <sub>3</sub> <sup>-</sup>	7.70
10.5	Na <sub>2</sub> HPO <sub>4</sub> -OH <sup>-</sup>	12.6
11.0	Na <sub>2</sub> HPO <sub>4</sub> -OH <sup>-</sup>	21.6

<sup>a</sup> [4-Nitrophenyl hydrogen diphenate] 2 × 10<sup>-5</sup>M; 30 °C; μ 1.0M (KCl).



pH-Rate for the hydrolysis of 4-nitrophenyl hydrogen diphenate. The curve is theoretical from equation (i) and the points are experimental

for the hydrolysis of monoanion of the ester, and k<sub>OH</sub> the bimolecular rate constant for hydroxide attack on the ionised ester. The pK<sub>a</sub> of the ester has been found to be 3.90 from the

**Table 3.** Rates of hydrolysis of aryl hydrogen diphenates

Ester	pH 6.0; μ 1.0M (KCl); 30 °C	
	λ/nm	10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>
4-Nitrophenyl hydrogen diphenate	320; 400	3.30; 2.65 <sup>a</sup>
3-Nitrophenyl hydrogen diphenate	310; 390	0.192; 0.216 <sup>b</sup>
4-Chlorophenyl hydrogen diphenate	285	0.0363
Phenyl hydrogen diphenate	280	0.004 95
4-Methoxyphenyl hydrogen diphenate	285	0.001 46
4-Nitrophenyl benzoate	320	0.004 22
Diphenic anhydride	280	33.3

<sup>a</sup> In D<sub>2</sub>O; k<sub>H<sub>2</sub>O</sub>/k<sub>D<sub>2</sub>O</sub> 1.22. <sup>b</sup> In D<sub>2</sub>O; k<sub>H<sub>2</sub>O</sub>/k<sub>D<sub>2</sub>O</sub> 0.90.

**Table 4.** Rate dependence on temperature <sup>a</sup>

Temp. (°C)	30	40	50
10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>	3.30	10.7	29.0
E <sub>a</sub>	87.864 kJ mol <sup>-1</sup>	ΔH‡ 85.374 kJ mol <sup>-1</sup>	
ΔS‡	-29.92 J mol <sup>-1</sup> K <sup>-1</sup>	ΔG‡ 94.163 kJ mol <sup>-1</sup>	

<sup>a</sup> [4-Nitrophenyl hydrogen diphenate] 2 × 10<sup>-5</sup>M; [NaH<sub>2</sub>PO<sub>4</sub>] 8 × 10<sup>-2</sup>M; pH 6.0; μ 1.0M (KCl).

**Table 5.** Effect of aniline buffer on rate <sup>a</sup>

10 <sup>3</sup> [aniline]/M	10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>
0.50	3.25
1.00	3.29
2.00	3.34
4.00	3.26
8.00	3.34

<sup>a</sup> For [4-nitrophenyl hydrogen diphenate] 2 × 10<sup>-5</sup>M; pH 6.0; μ 1.0M (KCl); 30 °C.

pH-rate profile and this value is in agreement with the value determined potentiometrically (4.10). In this pH-independent range (pH 5–8) the rates of hydrolysis of the other aryl esters have been determined (Table 3).

The pH-independent rates of hydrolysis of the monoaryl hydrogen diphenates obey the Hammett and the Brønsted equations (2) and (3) respectively, the Hammett reaction

$$\log k_{\text{obs}} = 2.19\sigma - 2.27 \quad (2)$$

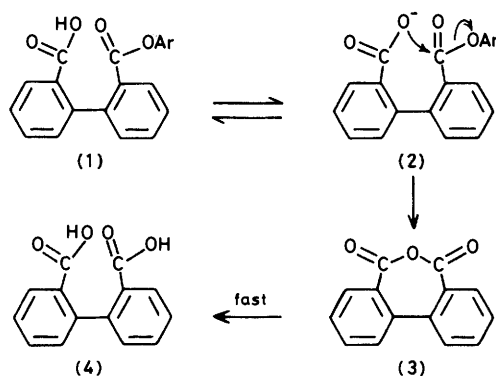
$$\log k_{\text{obs}} = -0.95 \text{p}K_{\text{a}} + 7.5 \quad (3)$$

constant and the β value being +2.19 and -0.95 respectively. In the pH-independent region the rates of hydrolysis are not much affected by transfer to solvent D<sub>2</sub>O (Table 3). For the 4-nitrophenyl ester the reactions have been carried out at 40 and 50 °C and the Arrhenius parameters evaluated from the slope of the regression line for a correlation of log k<sub>obs</sub> versus 1/T (Table 4). At pH 6.0 the hydrolysis of the 4-nitrophenyl ester is not catalysed by aniline for reactions conducted in aniline buffers (Table 5), but the product of the reaction has been found to be NN'-diphenylbiphenyl-2,2'-dicarboxamide.

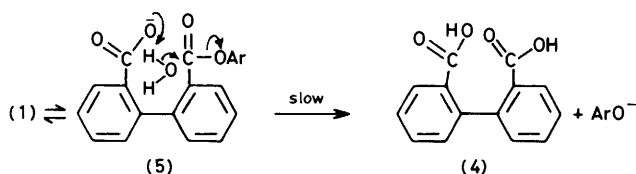
## Discussion

The rate law for the hydrolysis of 4-nitrophenyl hydrogen diphenate is given by equation (1). At low pH regions (pH < 2) only the first term in the rate expression is significant and this represents the reaction of the un-ionised ester. In the pH-independent range (pH 5–9) the second term in the rate

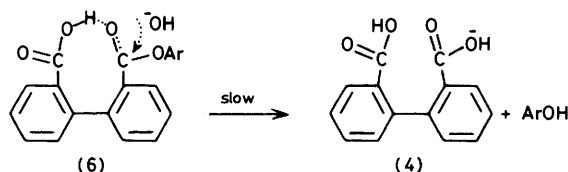
## (a) Intramolecular nucleophilic catalysis



## (b) Intramolecular general base catalysis



## (c) Intramolecular general acid-specific base catalysis



Scheme

expression becomes important and this corresponds to the reaction of the ionised ester. Above pH 9 bimolecular attack by the hydroxide ion on the ionised ester takes over. In the pH-independent region the hydrolysis of 4-nitrophenyl hydrogen diphenate is *ca.* 800 times faster than that of 4-nitrophenyl benzoate, which cannot be accounted for by normal substituent effects. However, such high reactivities may be easily explained by invoking participation by the neighbouring carboxy-group in the reaction. The carboxy-group can act as an intramolecular catalyst both in the ionised and un-ionised forms. In the un-ionised form it can function as a general acid catalyst and such catalysis have been observed in the hydrolysis of several ortho esters and acetals.<sup>7</sup> A carboxylate ion can function as a nucleophilic catalyst<sup>8</sup> or as a general base catalyst.<sup>9</sup> The possible pathways for the hydrolysis of the monoaryl diphenates are detailed in the Scheme. The general base catalysis and its kinetically equivalent general acid assistance to hydroxide attack [Scheme (c)] demand a high value for the ratio  $k_{H_2O}/k_{D_2O}$  ( $K > 2$ ) while for nucleophilic attack scheme (a) it would be around unity. The observed solvent isotope effect values are in agreement with the latter proposal. Discrimination between nucleophilic and the general base catalysis is also rendered possible by a study of the entropy of activation. Intramolecular nucleophilic catalysis, being a unimolecular process, will be entropically more favourable than intramolecular general acid or general base catalysis which are essentially bimolecular reactions. The observed low negative entropy of activation is thus indicative of nucleophilic catalysis.

The mechanism proposed derives further substantiation from structure-reactivity correlations for variations in the leaving group. The pH-independent rate of hydrolysis of monoaryl diphenates is found to be affected to a large extent by changes in the leaving group, characterised by high Brønsted exponent ( $\beta -0.95$ ) and high Hammett reaction constant ( $\rho +2.19$ ). Such sensitivity to the changes in the leaving group is expected of nucleophilic catalysis.<sup>10</sup> In the light of the above arguments it may be concluded that hydrolysis of aryl hydrogen diphenates proceeds by an intramolecular nucleophilic attack by the neighbouring carboxylate ion resulting in the formation of the anhydride intermediate. However, the intermediate diphenic anhydride could not be detected by spectrophotometric procedures. An independent kinetic study of the hydrolysis of diphenic anhydride at pH 6.0 indicates that the anhydride hydrolyses at least ten times faster than the ester. The ready hydrolysis thus precludes its detection. But when the reactions are conducted in aniline buffers at pH 6.0, the product is found to be *NN'*-diphenyl-biphenyl-2,2'-dicarboxamide, which could well be the product of the interaction of aniline with the intermediate anhydride. Direct attack by aniline on the ester which could also lead to this product is ruled out because of the absence of catalysis of hydrolysis (Table 5). Thus intramolecular nucleophilic catalysis could explain all the observed phenomena.

A comparison of the rate enhancement observed for the hydrolysis of 4-nitrophenyl hydrogen diphenate with those obtained for the intramolecular cyclization of monoaryl esters of dicarboxylic acids can help one to form an idea of the efficiency of such intramolecular reactions. The effective molarity for the intramolecular cyclisation of 4-nitrophenyl hydrogen diphenate may be evaluated from the catalytic coefficient of the benzoate ion in the hydrolysis of aryl acetates. The catalytic coefficient of the benzoate ion may be calculated from known catalytic coefficients<sup>11</sup> and this has a value of  $1.7 \times 10^{-6} \text{ l mol}^{-1} \text{ s}^{-1}$ . The effective molarity for the intramolecular cyclisation of 4-nitrophenyl hydrogen diphenate turns out to be *ca.* 200.

Bruice *et al.*<sup>2</sup> have reported the effective molarity for the intramolecular cyclisations of several dicarboxylates and have explained the efficiency of such processes on the basis of restriction of rotamer distribution in the ground state. It is contended that the most favourable ground-state conformation would have the two carboxy-groups extended into the solvent from where attack would be difficult. Removal of rotational degrees of freedom would bring the two carboxy-groups closer and would result in rate acceleration. If this were to be the only criterion, the effective molarity for the cyclisation of diphenates should be close to that of succinates, since both have the same number of rotational degrees of freedom around the reaction centre, but surprisingly intramolecular catalysis in diphenates is 200 times less efficient than in succinates. The reason for this reduced rate acceleration could be traced to the significant role of the alignment of the orbitals on the efficiency of intramolecular catalysis. Since the collision of the nucleophile and the carbonyl group will be effective only on a small portion of the surface of each, the reaction velocities will be sensitive to proper orientation of the reacting groups. Hence steric factors which affect the favourable alignment of the orbitals might reduce the efficiency of such processes. Although the two phenyl groups in diphenates have freedom of rotation, the presence of the aryloxy-function possibly prevents the proper alignment of the ester carbonyl group with respect to the carboxylate anion. That the carboxylate anion in diphenates is not very close to the ester group has been proved by the salt effects on the hydrolysis of the monomethyl ester of diphenic acid.<sup>12</sup> Whether introduction of substituents would freeze the con-

formation in a favourable alignment and thus lead to rate accelerations is being currently studied.

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