Calculation of deuterium percentage K in **5** and **6** is made by using the formula

$$K = \frac{I_{274} - kI_{273}}{I_{274} - kI_{273} + I_{273}} \times 100$$

I_{274} is the intensity of the corresponding peak, and $k = I_{274}/I_{273}$ for the nondeuterated compound.

Catalysis of the Enolization of Acetone by Mono- and Dicarboxylate Bases. The Role of Hydrogen Bonding

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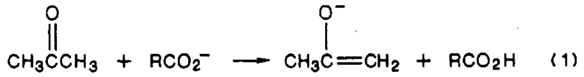
The enolization of acetone catalyzed by a series of aliphatic carboxylate bases (eq 1) was studied by Bell and Lidwell,[1] who reported a Brønsted exponent β of 0.88 for the four bases that comprised the series. As a part of a study of steric and other effects in proton-transfer reactions,[2] we have reexamined and greatly extended their series and have included in it a considerable number of dicarboxylic acid dianions.



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + RCO_2^- \longrightarrow CH_3\overset{O^-}{\overset{|}{C}}{=}CH_2 + RCO_2H \quad (1)$$

In Tables I and II, the rate constants for the reaction shown in eq 1 are given for the anions of 12 monocarboxylic acids and the dianions of 13 dicarboxylic acids, together with the corresponding pK values. The Brønsted plot for these bases is shown in Figure 1 and includes appropriate statistical corrections.[3,4] (The number of basic sites in the catalyst and the number of proton sites in its conjugate acid are given by q and p, respectively; q and p are deemed to be 2 and 1 for monocarboxylate catalysts and 4 and 1 for dicarboxylate catalysts.) The monocarboxylate ions fall on the straight line on the left side of the figure, which is governed by eq 2 (correlation coefficient 0.9974).

$$\log (k_{A^-}/q) = -10.90\ (\pm 0.10) + 0.885\ (\pm 0.020)(pK + \log p/q) \quad (2)$$

The Brønsted exponent for this line, 0.89, is virtually identical with that reported by Bell and Lidwell (0.88) for their much smaller set. Such high values of β are generally accepted as being indications of "late" transition states.[5,6]

The behavior of dicarboxylate bases (Table II), which appear on the right side of Figure 1, is not so straightforward. There is a group of eight of these bases that fall on a straight line that is displaced from that of the monocarboxylate bases, but is almost parallel to it; it is governed by eq 3 (correlation coefficient 0.9926).

$$\log (k_{A^{2-}}/q) = -11.24\ (\pm 0.19) + 0.865\ (\pm 0.043)(pK_2 + \log p/q) \quad (3)$$

Table I. Data for the Enolization of Acetone Catalyzed by Monocarboxylate Anions in Water at 25 °C, Ionic Strength 0.1

acid	pK^a	$10^7\ k_{A^-}$, M^{-1} s^{-1}
$C_6H_5CHOHCO_2H$	3.41	0.143 ± 0.058
$CH_3OCH_2CO_2H$	3.57	0.243 ± 0.039
$HOCH_2CO_2H$	3.83	0.339 ± 0.031
$C_6H_5CH_2CO_2H$	4.31	1.19 ± 0.09
CH_3CO_2H	4.76	2.45 ± 0.06
CD_3CO_2H	4.77^b	2.31 ± 0.13
$CH_3CH_2CH_2CO_2H$	4.82	2.79 ± 0.05
$(CH_3)_2CHCO_2H$	4.86	3.03 ± 0.41
$CH_3CH_2CO_2H$	4.87	3.22 ± 0.02
c-$C_6H_{11}CO_2H$	4.91	3.19 ± 0.41
$(CH_3)_3CCH_2CO_2H$	5.01^c	4.24 ± 0.05
$(CH_3)_3CCO_2H$	5.03	4.02 ± 0.09

[a] Values from ref 15 unless otherwise noted. [b] Reference 16. [c] Determined titrimetrically in this work.

Table II. Data for the Enolization of Acetone Catalyzed by Dicarboxylate Anions in Water at 25 °C

no.	acid	pK_2	$10^7\ k_{A^{2-}}$,^{a} M^{-1} s^{-1}	$K_1/2K_E$
1	2-methoxyisophthalic	4.32^b	0.319 ± 0.057	
2	5-bromoisophthalic	4.36^c	0.383 ± 0.004	
3	5-iodoisophthalic	4.41^b	0.512 ± 0.039	
4	isophthalic	4.75^b	0.985 ± 0.020	0.93^b
5	5-methylisophthalic	4.82^d	1.09 ± 0.05	0.91^b
6	phthalic	5.41^{b,e}	2.78 ± 0.11	1.1^f
7	3-methylglutaric	5.44^g	4.04 ± 0.34	1.0^b
8	succinic	5.63^h	4.96 ± 0.32^i	1.1^{d,j}
9	3,3-dimethylglutaric	6.45^g	7.74 ± 0.02	5.0^b
10	*meso*-2,3-diethylsuccinic	6.46^e	13.5 ± 0.07	2.4^{d,k,l}
11	(±)-2,3-diethylsuccinic	6.60^e	7.29 ± 0.18	8.9^{d,kl}
12	diethylmalonic	7.29^e	15.9 ± 1.5	16.0^f
13	tetramethylsuccinic	7.41^e	23.5 ± 0.52	13.5^{d,k}

[a] Rate constants measured at 0.05 M ionic strength except where noted. [b] Value determined in this work. [c] Determined from a Hammett plot. [d] Reference 4, p 35. [e] Reference 15. [f] Reference 10. [g] Reference 17. [h] Reference 18. [i] Ionic strength 0.10 M. [j] Reference 19. [k] Reference 20. [l] Water–ethanol, 1:1.

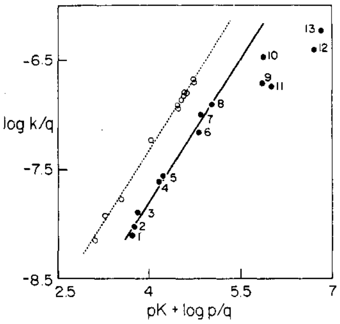


Figure 1. Brønsted plot for enolization of acetone catalyzed by monocarboxylate anions (open circles) and dicarboxylate dianions (closed circles). The numbers that identify the dicarboxylic acids refer to Table II.

As can be seen, the slopes of the two lines, which represent the respective Brønsted exponents, are quite close, 0.89 and 0.87 (neglecting the five deviating points), suggesting that the presence of an extra unit of negative charge in the base does not have a great effect on the extent of proton transfer in the transition state. What is the cause, then, of the lateral displacement of the line (by roughly 0.5 pK units) in the direction that suggests that a dianion is *less* effective in removing a proton from acetone than is a monoanion of the same equilibrium base strength? Such an effect has been observed previously in other systems,[7,8] without being satisfactorily explained. It

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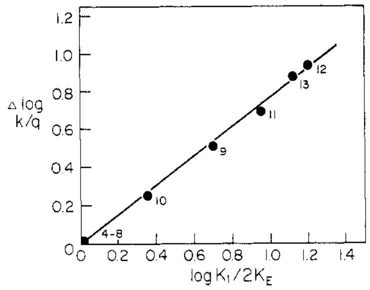

Figure 2. Linear free energy plot for catalysis by dicarboxylate dianions. The *y* axis represents the vertical displacement of the points from the line drawn in Figure 1; the *x* axis is a measure of the degree of hydrogen bonding in the monoanion (the protonated catalyst). The slope of the line is 0.76.

should be pointed out that it is common practice in Brønsted correlations to use thermodynamic pK values to represent equilibrium base strengths even though rate measurements are seldom corrected to zero ionic strength. This is usually of little consequence since within a catalytic series ionic strength effects (if they exist at all) will be essentially the same for all members of the series. In our case, rate measurements were made at ionic strengths of 0.05–0.10 and we found, in fact, the effect of ionic strength on the rate of proton abstraction by either monoanion or dianion to be very small. However, the basis of rate comparisons using the the Brønsted equation is the equilibrium strength of the catalyst, and it makes a significant difference whether or not one uses thermodynamic pK values for the two series that differ in charge type. Thus, the two lines drawn in Figure 1, which are displaced by just over 0.5 pK units, can be brought closer together by choosing for the x axis pK values at the ionic strengths at which the rate measurements were made. Indeed, at an ionic strength of 0.5, the lines would be displaced by less than 0.2 pK units, assuming that the rate constants do not change and that the pK values of the two series can be calculated reliably at such an ionic strength by means of the Debye–Hückel equation.[9] Since the choice of pK conditions is an arbitrary one, we prefer to simply note that monocarboxylate and dicarboxylate anions belong to different Brønsted series having essentially the same slope.

There are five deviating points in Figure 1, representing compounds 9–13, and it can be shown that their behavior is a result of hydrogen bonding in the dicarboxylic acid monoanions. In 1956 Westheimer and Benfey used the acid strengths of dicarboxylic acids compared to those of the corresponding monomethyl esters as a test for the presence of hydrogen bonding in the monoanions of the former.[10,11] In the absence of hydrogen bonding, the strength of the dicarboxylic acid, K_1, should be twice that of the ester, K_E (the statistical factor), assuming that carbomethoxyl and carboxyl groups transmit the same electronic effect to the dissociating proton. In Table II, values of $K_1/2K_E$ are listed, and it can be seen that the deviating bases in Figure 1 all have values of this quantity that range between 2.4 and 13.5, whereas those that obey the Brønsted equation all have values that are essentially unity. The significant difference between the behavior of the diastereomers **10** and **11** is due to the ethyl groups in the hydrogen-bonded forms being eclipsed in **10** but not in **11**, a condition that was recognized by Eberson (20).

Table III. Dissociation Constants of Isophthalic Acids in Water at 25 °C, Corrected to Zero Ionic Strength[a]

substituent	pK_1	pK_2
H	3.61	4.75
5-OH	3.56	4.62
5-OCH$_3$	3.46	4.67
5-I	3.28	4.41
5-F	3.24	4.39
5-NO$_2$	2.88	4.04
2-OCH$_3$	2.91	4.32

[a] Calculated pK_1 and pK_2 values for the 5-bromo derivative are 3.21 and 4.36, and for the 5-methyl derivative, 3.68 and 4.82. The ρ_1 and ρ_2 values are 1.05 and 1.02, respectively.

A quantitative correlation between the degree of hydrogen bonding in the monoanions and the catalytic constants of the dianions has been made in the following way. The vertical displacements of the points in Figure 1 (Δ log k/q) have been calculated by using eq 3, and these values have been plotted against the corresponding values of log $K_1/2K_E$. The result is the linear free energy plot shown in Figure 2. It is clear that the deviations from the Brønsted plot are a direct result of hydrogen bonding in the monoanion or, rather, of such bonding not being present in the initial product of proton transfer. That is, the catalytic strength of the base is not well represented by the equilibrium acid strength of the monoanion in these cases, since relaxation to the hydrogen-bonded equilibrium condition presumably occurs in a subsequent operation. The slope of the line in Figure 2 is less than unity (0.76), and it might be argued that a degree of hydrogen bonding is present in the transition state in all these cases. If this were so, it would be curious to find as good a linear relationship as that we have observed, since the geometry of the various catalytic species is somewhat diverse and, perhaps, one would not have expected the same proportion of hydrogen bonding in the transition state in all cases. At any rate, it is clear that for a dicarboxylate ion the equilibrium base strength of the catalyst is only a good measure of its catalytic strength in a proton-transfer reaction in the absence of hydrogen bonding in the equilibrium state of the monoanion.

Experimental Section

Rate and pK Measurements. The rates of enolization of acetone in aqueous solution were determined iodometrically at 25 °C by following the decrease in absorbance of the triiodide ion at 353 nm, essentially as previously described.[2] The buffer-ratio method was used to calculate values of k_{A^-} and $k_{A^{2-}}$, and it was shown that overlapping of ionization processes in several of the dicarboxylic acids (those whose pK_1 and pK_2 values are close) does not vitiate the treatment. In the case of some stronger acids, e.g., chloroacetic, iodoacetic, and oxalic acids, catalysis by the anion (or dianion) made very small contributions to the rate, which caused large standard errors in the rate constants and prevented their being included in the treatment.

The pK values of isophthalic acids, which are know for 1:1 aqueous methanol solvent,[12] were determined titrimetrically in water and converted to the standard state. The standard deviation

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was ±0.02 pK units in most cases. Inexplicably, 5-bromoisophthalic acid gave a value of pK_2 significantly higher than that of the other 5-halo compounds, despite repeated redeterminations and checks of the compound's identity and purity. It is possible that incomplete solubility is the cause since a similar effect was noted in the case of 5-methylisophthalic acid, where low solubility is clearly a major problem. For these two acids we calculated pK_2 from a Hammett plot of the well-behaved compounds. In order to have sufficient data to make such a calculation, we determined pK values for a number of other 5-substituted isophthalic acids, not all of which were used as catalysts. The data for such compounds and for the 2-methoxy derivative are given in Table III. References for the pK values of the other acids are given in the tables.

Materials. Many of the acids are commercially available. The isophthalic acids, except for the 2-methoxy derivative, had been previously prepared in this laboratory.[12] Tetramethylsuccinic acid was obtained by hydrolysis of its dimethyl ester, which was prepared from methyl 2-methylpropanoate by the method of Inaba and Ojima.[13] 2,3-Dimethylsuccinic acid[14] was prepared from methyl butanoate by the same method. The (±) and meso forms were separated by crystallization from benzene, with the meso form being the less soluble component. Further recrystallization of the separated fractions from water gave the pure meso compound, mp 211–212 °C, and the (±) form, mp 133–134 °C.

The monomethyl esters of 3-methylglutaric and 3,3-dimethylglutaric acids were synthesized by the methanolysis of the corresponding anhydrides.

2-Methoxyisophthalic acid was prepared by the aqueous permanganate oxidation of 2,6-dimethylanisole: yield 97%; mp 220–222 °C. Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.19; H, 4.20. We thank Dr. K. Nagarajan for the preparation of this compound.

Acknowledgment. The financial support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. $C_6H_5CHOHCO_2^-$, 769-61-9; $CH_3OCH_2CO_2^-$, 20758-58-1; $HOCH_2CO_2^-$, 666-14-8; $C_6H_5CH_2CO_2^-$, 7631-42-7; $CH_3CO_2^-$, 71-50-1; $CD_3CO_2^-$, 21845-14-7; $CH_3(CH_2)_2CO_2^-$, 461-55-2; $(CH_3)_2CHCO_2^-$, 5711-69-3; $CH_3CH_2CO_2^-$, 72-03-7; c-$C_6H_{11}CO_2^-$, 3198-23-0; $(CH_3)_3CCH_2CO_2^-$, 22402-43-3; $(CH_3)_3CCO_2^-$, 29650-96-2; acetone, 67-64-1; 2-methoxyisophthalate dianion, 119695-34-0; 5-bromoisophthalate dianion, 119695-35-1; 5-iodoisophthalate dianion, 119695-36-2; isophthalate dianion, 42966-02-9; 5-methylisophthalate dianion, 119695-37-3; phthalate dianion, 3198-29-6; 3-methylglutarate dianion, 68124-57-2; succinate dianion, 56-14-4; 3,3-dimethylglutarate dianion, 20187-45-5; *meso*-2,3-diethylsuccinate dianion, 119695-38-4; (±)-2,3-diethylsuccinate dianion, 119695-39-5; diethylmalonate dianion, 63238-97-1; tetramethylsuccinate dianion, 119695-40-8; 5-hydroxyisophthalic acid, 618-83-7; 5-methoxyisophthalic acid, 46331-50-4; 5-fluoroisophthalic acid, 1583-66-0; 5-nitroisophthalic acid, 618-88-2; 2,6-dimethylanisole, 1004-66-6.

Mechanistic Implications of 1,3,2λ^5-Dioxaphospholanes in the Mitsunobu Reaction

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Recently, we reported a highly chemoselective monobenzoylation of unsymmetrical 1,2-diols (i.e., 1,2-propanediol and 1-phenyl-1,2-ethanediol), affording both the *kinetically* and *thermodynamically* least stable secondary benzoate.[1] This monobenzoylation occurs with either of two reagent formulations, triphenylphosphine (TPP) and benzoyl peroxide (BPO) or TPP, diethyl azodicarboxylate (DAD), and benzoic acid (BA). The latter characterizes the reagent formula popularized by Mitsunobu and co-workers.[2a] In both systems, formation of 1,3,2λ^5-dioxaphospholane **1** emerges as the key intermediate. Hydrogen-bonding interactions and ultimately proton transfer to the least hindered oxygen of **1** initiates chemoselective ring opening to form largely the C-2 secondary phosphonium salt. Finally, benzoate anion nucleophilic displacement of triphenylphosphine oxide (TPPO) affords predominantly the C-2 benzoate with inversion of configuration at the C-2 carbinol stereocenter (Scheme I).

Table I. Chemoselective Benzoylations of 1,2-Diols Using the Mitsunobu Reaction

diol	benzoates,[a] %		
	secondary	primary	di
1,2-propanediol	88	10	2
1-phenyl-1,2-ethanediol	96	2	2

[a] See the Experimental Section for the details of the analytical analyses.

The mechanistic discernment of the Mitsunobu reaction with respect to the initial redox chemistry has received substantial documentation.[2] Quite recently, Walker and co-workers[3] proposed that the order of addition of alcohol and acid to betaine **2** has a profound effect on the reaction pathway, implying potential duality of mechanism. For example, addition of 2 equiv of a generic alcohol, ROH, to betaine **2** liberates diamine **3** and ultimately affords σ^5-dioxaphosphorane **4** (Scheme II, path a). Addition of HX effects loss of 1 equiv of ROH to give oxaphosphonium salt **6**. In the alternative route (Scheme II, path b), the acid, HX, is added initially to betaine **2**, effecting immediate protonation and affording phosphonium salt **5**, which upon addition of the alcohol undergoes an apparent slow conversion to oxaphosphonium salt **6** with no formation of intermediate dialkoxyphosphorane **4**. Walker et al. based their conclusions on inspection of the ^{31}P NMR spectrum, which indicates only the presence of phosphonium salt **6**.

The experiments described below are designed to test this suggestion by employing unsymmetrical 1,2-diols as probes to detect the formation of 1,3,2λ^5-dioxaphosphorane intermediates directly as well as through the identity and product ratios of the resulting diastereomeric benzoates. The predictions are (i) if benzoate substitution at C-1 predominates, the presence of a 1,3,2λ^5-dioxaphospholane would seem unlikely while (ii) an abundance of C-2 benzoate substitution *requires* the intermediacy of a 1,3,2λ^5-dioxaphospholane.

Results and Discussion

When 1 equiv of benzoic acid is added to a mixture of TPP and DAD in tetrahydrofuran (THF) solvent followed by the addition of an unsymmetrical 1,2-diol, a high product ratio favoring the C-2 benzoate is observed (see Table I).[4] We believe the preponderance of the C-2

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