J. Am. Chem. Soc. **1994,** *116,* 5601-5606

Hydrolysis of Orthocarbonates. Evidence for Charge Imbalance in the Transition State for the General Acid Catalyzed Process

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Received December 8, 1993®

Abstract: Catalytic constants have been measured for the hydrolysis of a range of aryl orthocarbonates, in which both the leaving group and trioxocarbenium ion moiety have been systematically varied, by neutral carboxylic acids (trichloroacetic, difluoroacetic, dichloroacetic, malonic, chloroacetic, and acetic) at 70.0 °C in 60% water–40% acetonitrile, $I = 1.0$ M (KCl). Curvature cannot be detected in Brønsted plots involving carboxylic acids only, but inclusion of the point for H_3O^+ suggests downward curvature (i.e. $p_x \geq 0$). β_{lg} Plots are curved downward (i.e. $p_{y'} = -\partial\beta_{lg}/\partial pK_{lg} > 0$). Substitutent effects in the tris(aryloxy)carbenium ion fragment were quantitated by use of the experimental aqueous pK_a values of the phenol (pK_{rc}), rather than Hammett σ values, since this gave better correlations for the spontaneous reactions (Kandanarachchi, P.; Sinnott, M. L. *J. Am. Chem. Soc.*, preceding paper in this issue). Cross coefficients are large and not constant: $p_{xy'}$ (measured as $\partial\alpha/\partial pK_{lg}$ rather than $-\partial\beta_{lg}/\partial pK_{HA}$) varies from 0.26 for $(PhO)_3C^+$ to 0.16 for $(pMeOC_6H_4O)_3C^+$. Likewise, p_{xy} (measured as $-\partial\alpha/\partial pK_{rc}$ rather than $-\partial\beta_{rc}/\partial pK_{HA}$) experiences large changes with the leaving group pK. Data to estimate $p_{yy'}$ ($\partial\beta_{rc}/\partial pK_{lg}$) are more limited, but it too changes with the pK_a of the catalyzing acid. These data indicate that a two-dimensional More O'Ferrall–Jencks diagram, with one axis representing both C–O cleavage and the ability of substituents in the tris(aryloxy)carbenium ion moiety to sense positive charge development, is inadequate to represent this reaction: separate axes are required for carbon–oxygen bond cleavage and development of carbon–oxygen double-bond character.

In the preceding paper we showed that, in aryl orthocarbonates hydrolyzed by pH-independent and general acid catalyzed processes and in mixed orthocarbonates of the type $(ArO)_3COAr'$, where Ar'OH was at least 1 pK unit more acidic than ArOH, the hydrolysis to $(ArO)_2CO$ by the general acid catalyzed pathway was initiated by loss of Ar'OH.[1] We found that uncatalyzed loss of a leaving group from $(ArO)_3C$–X was remarkably slow, slower even than loss of the same group from a tetrahydropyranyl or a 3-(*p*-anisyl)-1-methoxypropyl moiety. The lifetimes of the cations formed from these reactions are very different, though. Trialkoxycarbenium ions have lifetimes of milliseconds in water;[2] the azide-trapping experiments described in the previous paper indicated that tris(aryloxy)carbenium ions have lifetimes of at least several microseconds. Azide trapping however indicates a picosecond lifetime for the 3-(*p*-anisyl)-1-methoxypropyl cation.[3] These data therefore favored the idea that the slow rate of orthocarbonate hydrolysis arises from a destabilization of the transition state by the inductive effects of the three oxygen atoms, before conjugation is fully developed ("transition-state imbalance"), but they could not rule out stabilization of the orthocarbonate substrate because of accumulated n–σ* interactions.[4] We now present data pertaining to the general acid process. The relationships between the various structure–reactivity coefficients and interaction coefficients, which arise necessarily out of the mathematics of a simple two-dimensional More O'Ferrall–Jencks diagram, fail comprehensively for the hydrolysis of orthocarbonates. It follows that two axes are inadequate to represent all of the bonding changes during this process. A third axis, representing carbon–oxygen double-bond formation, should be added. This, detailed analysis of the general acid catalyzed process supports the "transition-state destabilization" explanation for the inertness of orthocarbonates.

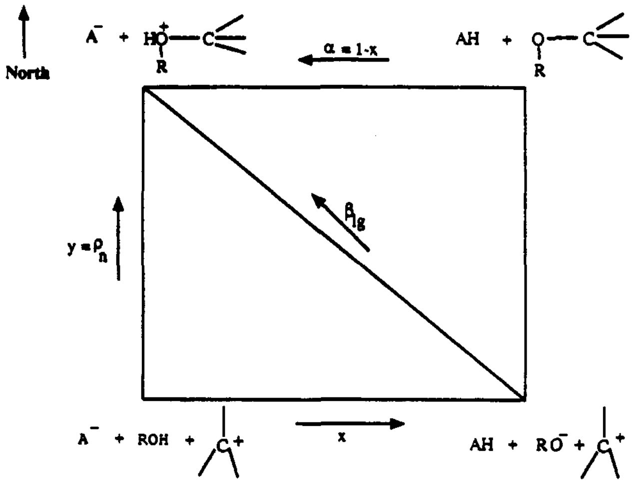

Figure 1. Two-dimensional More O'Ferrall–Jencks diagram for a class *n* type reaction, with the *x* axis representing proton transfer and the *y* axis representing both carbon–oxygen bond cleavage and the ability of substituents in the oxocarbenium ion moiety to sense positive charge development.

Structure–reactivity of a class *n* reaction, such as the general acid catalyzed hydrolyses of acetals and ortho esters, are conventionally represented as in Figure 1.[5] (Class *n* reactions are those in which there is proton transfer to the leaving group or from the nucleophile.) The *x* axis, representing proton transfer, is related to the Brønsted α value. The *y* axis, representing both C–O cleavage and oxocarbenium ion charge development, has some linear relationship to the Hammett ρ value. Free energy was originally represented by illustrative contour lines, as in

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® Abstract published in *Advance ACS Abstracts,* May 15, 1994.

(1) Kandanarachchi, P.; Sinnott, M. L. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Steenken, S.; Buschek, J.; McClelland, R. A. *J. Am. Chem. Soc.* **1986,** *108,* 2808.

(3) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989,** *111,* 7888.

(4) Hine, J. *J. Am. Chem. Soc.* **1963,** *85,* 3239.

(5) (a) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970,** 274. (b) Jencks, W. P. *Chem. Rev.* **1972,** *72,* 705.

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ordinary topographical maps, but these are now commonly omitted. A detailed mathematical treatment of such diagrams[6] was based upon the supposition that the free energy surface, at least in the vicinity of the transition state, could be represented by linear and square terms only, i.e.

$$\Delta G/2.303RT = ax^2 + by^2 + cxy + dx + ey + f \quad (1)$$

Such approximations of energy surfaces using no higher than square terms (parabolas in two dimensions) lie at the heart of much successful modern reaction theory (such as Marcus theory), and they are unlikely to be seriously incorrect. Very major departures from the mathematical consequences of eq 1 must therefore have their origins in the inappropriateness of the model for the reaction being considered.

A consequence of eq 1 is that interaction coefficients are constants. For a class *n* reaction p_x is defined as the curvature of Brønsted plots.

$$p_x = \partial\alpha/\partial pK_{HA} = -2b/(4ab - c^2) \quad (2)$$

Likewise it is possible to define p_y as the curvature of Hammett plots (eq 3). However, whereas Brønsted α values are by their definition normalized, Hammett ρ values must be normalized with respect to the ρ value for equilibrium generation of the ion to relate p_y to the constants of eq 1. For clarity in the following discussion, normalized parameters are underlined (eq 3)

$$p_y = \partial\rho/-\partial\sigma; \quad \underline{p_y} = \partial\underline{\rho}/-\partial\sigma = -2a/(4ab - c^2) \quad (3)$$

A cross-interaction coefficient p_{xy} describes the variation of α with σ or of ρ with pK_{HA} (eq 4), and its normalized value is related to the constants of eq 1 by eq 5:

$$p_{xy} = \partial\alpha/\partial\sigma = \partial\rho/-\partial pK_{HA} = -\partial^2(\log k)/\partial\sigma\, \partial pK_{HA} \quad (4)$$

$$\underline{p_{xy}} = \partial\alpha/\partial\sigma = \partial\underline{\rho}/-\partial pK_{HA} = c/(4ab - c^2) \quad (5)$$

Because measurement of the effect of leaving group acidity is one of the simplest measurements to make, it is conventional to define an axis (drawn in a "NW–SE" fashion in Figure 1) which measures change in effective charge on the leaving group. $p_{y'}$ is defined as the curvature of β_{1g} plots, and its normalized value is related to the parameters of eq 1 by eq 6:

$$p_{y'} = \partial\beta_{1g}/-\partial pK_{1g}; \quad \underline{p_{y'}} = -2(a + b + c)/(4ab - c^2) \quad (6)$$

Likewise, a cross-interaction coefficient $p_{xy'}$ can be defined, and its normalized value can be related to the constants of eq 1 by eq 7:

$$p_{xy'} = -\partial\beta_{1g}/\partial pK_{HA} = \partial\alpha/\partial pK_{1g}; \quad \underline{p_{xy'}} = (c + 2b)/(4ab - c^2) \quad (7)$$

The invariance of interaction coefficients is not affected by the requirement for normalization, since this only introduces a constant.

In the present system it is convenient to use the measured aqueous pK_a of the phenol, rather than the Hammett σ value, to quantify the effects of substituents in the trioxocarbenium ion moiety: these give rise to pK_{rc} and β_{rc} values. Because the same electronic effect affects σ and pK_a in opposite senses (electron-withdrawing substituents increase σ but decrease pK_a), we must write

$$p_{xy} = -\partial\alpha/\partial pK_{rc} = -\partial\beta_{rc}/\partial pK_{HA} = -\partial^2(\log k)/\partial pK_{rc}\, \partial pK_{HA} \quad (8)$$

$$\underline{p_{xy}} = -\partial\underline{\alpha}/\partial pK_{rc} = -\partial\underline{\beta_{rc}}/\partial pK_{HA} = c/(4ab - c^2) \quad (9)$$

We now present evidence that, not only are p_{xy} and $p/_{xy'}$ not constant in the orthocarbonate system, they change so drastically that p_{xy} changes sign.

Results and Discussion

Table 1 gives catalytic constants for all the reactions measured: in general, six acids were used for the determination of each catalytic constant, but for some substrates it was not possible to use all six acids. It should be emphasized that both the basic form of the catalyzing acids and the inert electrolyte are 1:1 salts, so that in this sense it is not necessary to invoke the concept of "ionic strength", as $I = {}^1/_2\Sigma z_i^2 c_i$. In our experiments the concentration of 1:1 electrolyte was kept constant. The pK_{HA} values moreover refer to the measured value in the reaction medium used for the experiments, not thermodynamic pK_a values. It was assumed that the temperature corrections for neutral carboxylic acids (in any event small) would be constant across the series of general acids used.

In Figure 2a are displayed representative Brønsted plots for various substrates with only carboxylic acids included. It is clear that these plots are essentially straight, although if the point for H_3O^+ is included (Figure 2b), a downward curvature is apparent. However, the switch from a neutral to a cationic acid (for which temperature and medium effects would be very different), as well as the uncertain statistical correction for H_3O^+, could well account for these differences. For all systems studied, therefore, $p_x \geq 0$. Derived Brønsted α values for carboxylic acids are given in Table 3.

Figure 3 shows the Brønsted plots for $(PhO)_3COAr'$ for various substituents in Ar′. The data clearly show that there is a trend in the α value to increase as the leaving group becomes more basic. This is a precedented type of behavior seen with class *n* reactions in acetal-type systems and was, for example, observed by Capon and Nimmo in the hydrolysis of methyl (substituted phenyl) acetals of benzaldehyde, by Gravitz and Jencks in the general acid catalyzed decomposition of alcohol adducts of a phthalimidium cation (for which $p_{xy'} = 0.07$), and (in the microscopic reverse) by Richard and Jencks in the general base catalyzed addition of alcohols to carbocations.[8-10] However, the derived $p_{xy'}$ parameters are not constant with respect to variation of the substituents in the trioxocarbenium ion moiety, as is shown by Figure 4. The $p_{xy'}$ values are 0.16 ± 0.03, 0.20 ± 0.04, and 0.26 ± 0.02 for Ar = *p*-anisyl, *p*-cresyl, and phenyl, respectively. The observed values of $p_{xy'}$ are very large. They are far too large to have arisen from electrostatic effects that are not associated with bonding changes. From Hine's data,[11] it can be estimated that electrostatic effects contribute about 0.024 to $p_{xy'}$ values for hydrogen ion catalyzed exchange of the hydroxylic hydrogen atoms of phenols and benzoic acid in methanol. Therefore the high value of $p_{xy'}$ indicates a direct coupling between carbon–oxygen bond cleavage and proton donation from the catalyzing acid.

Moreover, the values of $p_{xy'}$ vary systematically with the electronic nature of the substituents in the trioxocarbenium ion moiety, when in the light of a simple treatment they should be constant. Whilst the system does not permit accurate determination of a third-order interaction coefficient $p_{xy'}$ (defined as $\partial p_{xy'}/\partial\beta_{rc}$), because of the limited range of reaction center substituents available, the error bars establish unequivocally that the change is real, and require a large value, around −0.3.

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[6] Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.
[7] Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.
[8] Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans 2* **1975**, 1113.
[9] Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 507.
[10] Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383.
[11] Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766.

Table 1. Catalytic Constants ($10^4 k_{HA}$, $M^{-1} s^{-1}$) for General Acid Catalyzed Hydrolysis of Aryl Orthocarbonates at 70 °C in 40% Acetonitrile–60% Aqueous Buffer ($I = 1.00$ M, KCl)

Orthocarbonates of the Type $(PhO)_3COAr'$

	substituents in Ar′				
catalyzing acid	H	*m*-CN	*m*-NO_2	*p*-CN	*p*-NO_2
trichloroacetic	16.0	22.3	28.6	30.4	48.9
difluoroacetic	2.58	9.6	8.62	15.5	25.3
dichloroacetic	2.21	5.14	8.34	11.9	22.5
malonic	0.184	1.29	3.63	6.38	30.5
acetic		0.074	0.229	0.360	7.11
H_3O^+	68.2	10.7	33.2	41.9	

Orthocarbonates of the Type $(p\text{-}CH_3C_6H_4O)_3COAr'$

	substituents in Ar′			
catalyzing acid	*p*-Me	*m*-CN	*p*-CN	*p*-NO_2
trichloroacetic	67.3	110	77.5	219
difluoroacetic	8.15	18.8	43.9	94.1
dichloroacetic	4.60	14.5	27.9	104
malonic	0.761		18.7	57.8
chloroacetic	0.312	6.38		25.0
acetic		0.392	1.08	10.3
H_3O^+	129	90.7		

Orthocarbonates of the Type $(p\text{-}OMeC_6H_4O)_3COAr'$

	substituents in Ar′				
catalyzing acid	*p*-OMe	*p*-Cl	*m*-F	*m*-CN	*p*-CN
trichloroacetic	87.0	85.2	88.3	138	154
difluoroacetic	14.0	15.8	14.0	31.6	59.7
dichloroacetic	9.75	14.3	16.4	33.6	55.1
malonic	2.45	5.01	4.69	10.4	38.0
chloroacetic	1.06	1.14	2.36		15.0
acetic				0.943	2.12
H_3O^+	309	228	119	144	

Orthocarbonates of the Type $(ArO)_3CO\text{–}p\text{-}C_6H_4NO_2$

	substituents in Ar				
catalyzing acid	*p*-Cl	*p*-F	*m*-Me	*p*-*tert*-Bu	3,4-diMe
trichloroacetic	6.89	23.9	205	241	784
difluoroacetic	1.81	8.95		102	
dichloroacetic	2.47	10.7	93.8	105	264
malonic	2.27	7.60		62.2	81.1
chloroacetic	1.03	3.01	23.3	34.2	
acetic	0.205	1.47	11.5	8.14	20.5

Orthocarbonates of the Type $(ArO)_3CO\text{–p-}C_6H_4CN$

	substituents in Ar	
catalyzing acid	*m*-Me	*p*-F
trichloroacetic	65.9	15.8
difluoroacetic	38.8	
dichloroacetic	21.4	2.91
malonic	16.9	1.11
acetic	0.793	0.101

Table 2. Brønsted α Values for Tris(Substituted)phenyl) *p*-Nitrophenyl Orthocarbonates

substituent in phenyl group	Brønsted coefficient
p-chlorophenyl	0.31 ± 0.031
p-fluorophenyl	0.26 ± 0.029
phenyl	0.21 ± 0.018
m-methylphenyl	0.28 ± 0.038
p-methylphenyl	0.29 ± 0.032
p-*tert*-butylphenyl	0.32 ± 0.014
3,4-dimethylphenyl	0.34 ± 0.021

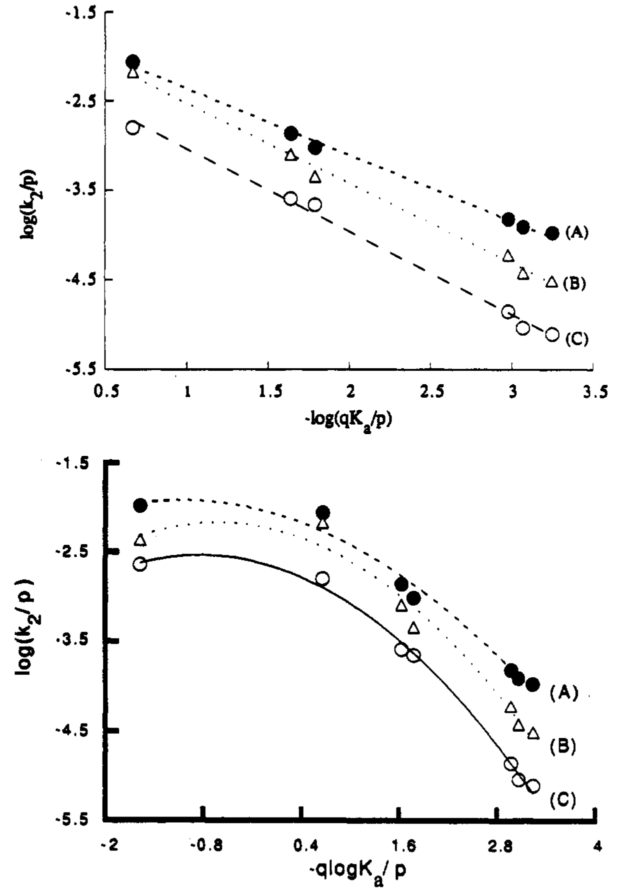

Figure 2. (a, top) Brønsted plots for hydrolysis of (A) tetraphenyl orthocarbonate, (b) tetrakis(*p*-methylphenyl) orthocarbonate, and (C) tetrakis(*p*-methoxyphenyl) orthocarbonate by monobasic carboxylic acids. (b, bottom) The same data as in part a, but with inclusion of the point for the solvated proton.

Table 3. Brønsted α Values for Orthocarbonates of the Type $(ArO)_3COAr'$

	substituents in Ar		
substituents in Ar′	H	*p*-Me	*p*-OMe
p-OMe			0.75 ± 0.02
p-Me		0.89 ± 0.03	
H	0.93 ± 0.03		
p-Cl			0.68 ± 0.04
m-F			0.61 ± 0.02
m-CN	0.58 ± 0.05	0.49 ± 0.05	0.48 ± 0.04
m-NO_2	0.46 ± 0.02		
p-CN	0.43 ± 0.01	0.41 ± 0.01	0.39 ± 0.01
p-NO_2	0.21 ± 0.02	0.29 ± 0.03	

Although, with the exception of the point for the solvated proton, Brønsted plots are essentially straight, β_{lg} plots are curved (i.e. $p_{y'} \neq 0$). Plots for mixed orthocarbonates of the type $(ArO)_3$-COAr′ are shown in Figure 5. As can be seen, these β_{lg} plots are curved downward ($p_{y'} > 0$); i.e., the negative value of β_{lg} increases as the leaving group becomes more basic. A similar behavior is observed when operational p*K* values for leaving groups were measured in 40% aqueous acetonitrile, 1.0 M in KCl, rather than using thermodynamic p*K* values (the change in medium results in an essentially constant change in p*K*). Therefore, the curvature in β_{lg} plots is real, not an artifact of medium effects on p*K* values. The curvature of the β_{lg} plots is opposite to that observed by Capon and Nimmo in the general acid catalyzed hydrolyses of PhCH(OMe)–OAr, where β_{lg} plots were bowl-shaped. There is however a possibility that some of these data (which were obtained by monitoring benzaldehyde, not phenol, formation) may be complicated by comparable rates of acetal hydrolysis and hemiacetal breakdown.[12]

The effects of substituents in the tris(aryloxy)carbenium ion moiety were correlated with the pK_a values of the phenols attached to the carbenium ion center, rather than Hammett σ values, since

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(12) Przystas, T. J.; Fife, T. H.; *J. Am. Chem. Soc.* **1981**, *103*, 4884.

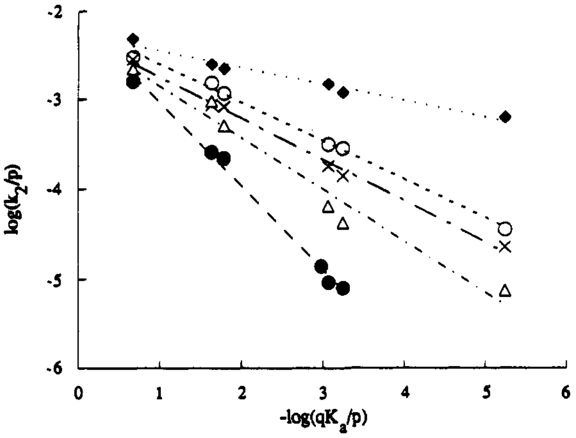

Figure 3. Brønsted plots for orthocarbonates of the type $(PhO)_3COAr'$, where the substituents in Ar′ are as follows: ●, none; △, *m*-CN; ×, *m*-NO_2; ○, *p*-CN; ◆, *p*-NO_2.

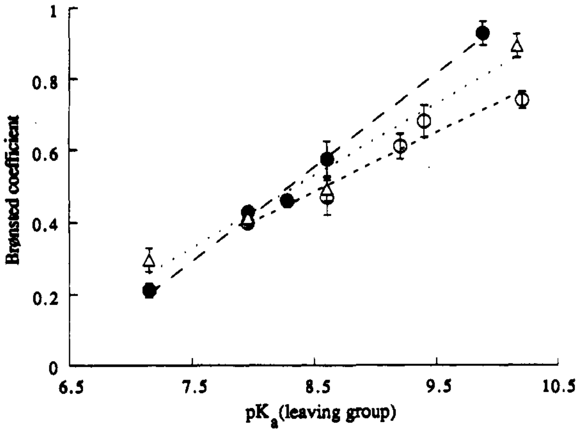

Figure 4. Variation of Brønsted α with the leaving group when the substituents in the oxocarbenium ion are as follows: ●, none; △, *p*-Me; ○, *p*-OMe.

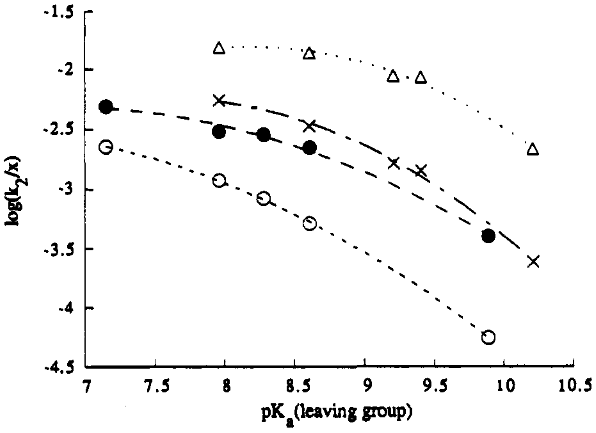

Figure 5. β_{lg} plots for orthocarbonates of the type $(PhO)_3COAr'$ in trichloroacetic acid (●) and dichloroacetic acid (○) and of the type $(p\text{-}MeOC_6H_4)_3COAr'$ in trichloroacetic acid (△) and dichloroacetic acid (×). The parameter x is a statistical correction factor applied to the symmetrical orthocarbonates.

better correlations for the spontaneous reactions were obtained in this way. However, the requirement, dictated by the necessity that one mode of C–OAr bond fission only be observed, that the leaving group pK_a be at least 1 pK unit more acidic than the phenols forming the trioxocarbenium ion fragment limits the range of pK_{rc} values that can be used with any system. The result is that β_{rc} plots are scattered and for the general acid catalyzed reactions not discernibly better than Hammett plots. β_{rc} values and correlation coefficients are set out in Table 4.

Table 4. β(reaction center) Values for General Acid Catalyzed Hydrolysis of Mixed Orthocarbonates

catalyzing acid	$(ArO)_3CO\text{-}p\text{-}C_6H_4NO_2$	$(ArO)_3CO\text{-}p\text{-}C_6H_4CN$
trichloroacetic	1.94 (r = 0.94)	1.82 (r = 0.92)
difluoroacetic	2.04 (r = 0.95)	1.57 (r = 0.92)
dichloroacetic	1.96 (r = 0.94)	1.75 (r = 0.94)
malonic	1.72 (r = 0.94)	1.98 (r = 0.92)
acetic	1.80 (r = 0.91)	2.08 (r = 0.95)
spontaneous	2.54 (r = 0.98)	3.14 (r = 0.97)

These values can be compared with those obtained for generation and collapse of tris(aryloxy)carbenium ions in spontaneous reactions: for the addition of water to $(ArO)_3C^+$, a β_{rc} value of −0.3 was obtained, compared to one of 2.5_4 for the spontaneous hydrolysis of $(ArO)_3C\text{–}O\text{-}p\text{-}C_6H_4NO_2$. If complications due to the different leaving groups and likely different conformations of the tetraaryl and triaryl orthocarbonates are neglected, then an equilibrium β_{rc} of around +3 can be estimated for the generation of tris(aryloxo)carbenium ions. This value, corresponding to the generation of approximately a full positive charge on each of the three oxygen atoms, is clearly unphysical. In the previous paper we advanced arguments as to why the β_{rc} values for spontaneous reactions might be greater than that for equilibrium formation of the trioxocarbenium ion, but this rationalization required the existence of substantial transition-state imbalance. If there is no transition state imbalance, the values of β_{rc} in Table 4 would indicate that oxocarbenium ion character is somewhat over half developed at the transition states of the general acid catalyzed processes.

The absolute values of β_{lg}, α, and β_{rc}, even in the absence of a consideration of their interactions, present the interpretation of these data in terms of a simple two-dimensional More O'Ferrall–Jencks diagram with significant difficulties. The values of β_{rc} require the transition states to lie in the south-central part of the diagram. Since Brønsted α values are 0.3 or higher for most cases, these parameters on conventional interpretation require the transition states to lie in the western portion of the diagram. Finally, β_{lg} values are negative (in some cases strongly so), indicating that the transition state must lie in the portion of the diagram to the south and east of the β_{lg} = 0 diagonal. Qualitatively, therefore, the transition state is confined to a small part of the northerly portion of the south–southwest octant. However, all our data indicate that the transition state experiences quite large changes in structure as a consequence of changes in substituent, and such changes are qualitatively incompatible with the confinement of the transition state to a small portion of a conventional two-dimensional More O'Ferrall–Jencks diagram.

One set of such changes can be expressed as p_{xy}. Because of the noisiness of β_{rc} plots, this was determined as $\partial\alpha/\partial pK_{rc}$ rather than $\partial\beta_{rc}/\partial pK_{HA}$. Plots of Brønsted α versus pK_{rc} are shown in Figure 6 for three leaving groups: *m*-cyanophenoxy, *p*-cyanophenoxy, and *p*-nitrophenoxy. It is clear that p_{xy} is not constant, since it changes with leaving group, from −0.32 ± 0.01 for *m*-cyanophenol as a leaving group through −0.09 ± 0.05 for *p*-cyanophenol as a leaving group to 0.04 ± 0.05 for *p*-nitrophenol as a leaving group. The value of $p_{xyy'}$ indicated by these data (~ −0.3) is the same as that indicated by the estimation of $p_{xyy'}$ as $\partial p_{xy'}/\partial pK_{rc}$. Despite the constraints imposed by the orthocarbonate system on the range of substituents that can be studied, it is clear that large third-order interaction coefficients are required to describe the system.

Capon and Nimmo,[8] in their study of phenyl methyl acetals of substituted benzaldehydes, found an unambiguous trend for Brønsted α to decrease as the oxocarbenium ion became more stable. This is the trend exhibited by the *p*-cyanophenyl and *m*-cyanophenyl orthocarbonates but not the *p*-nitrophenyl compounds.

It should be emphasized that the wholesale failure of the quantitative aspects of the description of the hydrolysis of

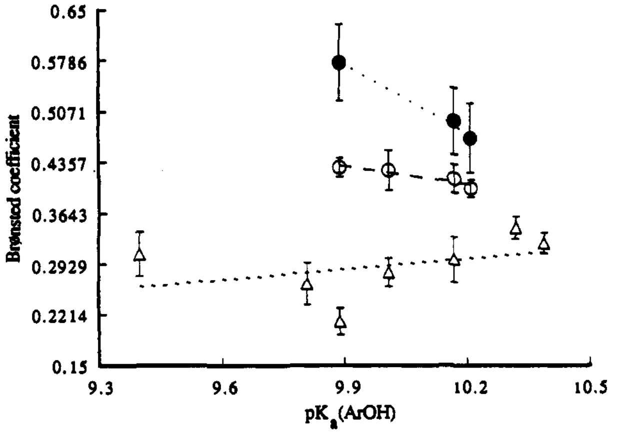

Figure 6. Variation of Brønsted α with pK_a of phenolic groups in the oxocarbenium ion moiety, when the leaving groups are as follows: ●, *m*-CN; ○, *p*-CN; △, *p*-NO$_2$.

orthocarbonates in terms of a simple two-dimensional free energy profile is unlikely to be a consequence of the triaryl orthocarbonate being a kinetically significant intermediate. Routine qualitative organic chemical prejudice would tend to discount the idea of a tetrahedral intermediate building up in reactions which had half-lives of hours at 70 °C anyway, but in any event in all cases clean first-order kinetics were observed, and nothing, other than orthocarbonate, carbonate, and phenol, could be detected on HPLC analysis of partly reacted mixtures.

It is significant that the necessity of third-order interaction coefficients for two examples of a class *n* reaction, involving additions of alcohols to the extensively delocalized cations $Me_2NpC_6H_4$–CH^+Me and $MeOpC_6H_4$–CH^+Me, was discovered by Ta-Shma and Jencks.[13] The requirement for third-order coefficients was attributed to the breakdown of the fundamental assumptions of the conventional treatment as the transition state approached the edges of the diagram.

Our present data on orthocarbonates likewise show that a simple two-dimensional More O'Ferrall–Jencks treatment cannot be used to describe the acid-catalyzed hydrolyses of orthocarbonates. The data in the previous paper indicated that the surprising overall inertness of orthocarbonates and the slowness of the reactions of trioxocarbenium ions had their origin in the phenomenon of transition-state imbalance, in which the development of conjugative stabilization lags behind bond cleavage. Extensive data from Richards' group on 4-methoxybenzyl carbocations has provided evidence for a similar phenomenon: that, in the cation-generation-direction, conjugative stabilization lags behind bond cleavage.[14] It is therefore clear that carbon–oxygen bond cleavage and the development of conjugation cannot be represented as a single process, and therefore two-dimensional More O'Ferrall–Jencks diagrams which describe the two processes on a single axis will fail.

We suggest that, for reactions of the present type, the conventional More O'Ferrall–Jencks diagram be extended into a third dimension to take into account the fact the reaction center–leaving group bond cleavage and the development of conjugation are imperfectly coupled. Such a diagram is shown diagrammatically in Figure 7: the conventional two-dimensional diagram, predicted on the assumption that the development of conjugation and carbon–oxygen cleavage are exactly in step, corresponds to a plane through the cube, extending from the near north to front south edge, with the *z* axis corresponding to carbon–oxygen double-bond formation and the *y* axis to carbon–oxygen cleavage. Addition of an extra axis to a More O'Ferrall–Jencks diagram has already been proposed to describe general acid catalysis of

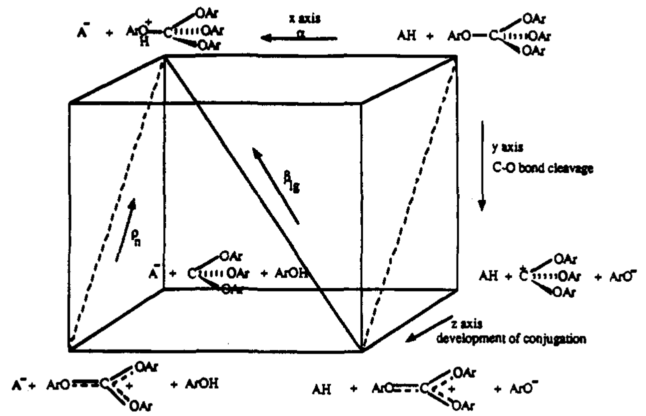

Figure 7. Schematic three-dimensional free energy profile for the hydrolysis of orthocarbonates with the *x* axis representing proton transfer, the *y* axis representing carbon–oxygen bond cleavage, and the *z* axis representing the development of carbon–oxygen double-bond character.

an S_N2 reaction at sulfur.[15] In reality the diagram corresponds to a prism rather than a cube, since the portion of the diagram north and in front of the conventional two-dimensional diagram corresponds to the physically unrealistic situation in which conjugation runs ahead of carbon–oxygen cleavage and the central carbon is greater than tetravalent.

Conclusion. The surprising overall inertness of orthocarbonates, the inability of simple two-dimensional free energy surfaces to describe transition-state structural changes in their general acid catalyzed reactions, and the slowness of the reactions of trioxocarbenium ions with water all have their origin in the same phenomenon: transition-state imbalance, in which the development of conjugative stabilization lags behind bond cleavage. Such phenomena have long been recognized in carbanion chemistry, in, for example, the anomalously slow deprotonation of nitromethane, despite a thermodynamic pK_a comparable to that of phenol.[16] They require no abandonment of the Born–Oppenheimer approximation, since full development of conjugation requires substantial geometrical change in the rest of the molecule. It is the requirement for this geometrical change which gives rise to the phenomenon. Transition-state imbalance in carbenium ion reactions therefore is, as expected, most marked in reactions of orthocarbonates, where a highly sterically constrained ground state has to undergo major geometrical rearrangement to give rise to a low-energy trioxocarbenium ion.

Very recent evidence, however, suggests that such transition-state imbalance may be significant in some enzyme-catalyzed reactions of glycosides (presumably because the geometrical changes on formation of a glycosyl cation-like transition state have to be accompanied by substantial movements of the protein). A multiple kinetic isotope effect study of the hydrolysis of inosine by *Crithidia fasciculata* permitted the calculation of a molecular electrostatic potential surface for the enzymic transition state which revealed that most of the positive charge accumulated on the glycon at the transition state was on carbon rather than oxygen.[17,18]

Experimental Section

Orthocarbonates are described in the previous paper, as is the kinetic system. All first-order rate constants were measured in duplicate and were reproducible to within 5%. Catalytic constants were obtained from measurements of first-order rate constants at, minimally, five buffer concentrations.

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[13] Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040.

[14] Amyes, T. L.; Stevens, I. W.; Richard, J. P. *J. Org. Chem.* **1993**, *58*, 6057.

[15] Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.* **1985**, *107*, 7572.

[16] Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Chapman and Hall: London, 1973.

[17] Horenstein, B. A.; Parkin, D. W.; Estupiñán, B.; Schramm, V. L. *Biochemistry* **1991**, *30*, 10788.

[18] Horenstein, B. A.; Schramm, V. *Biochemistry* **1993**, *32*, 9917.

First-order rate constants were determined by direct fitting of absorbance to exponentials using the nonlinear least squares program Kaleidagraph. Wavelengths at which hydrolyses were followed were 350 nm for all compounds which had *p*-nitrophenyl as the leaving group, 298 nm for all compounds having a *p*-methoxyphenyl group as the oxocarbenium ion, 285 nm for compounds having *p*-methyl or *m*-methylphenyl as the oxocarbenium ion, and 278 nm for all compounds which had phenyl groups as the oxocarbenium ion. Catalytic constants were determined from plots of first-order rate constants at at least five buffer concentrations against buffer concentration. It was confirmed that the acid form of the buffer was the only catalyzing species for tetraphenyl orthocarbonate (data displayed in the previous paper) and tetrakis(*p*-methoxyphenyl) orthocarbonate.

pK_a values of catalytic acids in 40% aqueous dioxane, 1.0 M in KCl, were taken as the apparent pH value of solution of half-neutralized acid in this medium, as registered by a combination electrode (ORION) calibrated in pure aqueous solution with standard buffers. The same electrode was reserved for use with 40% aqueous acetonitrile during the whole course of experiments. The pK_a values derived are purely operational, but their use will correct for differential effects of the medium, as compared with pure water. Values taken are for acetic acid, 5.55; chloroacetic acid, 3.55; malonic acid, 3.07; dichloroacetic acid, 2.09; difluoroacetic acid, 1.94; and trichloroacetic acid, 0.97.

When a similar procedure was adopted to correct for the pK_a of the phenols, it was found that the correction was constant, so for the determination of structure–reactivity parameters, thermodynamic pK_a values[19] were used.

Acknowledgment. We thank the NIH for support of this work through Grant GM 42469 (to M.L.S.).

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[19] Serjeant, E. P.; Dempsey, B., Eds. *Ionization Constants of Organic Acids in Aqueous Solution*; Pergamon: New York, 1979.