Intramolecular Catalysis. Part 4.[1] The Intramolecular Cannizzaro Reaction of Biphenyl-2,2′-dicarbaldehyde, [α,α′-$^2H_2$]Biphenyl-2,2′-dicarbaldehyde and 4,4′- or 5,5′- or 6,6′-Disubstituted Biphenyl-2,2′-dicarbaldehydes

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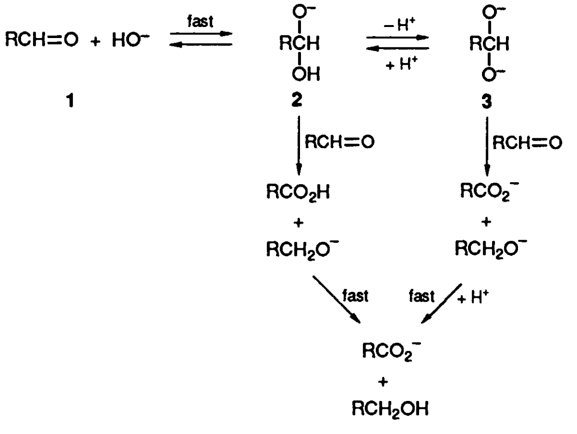
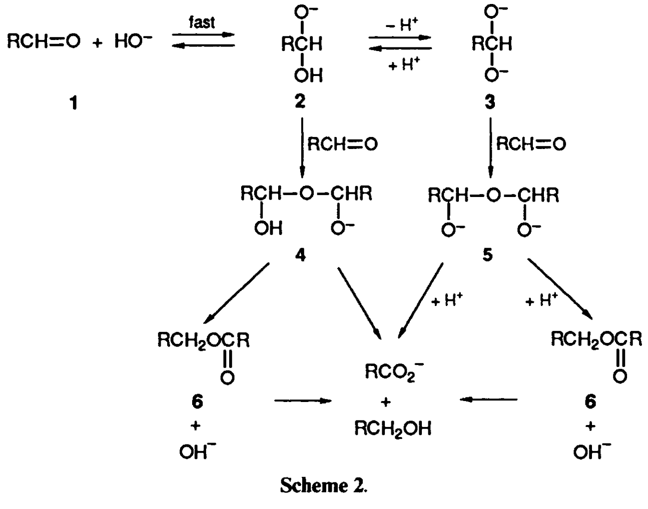
Biphenyl-2,2′-dicarbaldehyde, along with its α,α′-[$^2H_2$] isomer, and a series of 4,4′-, 5,5′- and 6,6′-disubstituted biphenyl-2,2′-dicarbaldehydes have been shown to undergo Cannizzaro reactions in 30% (v/v) dioxane–water containing base. The reaction has been shown to be intramolecular and of the third order; first order in substrate and second order in base. The rate coefficients have been measured at several temperatures and activation parameters evaluated. Studies of solvent isotope, solvent and salt effects have been made. The kinetic isotope effect, k_H/k_D, was found to be *ca.* 1.8. The effect of 4,4′- and 5,5′-disubstitution was assessed by use of the Hammett equation to give ρ at 30 °C to be *ca.* 4.6. Severe steric effects were noted for 6,6′-dimethyl substitution. The alkaline hydrolysis of the corresponding ε-lactones of 2′-hydroxymethylbiphenyl-2-carboxylic acids was studied under the same conditions. The intermediacy of the lactones in the intramolecular Cannizzaro reaction can be excluded. The evidence for the Cannizzaro reaction indicates a mechanistic pathway involving rate-determining hydride transfer from the dianion of a hydrated formyl group to the second formyl group. An estimate is made of effective concentration of the intramolecular hydride transfer.

The Cannizzaro reaction is the base-catalysed disproportionation of an aldehyde, without α-H, to equimolar amounts of the corresponding primary alcohol and carboxylic acid anion. The Cannizzaro reaction has been reviewed[2] and the mechanism of reaction investigated in detail.[3] The kinetic order of the reaction has been found to be third or fourth, or a combination of both, *i.e.* second order in aldehyde and first or second order in base.[3] The Hammett reaction constant, ρ, for the Cannizzaro reaction of a series of *meta-/para*-substituted benzaldehydes with base in 50% aqueous methanol at 100 °C is 3.76.[4,5] Both kinetic solvent isotope and isotope effects have been studied. The kinetic solvent isotope effect, k_{ROD}/k_{ROH}, for benzaldehyde in 74% aqueous methanol at 99 °C is about 1.8.[3] Using [α-^3H]- and [α-^2H]-benzaldehyde, the kinetic isotope effect has been found to be 1.2–1.4[3,6] and 1.4–1.8,[6,7] respectively, under a variety of conditions. Although radical mechanisms have been proposed,[8] they can be considered to be excluded for the Cannizzaro reaction conducted in homogeneous aqueous solution. The mechanisms offered may be simplified to those shown in Schemes 1 and 2. The rate determining steps and detailed paths in such Schemes can be various. Swain *et al.*[3] have used the technique of isotope dilution to study this mechanism.[3] All the evidence indicates the most likely main path for benzaldehyde is that shown in Scheme 1, with the hydride transfer step between **1** and **2** being rate-determining.[3]

Intramolecular Cannizzaro reactions have been known for some time. However, the mechanisms of 'true' intramolecular Cannizzaro reactions have received little attention. Glyoxal rearranges to lactic acid, which is first order in substrate and second order in base,[9] and has been shown to be intramolecular.[10] Phthalaldehyde is extensively hydrated in aqueous solution[1,11] and a preliminary investigation of the mechanism of its Cannizzaro reaction to form *o*-hydroxymethylbenzoic acid has been made.[12] A number of studies[13–16] of the base-catalysed rearrangements of phenylglyoxal, a keto aldehyde, to mandelic acid have been made. The reaction was shown to be intramolecular by the failure of deuterium from the solvent



Scheme 1.



Scheme 2.

Table 1. The physical constants of the substituted ε-lactones of 2′-(hydroxymethyl)-2-biphenylcarboxylic acid

			Found (%)			Required (%)			
Substituent	m.p./°C	Formula	C	H	Other	C	H	Other	Recrystallization solvent
5,5′-Cl, Cl	149–150.5	$C_{14}H_8Cl_2O_2$	60.2	3.0	25.1 (Cl)	60.2	2.9	25.4 (Cl)	95% aqueous ethanol
5,5′-Br, Br	141–142.5	$C_{14}H_8Br_2O_2$	45.5	2.2	43.3 (Br)	45.7	2.2	43.5 (Br)	95% aqueous ethanol
6,6′-Me, Me	121–123	$C_{16}H_{14}O_2$	80.5	5.7		80.7	5.9		Light petroleum (b.p. 80–100 °C)
4,4′-Me, Me	181.5–182.5	$C_{16}H_{14}O_2$	80.3	5.6		80.7	5.9		Light petroleum (b.p. 80–100 °C)
4,4′-OMe, OMe	178–179	$C_{16}H_{14}O_4$	70.9	5.1		71.1	5.2		Light petroleum (b.p. 80–100 °C)

D_2O to become attached to the α-carbon.[14] The kinetic order of the reaction apparently depends on the solvent and is either first or second order in base.[13,16] The rates of this reaction for a series of *meta*/*para*-substituted phenylglyoxals at pH 12 has been determined and gave a Hammett reaction constant, ρ, of about 2.0.[17]

The Cannizzaro reaction of biphenyl-2,2′-dicarbaldehyde was first reported by Kenner and Turner.[18] This reaction, and that of the α,α′-dideuterio and several disubstituted compounds, have been investigated in this study. The rates of reaction, activation parameters, kinetic solvent isotope and isotope effects, isotope labelling and studies of possible intermediates are reported.

Experimental

Materials.—Biphenyl-2,2′-dicarbaldehydes were prepared by either the Ullmann reaction of appropriately substituted 2-iodobenzaldehydes,[19,20] the ozonolysis of phenanthrene, followed by reduction by sodium iodide,[21] or the reduction of substituted 9,10-phenanthraquinones by $LiAlH_4$, followed by oxidation by sodium periodate of the resultant diol.[22,23] The ε-lactones of 2′-(hydroxymethyl)biphenyl-2-carboxylic acids were prepared by acidification of the products of the intramolecular Cannizzaro reaction. The syntheses of new compounds are described below.

[α,α′-$^2H_2$]Biphenyl-2,2′-dicarbaldehyde.—This compound was prepared by the reduction of 9,10-phenanthraquinone by $LiAlD_4$, followed by oxidation by sodium periodate in aqueous methanol, m.p. 63.5–64 °C (lit.,[24] 63 °C). This compound had been previously prepared by reduction by $LiAlD_4$ of diphenic acid bis-*N*-methylanilide.[24]

5,5′-Dichlorobiphenyl-2,2′-dicarbaldehyde.—4-Chloro-2-iodobenzaldehyde was prepared from the hexamethylenetetramine salt of 4-chloro-2-iodobenzyl bromide. A mixture of 4-chloro-2-iodobenzaldehyde (6 g, 22.4 mmol), copper bronze (4 g, 63 mmol) and dimethylformamide (30 cm^3) was refluxed for 4 h with stirring under a nitrogen atmosphere. After cooling and filtration, the solvent was removed under reduced pressure and the dialdehyde product recrystallised from light petroleum (b.p. 80–100 °C), m.p. 98–99 °C (1.3 g, 42%) (Found: C, 60.2; H, 3.0; Cl, 25.1. $C_{14}H_8Cl_2O_2$ requires: C, 60.2; H, 2.9; Cl, 25.4%).

ε-Lactone of 2′-(hydroxymethyl)-2-biphenylcarboxylic Acid.—A mixture of biphenyl-2,2′-dicarbaldehyde (1 g, 4.8 mmol) and 5% sodium hydroxide solution (100 cm^3) was refluxed for 2 h. The clear solution was cooled to 5 °C and acidified to pH 1 by the dropwise addition of dilute hydrochloric acid. The solution was maintained at 5 °C for 2 h, whereupon the precipitate was filtered off, washed with water and dried. The compound was recrystallised from 95% aqueous ethanol, m.p. 134.5–135.5 °C (0.9 g, 90%) (lit.,[18] 132 °C).

Substituted ε-lactones of 2′-(hydroxymethyl)biphenyl-2-carboxylic Acid.—The lactones were prepared by the method described above, with the exception of the 6,6′-dimethyl lactone. The latter was prepared by a method similar to that described by Hadler and Kryger[22] for a similar acid.

All the products had IR, ^1H and ^{13}C NMR, and mass spectra in accord with the stated structures. The m.p.s, recrystallisation solvents and elemental analysis of the new lactones are shown in Table 1.

The solvents were prepared as previously described.[25]

Kinetic Procedure.—Rate coefficients for both the intramolecular Cannizzaro and hydrolysis reactions in 30% (v/v) dioxane–water at constant ionic strength (μ = 0.2 mol dm^{-3}) were determined spectrophotometrically by use of either a Unicam SP8000 spectrophotometer for 'slow' reactions or a Durram-Gibson model D-110 stopped-flow spectrophotometer for 'fast' reactions. The cell temperatures were controlled to ±0.05 °C by means of a Churchill thermoregulator. The conventional method was used down to half-lives of about 8–20 s. The cell temperatures were controlled to ±0.05 °C and the reactions were followed at suitable wavelengths, as shown in Tables 2 and 3 (normally those having the greatest difference between substrate and product). At least a ten-fold excess of base (4×10^{-4}–2×10^{-1} mol dm^{-3}) over substrate (4×10^{-5}–1×10^{-4} mol dm^{-3}) concentrations were used. For the Cannizzaro reaction, the ionic strength was held constant (0.2 μ) with sodium chloride. The final absorbance was assumed to be that measured after ten 'half-lives'. The reactions were all found to be first-order in substrate and were measured as k_1 values. The plots were strictly linear over at least three half-lives. For the Cannizzaro reaction, for each substrate and at each temperature, at least seven concentrations of hydroxide anion were used and the reactions were found to be precisely second-order in base. No significant component of the Cannizzaro reaction was found to be first-order in base. However, the alkaline hydrolysis reactions of the lactones were first-order in hydroxide anion. The products of both these reactions were the same, *i.e.* the anion of the corresponding carboxylic acids in quantitative yield in all cases. The carboxylic acids in this study can lactonise on acidification, *cf.* ref. 18. The rate coefficients for the Cannizzaro reaction of the dialdehydes are shown in Table 2 and those for the alkaline hydrolysis of the lactones in Table 3. The activation parameters for the reactions are shown in Table 4.

Isotope and Kinetic Solvent Isotope Studies.—Rate coefficients were determined both for biphenyl-2,2′-dicarbaldehyde and the [α,α′-$^2H_2$] isomer by making the measurements in duplicate under identical conditions at the same time. The rate coefficients

Table 2. Rate coefficients (k_3) for the intramolecular Cannizzaro reaction of substituted biphenyl-2,2′-dicarbaldehydes with sodium hydroxide in 30% (v/v) dioxane–water (μ = 0.2 mol dm^{-3}) at several temperatures[a]

Substituent	$k_2/10^{-2}$ dm^6 mol^{-2} s^{-1}				λ/nm
H	66.5 (21.4 °C)	86.1 (30.1 °C)	105 (38.3 °C)	136 (48.2 °C)	290
H[α,α'-$^2H_2$]	39.2 (21.4 °C)	47.8 (30.1 °C)	58.5 (38.3 °C)	75.1 (48.2 °C)	290
5,5′-Cl, Cl	583 (22.6 °C)	770 (31.0 °C)	970 (39.0 °C)	1270 (48.2 °C)	270
5,5′-Br, Br	573 (19.0 °C)	840 (29.0 °C)	1150 (39.0 °C)	1480 (48.2 °C)	275
6,6′-Me, Me	0.107 (25.3 °C)	0.132 (31.0 °C)	0.176 (39.0 °C)	0.273 (49.0 °C)	260
4,4′-Me, Me	23.4 (21.5 °C)	28.5 (29.6 °C)	36.6 (38.8 °C)	46.6 (50.1 °C)	270
4,4′-OMe, OMe	174 (21.1 °C)	219 (30.0 °C)	282 (39.5 °C)	371 (49.6 °C)	300

[a] Rate coefficients are the mean of at least five determinations and are reproducible to ±3%.

Table 3. Rate coefficients (k_2) for the alkaline hydrolysis of substituted ε-lactones of 2′-(hydroxymethyl)biphenyl-2-carboxylic acids 30% (v/v) dioxane–water at several temperatures[a]

Substituent	$k_2/10^{-2}$ dm^3 mol^{-1} s^{-1}	λ/nm
H	8.80 (32.4 °C) 5.56 (21.1 °C) 14.1 (39.9 °C) 23.2 (48.1 °C)	260
5,5′-Cl, Cl	39.6 (32.4 °C)	297.5
5,5′-Br, Br	49.0 (32.4 °C)	260
6,6′-Me, Me	0.990 (32.4 °C)	260
4,4′-Me, Me	3.63 (32.4 °C)	260
4,4′-OMe, OMe	20.8 (32.4 °C)	345

[a] See Table 1.

Table 4. Activation parameters for the intramolecular Cannizzaro reaction of substituted biphenyl-2,2′-dicarboxaldehydes with sodium hydroxide in 30% (v/v) dioxane–water (μ = 0.2 mol dm^{-3}) at 30.0 °C[a]

Substituent	$\Delta H^\ddagger$/kcal mol^{-1} [c]	$\Delta S^\ddagger$/cal mol^{-1} K^{-1} [c]
H	4.4	−44
H[α,α'-$^2H_2$]	4.0	−47
5,5′-Cl, Cl	5.1	−38
5,5′-Br, Br	5.7	−36
6,6′-Me, Me	6.9	−49
4,4′-Me, Me	4.0	−48
4,4′-OMe, OMe	4.4	−42
[Lactone	11.2	−27][b]

[a] Values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are accurate to within ±300 cal[c] mol^{-1} and ±1 cal[c] mol^{-1} K^{-1}, respectively. [b] Alkaline hydrolysis of ε-lactone of 2′-(hydroxymethyl)biphenyl-2-carboxylic acid in 30% (v/v) dioxane–water. [c] 1 cal = 4.184.

ratios determined thus are found to be as reproducible as the rate coefficients themselves, *i.e.* ±3%. The same method was used for the measurements in deuterium oxide. The product of the Cannizzaro reaction of [α,α'-$^2H_2$]biphenyl-2,2′-dicarbaldehyde was isolated after ten half-lives and found to be the [α,α'-$^2H_2$] lactone, which was at least 95% isotopically pure by ^1H NMR spectral analysis. The converse reaction was studied using biphenyl-2,2′-dicarbaldehyde in deuteroxide anion in deuterium oxide. The solution was acidified with DCl and the lactone product of this reaction was isolated. This showed no significant incorporation of deuterium into the product. The ^1H NMR spectra were recorded on a Bruker WP8057 spectrometer.

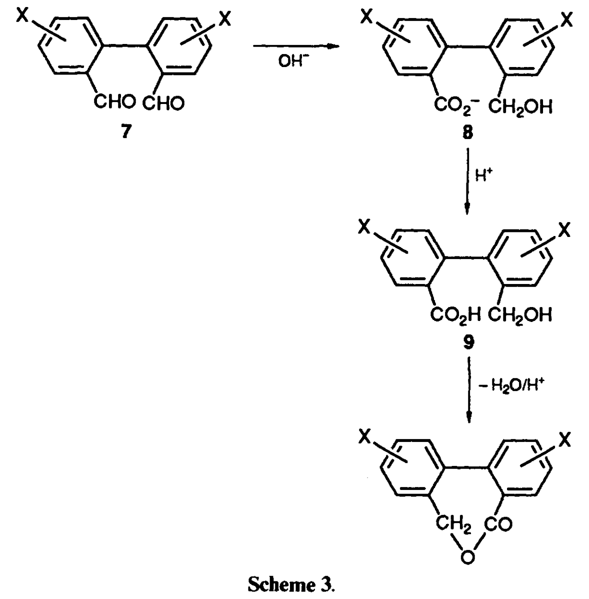
Intermediate Detection Studies.—Both benzoyl peroxide (radical initiator) and diphenylamine (radical inhibitor) (*cf.* ref. 13), (0.01 mol dm^{-3}), were found not to affect the rate coefficients significantly.

The Cannizzaro and hydrolysis reactions have very different activation parameters, Hammett reaction constants, and reaction orders in hydroxide anion (see later). On this basis it is possible to select conditions in which the diphenide, if formed as an intermediate in the Cannizzaro reaction, should be detected. The most favourable, available condition appears to be that of the rearrangement of 5,5′-dibromobiphenyl-2,2′-dicarbaldehyde at 1 °C in 0.2 mol dm^{-3} sodium hydroxide. The first-order rate coefficient ratio of the Cannizzaro to the hydrolysis reaction under these conditions is about four. A fast mixing technique was used in which the substrate in dioxane was rapidly added from a syringe to the aqueous base. Monitoring the UV spectra of a sample of this reaction mixture as a function of time showed that no lactone was formed as an intermediate in the Cannizzaro reaction. After 20 s, the pH of the solution was rapidly decreased to pH 6 by addition of acetic acid by use of a syringe. The solution was then extracted three times with methylene chloride. The combined methylene chloride extract contained no lactone, according to GLC analysis. Using the lactone itself as the substrate resulted in up to 30% recovery of the lactone, again according to GLC analysis with an inert compound, biphenyl, as a marker.

Results and Discussion

Hydration.—The possibility of hydration of the substituted biphenyl-2,2′-dicarbaldehydes was investigated by UV and ^1H NMR spectroscopy. Such techniques have been used to detect and quantitatively measure the hydration of phthaldehyde[1] and phenanthrene-4,5-dicarbaldehyde.[26] Examination of the spectra of biphenyl-2,2′-dicarbaldehydes in aqueous dioxane and in dioxane by both techniques gave no indication of the existence of a hydrate in the former solution, *i.e.* the dialdehyde form is present >98%. The UV spectra of the dialdehydes were almost identical in dioxane and 30% aqueous dioxane. Using ^1H NMR spectroscopy, the formyl hydrogen at δ 9.99 was observed in both solvent systems and integrated, relative to the eight aromatic hydrogens, as two. No signal corresponding to a hydrate hemiacetal hydrogen was observed. This would have been expected to be observed at about 3.7–4.0 ppm from the spectra of the cyclic hydrates of phthalaldehyde[1] and phenanthrene-4,5-dicarbaldehyde.[26] The stereo-electronic interactions between the formyl groups in the latter two dialdehydes favour hydration; unlike those in the biphenyl system in which coaxial twisting can relieve such interactions (see later).

Cannizzaro Reaction.—The products of the Cannizzaro reactions of the biphenyl-2,2′-dicarbaldehydes **7** are the anions of the 2-hydroxymethylbiphenyl-2′-carboxylic acids **8**, as shown in Scheme 3 below. On isolation under acid conditions, the acids **9** can cyclise to form the lactones **10**. The reaction is completely intramolecular as shown by conducting the



Scheme 3.

Cannizzaro reaction of the dialdehyde in D_2O and the [α,α′-$^2H_2$]dialdehyde in H_2O; both of which give no significant incorporation of the solvent isotope in the product.

Kinetics of the Cannizzaro Reaction.—The intramolecular Cannizzaro reaction is of the third order, *i.e.* first in substrate and second in base. This clearly implicates the intermediate dianion **11** or its ring tautomer **12**. The reaction, as shown in Table 5, is about 1.8 times faster in D_2O than in H_2O. This is in accord with other reactions which involve the formation of adducts of substrates, having carbonyl groups, and hydroxide (deuteroxide) anions.[27] The effect observed here and in the intermolecular Cannizzaro reaction of about 1.8 is approximately equal to the product of two such events for ester hydrolysis,[27] as would be expected for the formation of a dianion. Moreover, this result excludes any step involving rate determining ionisation in which a contribution from a primary isotope would be expected. The effects of increasing the ionic strength and dioxane content on the rate are shown in Table 6. Both results are those expected on the basis of the formation of a dianionic state. The positive salt effect observed here is comparable to that observed for the intramolecular Cannizzaro reaction of glyoxal.[9] The effect of increasing dioxane content is more complex; but the rate decreases are more drastic than those observed for the alkaline hydrolysis of methyl benzoate and related substrates.[27,28]

11 **12**

Substituent Effects on the Cannizzaro Reaction.—The effect of 4,4′- and 5,5′-disubstitution can be assessed by use of the Hammett equation, using *meta*- and *para*- σ values for the 4,4′- and 5,5′- substitutions, respectively, as shown in Table 7. The reaction constant, ρ, found at 30 °C of 4.62 can be compared with the value of about 3.76 reported for the Cannizzaro reaction of *meta*/*para*-substituted benzaldehydes in 50% aqueous methanol at 100 °C. These values are surprisingly close considering the temperature difference and that the intermolecular reaction is only first order in hydroxide. The alkaline hydrolysis of the corresponding disubstituted lactones under identical conditions has a ρ value equal to 3.45 (see later and Table 7) and of the *meta*/*para*-substituted methyl benzoates in 70% aqueous dioxane at 30 °C equal to 2.20.[25] The transition state for the intramolecular Cannizzaro reaction can be visualised as receiving polar substituent effects *via* both formyl groups. The symmetry of substitution denies any more sophisticated treatment. Thus, the 'effective' ρ = 2.31 per carbonyl group and is consistent with the stabilisation of the dianionic transition state; but does not describe the distribution of charge. This is in accord with the effect of substitution on the equilibria addition of hydroxide anions to benzaldehydes which has a ρ value of 2.24[29] or 2.76.[30]

Table 5. Rate coefficients (k_3) for the intramolecular Cannizzaro reaction of biphenyl-2,2′-dicarbaldehyde with sodium hydroxide (deuteroxide) in 30% (v/v) dioxane–water (–deuterium oxide) (μ = 0.2 mol dm^{-3}) at 29.6 °C[a]

Medium	10^2k_3/dm^6 mol^{-2} s^{-1}
30% (v/v) dioxane–water	7.00
30% (v/v) dioxane–deuterium oxide	12.7

[a] See Table 1.

Table 6. Rate coefficients (k_3) for the intramolecular Cannizzaro reaction of biphenyl-2,2′-dicarbaldehyde with sodium hydroxide in various % (v/v) dioxane–water compositions (μ = 0.2 mol dm^{-3}) and ionic strengths at 30.0 °C[a]

	10^2k_3/dm^6 mol^{-2} s^{-1}						
% (v/v) dioxane (μ = 0.2)	10	20	30	40	50	60	70
	135	108	92.0	86.0	108	142	186
Ionic/strength (μ)	0.2	0.3	0.4	0.6	0.7		
[30% (v/v) dioxane–water]	91.0	100	109	126	134		

[a] See Table 1.

Table 7. Hammett reaction constants for the intramolecular Cannizzaro reaction of 4,4′- and 5,5′-disubstituted biphenyl-2,2′-dicarbaldehydes in 30% (v/v) dioxane–water at 30.0 °C and for the alkaline hydrolysis of 4,4′-and 5,5′-disubstituted ε-lactones of 2-(hydroxymethyl)biphenyl-2′-carboxylic acids in 30% (v/v) dioxane–water at 32.4 °C

Reaction	ρ	log k_0	*s*	*r*	*n*
Cannizzaro	4.618	−0.162	0.278	0.995	5
Hydrolysis	3.448	−1.130	0.273	0.991	5

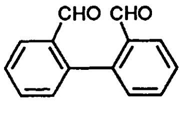
[a] *s* Is the standard deviation, *r* the correlation coefficient and *n* the number of substituents studied.

The drastically reduced rate observed for the 6,6′-dimethyl dialdehyde arises from the severe 'backside' steric 'bulk' interactions developed in the transition state as the 6- and 6′-methyl groups move to eclipse. It should be noted that a very much smaller effect occurs for the 6,6′-dimethyl lactone on hydrolysis (see below).

Kinetic Isotope Effect.—The kinetic isotope effect, k_H/k_D, of about 1.8 is very similar to those observed in other Cannizzaro reactions.[3] These have been considered to be small for a primary isotope effect;[3] although they are comparable to those observed in other hydride transfer reactions which apparently involve rate-determining hydride transfer.[31] It has been pointed out that the latter can involve an inverse secondary isotope effect.[31] This is also true for the Cannizzaro reaction where secondary isotope effects arise at both the site of addition of hydroxide and of transfer. The secondary contribution to the primary isotope effect can be estimated, for k_H/k_D, as about 0.73 on the basis of the effect on addition to aldehydes of water[32,33] or nucleophiles.[34] Thus, the true k_H/k_D value is about 2.4. This value is comparable to those found in other hydride transfer reactions;[31,35] but is still less than those predicted by theoretical studies.[36]

Activation Parameters for the Cannizzaro Reaction.—The entropies and enthalpies of activation for the intramolecular Cannizzaro reaction, shown in Table 4, clearly indicate the nature of the reaction. The entropies of activation are very large and negative. This clearly indicates the termolecular nature of the reaction and the specific orientation that must be arranged in the biphenyl for reaction to occur. The very low enthalpies of activation are a function of the favourable and concerted nature of the hydride transfer in the rate-determining step, following the addition and ionisation. The significant increase in $\Delta H^{\ddagger}$ noted for the 6,6′-dimethyl substrate clearly arises from the intense steric 'bulk' interactions occurring in the 'backside' of the molecules as the two methyl groups are compressed together in the transition state.

Stereochemistry of the 2,2′-*Biphenyldicarbaldehydes.*—The effects of 2-substitution on the stereochemistry of biphenyl has been investigated.[37] The effects of 2′-substituents on the reactivity of biphenyl-2-carboxylic acid gives reversed dipolar substituent effects and indicates that the conformation of the 2′,2-disubstituted biphenyl system appears to be close to that having orthogonal aryl groups.[38] A similar conformation for the biphenyl-2,2′-dicarbaldehyde would be a compromise between the coplanar s-*cis* (**13**) and s-*trans* (**14**) conformers. Such a compromise conformation will minimise steric 'bulk' interactions in both **7** and **8** and unfavourable dipole–dipole interactions in **7**. In an orthogonal 2,2′-diformylbiphenyl, the biaryl resonance interactions will be at a minimum, but the formylaryl groups can be coplanar and their resonance interactions maximised. For intramolecular reaction to occur, the formyl groups must be proximate and the coaxial twisting must be reduced from that of the orthogonal conformer to that of a conformer close to **7**. Severe 'bulk' interactions will occur if 6,6′-disubstituents are present (see earlier).



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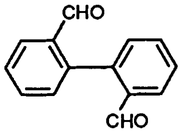

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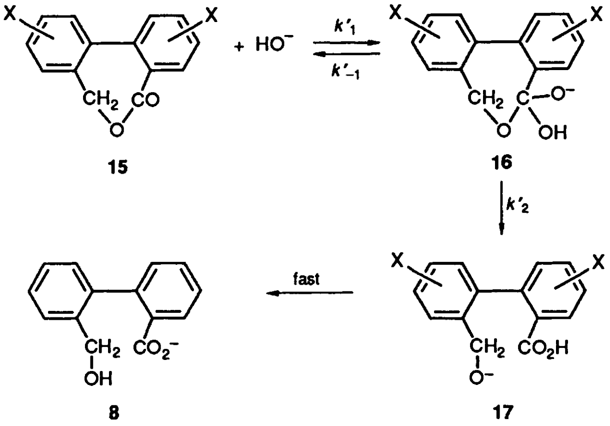
Lactone Hydrolysis.—The alkaline hydrolysis of the seven-membered lactones has been studied in 30% aqueous dioxane and is first-order in both substrate and base. The reactivity of lactones,[39] as well as the related pseudo-esters,[40] as a function of ring size is not as simple as was originally believed.[41] However, the hydrolysis of the parent ε-lactone (**15**; X = H) of the series (k_2 at 21.1 °C = 0.0556 dm^3 mol^{-1} s^{-1}) is less rapid than that of the five-membered phthalide (k_2 at 24.8 °C in $33\frac{1}{3}\%$ aqueous dioxane = 0.144 dm^3 mol^{-1} s^{-1}). This behaviour is similar to that of the corresponding ring-type methyl or phenyl pseudo-esters.[40–42]

The effect of 4,4′- and 5,5′-disubstitution has been assessed using the Hammett equation, as shown in Table 7. The reaction constant, ρ, equals 3.44. Substituent effects can be viewed as transmitted *via* the aryl and the oxymethylene groups. Using the transmission coefficients tabulated by Bowden[43] and the reaction constant for the hydrolysis of *meta*/*para*-substituted methyl benzoates under similar conditions would predict a ρ value of about 3.9.

The 6,6′-dimethyl lactone is hydrolysed only slightly more slowly than the 4,4′-isomer. The substituent polar effects in both isomers would be expected to be almost the same, *i.e.* the methyl groups are both *meta* to the carbonyl and hydroxymethylene groups. This result contrasts with the very much more marked steric effects noted in intramolecular Cannizzaro reaction for 6,6′-dimethyl substitution.

The activation parameters observed for the parent lactone, shown in Table 4, are those expected for a bimolecular reaction of this type and compare closely with those for pseudo-esters of related structure.[40,42] In Scheme 4 is shown the suggested reaction path for the lactone hydrolysis, with k_1 as the rate determining step.

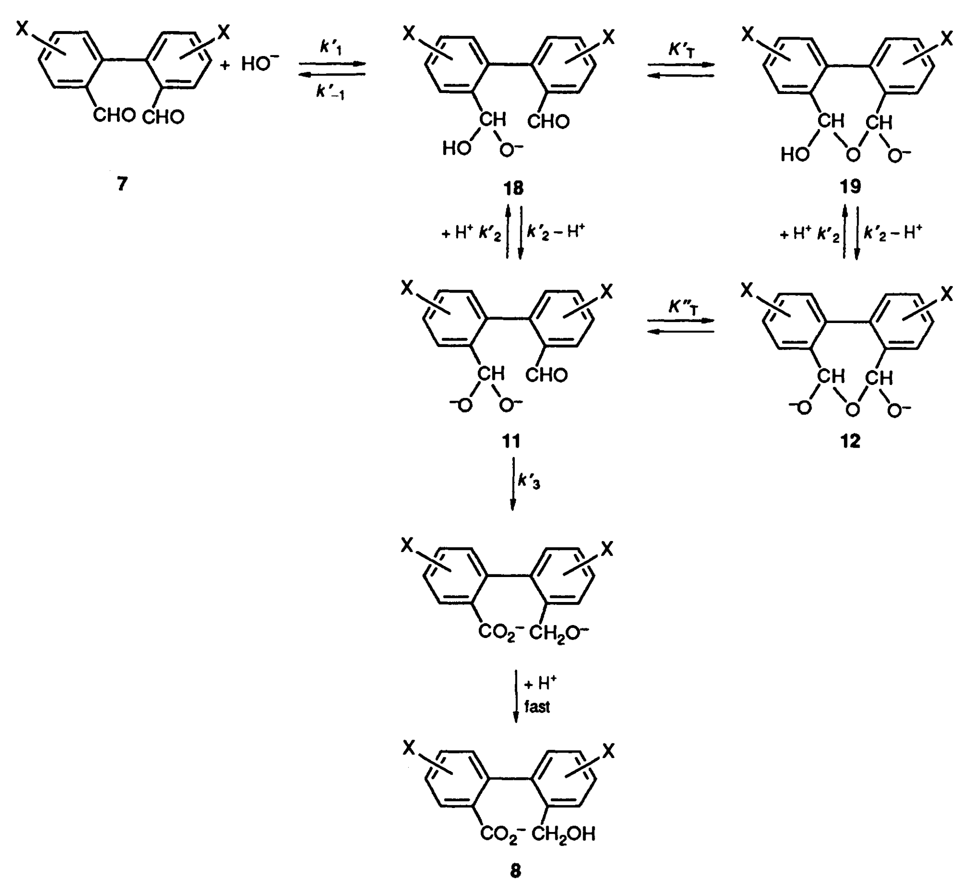


Scheme 4.

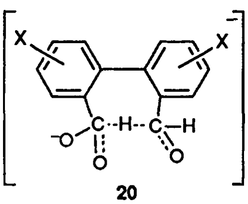
For the intramolecular Cannizzaro reaction studied here, it is possible directly to establish that intermediate lactones would be capable of isolation or direct determination under favourable conditions. This is unlike the intermolecular Cannizzaro reaction of benzaldehyde for which Swain *et al.*[3] used the method of isotopic dilution to exclude such intermediates (**6** in Scheme 2). The latter method is sophisticated; but not as simple or direct as the method used here (see the Experimental section). Mechanisms of the type shown in Scheme 2 can thus be excluded for this intramolecular reaction.

Proposed Mechanism for the Intramolecular Cannizzaro Reaction.—In Scheme 5 the suggested mechanistic pathway for the intramolecular Cannizzaro reaction of biphenyl-2,2′-dicarbaldehyde is shown. The involvement of the bridged dianion **12** is attractive as it would provide a 'holding' system for two formyl groups, while hydride transfer commences. As such a similar intermediate (**5** in Scheme 2) could be involved in the intermolecular Cannizzaro reaction. The rate-determining step in Scheme 5 would be k_3 and the transition state could be either **20**, from **11**, or **21**, from **12**. Structures **20** and **21** only differ in the partial bonding between the bridging oxygen and the carbon at the site of transfer present in **21**. At this time **20** must be preferred. The drive for hydride transfer to the electrophilic centre of the carbonyl group is unmistakable in **20**. As such, **20** involves a seven-membered ring which must be either strained or buckled or both.

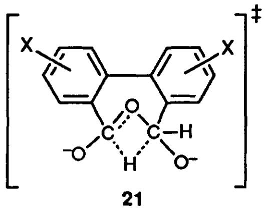
Effective Concentration of Intramolecular Transfer.—The effectiveness of an intramolecular reaction has been considered to be capable of quantification by calculation of its effective concentration.[44] The problem in such a calculation for the present study is that the model intermolecular process involving



Scheme 5.



20



21

benzaldehyde is third order, *i.e.* first order in base.[3,6] However, the Cannizzaro reaction in water of sodium *m*-formylbenzenesulphonate has been found to be of the fourth order, *i.e.* second order in base.[45] This reaction may be corrected approximately for the *meta*-SO_3^- substituent effect[46] using the ρ value found either in the present study or for benzaldehydes in 50% aqueous methanol.[4,5] An estimate of k_4 for benzaldehyde is then given as *ca.* 3×10^{-4} dm^{12} mol^{-4} s^{-1} at 40 °C. This results in an estimate of 4×10^3 for the effective concentration of the intramolecular Cannizzaro reaction studied here. It has been suggested that hydride transfer should also show large effective concentrations arising from a tight transition state.[47]

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