Studies on Cyclic Anhydrides. III. Equilibrium Constants for the Acid–Anhydride Equilibrium in Aqueous Solutions of Certain Vicinal Diacids

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Abstract: Equilibrium constants have been measured for the equilibrium diacid $\rightleftharpoons$ anhydride + H_2O in aqueous solutions of a number of vicinal diacids, chosen to correspond to relatively stable or very stable anhydrides. Such acids include di-, tri-, and tetraalkylsuccinic acids, certain alicyclic diacids, dialkylmaleic acids, and some alkyl substituted phthalic acids. In all cases, the driving force for formation of a stable anhydride appears to be relief of steric strain in the anhydride as compared to the corresponding diacid. Diisopropylmaleic anhydride has been prepared as a new compound. Low-melting 2,3-diethyl-2,3-dimethylsuccinic acid has been shown to possess the *dl* configuration by resolution.

The position of the equilibrium between a dicarboxylic acid and its anhydride in aqueous solution (eq 1) has been determined in several cases,[1,2]

$$\text{diacid} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{anhydride} + H_2O \qquad (1)$$

where equilibrium constant = $K = k_1/k_{-1} = C_{\text{anhydride}}/C_{\text{diacid}}$. For unsubstituted methyl-, 2,2-dimethyl-, and *dl*-2,3-dimethylsuccinic acid the equilibrium constant, K (defined as in eq 1), increases regularly with increasing methyl substitution. In all three cases the equilibrium concentration of the anhydride is very low, $C_{\text{anhydride}}$ being 0.025% at equilibrium in the most favorable case (*dl*-2,3-dimethylsuccinic acid). On the other hand, the anhydride is the predominant species in solutions of dialkylmaleic acids in water, the equilibrium constant being in the range of 3–5 for dimethyl-, methylethyl-, and diethylmaleic acid. In all systems studied, the un-ionized diacid is the kinetically active species in anhydride formation.

Also in the case of monocarboxylic acids an analogous equilibrium (eq 2) appears to exist,[3-5] although the

$$2RCOOH \rightleftharpoons (RCO)_2O + H_2O \qquad (2)$$

equilibrium lies strongly toward the acid. Thus, at the boiling point of acetic acid the equilibrium mixture contains about 0.03 % of the anhydride (and the corresponding amount of water, something which precludes the preparation of anhydrous acetic acid by any procedure that has distillation at atmospheric pressure as the final step[5]).

Since eq 1 is a simple analogy of several reactions employed as models for intramolecular catalysis,[6] *e.g.*, hydrolysis of aryl hydrogen succinates and glutarates,[7-10] phthalate monoesters,[11-13] and succinanilic acids,[14] we have extended our studies to systems in which diacid and anhydride exist in comparable concentrations at equilibrium to see which factors favor the formation of cyclic forms. We here report investigations on di-, tri-, and tetraalkylsuccinic acids, certain alicyclic 1,2 diacids, dialkylmaleic acids, and some substituted phthalic acids, all of which exhibit high or fairly high K values and therefore are likely to correspond to very fast cases of intramolecular catalysis in the systems mentioned above. These all proceed *via* a rate-determining step involving formation of an anhydride ring from an acyclic initial state.

Results and Discussion

Equilibrium constants were in most cases determined by the method described previously,[1] *i.e.*, by measuring the solvolysis rate constant, k_{-1}, separately (pH-stat method at pH 5.2–5.3, where the contribution from the forward going reaction is negligible[1]) and $k_1 + k_{-1}$ by measuring (spectrophotometrically) the rate constant for attaining equilibrium at such a low pH that the diacid is entirely in its un-ionized form (*i.e.*, by running the reaction in 0.05–0.1 M HCl; in separate experiments it was ascertained that pH has no influence on rate in this pH region). This method gives acceptable values of the equilibrium constant in the range of $0.1 < K < 10$. Outside this range, k_1 is obtained as a difference between two almost identical rate constants and hence is very sensitive to small experimental errors. As in the previous paper, we estimate the accuracy in K to ±10% when determined by this method.

In some cases where k_1 and k_{-1} both are small and the solubilities of the anhydrides are very low another method based on glpc analysis of the anhydride was employed. Equilibration was performed in a buffer of known pH, followed by quick cooling and adjustment of the pH to 8 by addition of sodium bicarbonate

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[1] L. Eberson, *Acta Chem. Scand.*, **18**, 1276 (1964), and references contained therein.

[2] T. Higuchi, L. Eberson, and J. D. McRae, *J. Amer. Chem. Soc.*, **89**, 3001 (1967).

[3] J. A. Knopp, W. S. Linnell, and W. C. Child, Jr., *J. Phys. Chem.*, **66**, 1513 (1962).

[4] W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 4464 (1966).

[5] L. W. Hessel, Dissertation, University of Leiden, Netherlands, 1968, p 44.

[6] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 14.

[7] E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, **82**, 5328 (1960).

[8] T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960).

[9] T. C. Bruice and U. K. Pandit, *Proc. Nat. Acad. Sci. U. S.*, **46**, 402 (1960).

[10] T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **87**, 4846 (1965).

[11] A. Agren, U. Hedsten, and B. Jonsson, *Acta Chem. Scand.*, **15**, 1532 (1961).

[12] L. Eberson, *ibid.*, **18**, 2015 (1964).

[13] J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, **88**, 747 (1966).

[14] T. Higuchi. L. Eberson, and A. K. Herd, *ibid.*, **88**, 3805 (1966).

Table I. Equilibrium Data (Equation 1) for Selected Vicinal Diacids in Aqueous Solution at 60° (**12**, **13**, and **14** were run at 20°)

Diacid	No.	$k_1 + k_{-1}$, min^{-1}	k_{-1}, min^{-1}	k_1, min^{-1}	$K = k_1/k_{-1}$	Ref
Succinic	**1**		1.22[a]	9×10^{-6}	7×10^{-6}	2
Methylsuccinic	**2**		1.41[a]	5.9×10^{-5}	4.2×10^{-5}	2
2,2-Dimethylsuccinic	**3**		1.07[a]	1.1×10^{-4}	1.0×10^{-4}	2
dl-2,3-Dimethylsuccinic	**4**		1.30[a]	3.2×10^{-4}	2.5×10^{-4}	2
Trimethylsuccinic	**5**	Not measurable	0.93[a]		<0.01[b]	This work
Tetramethylsuccinic	**6**	0.123	0.105	0.018	0.17 ± 0.02	This work
dl-2,3-Diethyl-2,3-dimethylsuccinic[h]	**7**	0.020	0.0045	0.0155	3.4 ± 0.4	This work
meso-2,3-Diethyl-2,3-dimethylsuccinic	**8**	0.020	0.0098	0.010	1.0 ± 0.1	This work
Tetraethylsuccinic	**9**	0.161			10 ± 3[c]	This work
dl-2,3-Diisopropylsuccinic	**10**	Not measurable			<0.1[b]	This work
dl-2,3-Di-*tert*-butylsuccinic	**11**				6 ± 2[c]	This work
Dimethylmaleic	**12**				5.3[d]	1
Methylethylmaleic	**13**				4.3[d]	1
Diethylmaleic	**14**				3.2[d]	1
Diisopropylmaleic	**15**	1.072	0.041	1.031	25 ± 3	This work
1,2-Diethyl-*cis*-1,2-cyclopropanedicarboxylic	**16**	Not measurable	0.70		<0.01[b]	
1,2-Diisopropyl-*cis*-1,2-cyclopropanedicarboxylic	**17**	0.0479	0.0369	0.011	0.30 ± 0.03	This work
Norbornane-*endo-cis*-2,3-dicarboxylic	**18**	0.310	0.193	0.117	0.60 ± 0.06	This work
2-Methylnorbornane-*endo-cis*-2,3-dicarboxylic	**19**	0.184	0.115	0.069	0.60 ± 0.06	This work
Bicyclo[2.2.2]octane-*cis*-2,3-dicarboxylic	**20**	0.230	0.177	0.053	0.30 ± 0.03	This work
3,6-Dimethylphthalic	**21**	0.92	0.77	0.15	0.20 ± 0.02[e]	This work
3,6-Diethylphthalic	**22**	0.78	0.31	0.47	1.5 ± 0.2	This work
3,6-Diiodophthalic	**23**		25[f]		<0.1[g]	This work

[a] Extrapolated from data published earlier (L. Eberson, *Acta Chem. Scand.*, **18**, 534 (1964)). [b] In this case $k_1 + k_{-1}$ was not measurable due to the fact that the equilibrium is shifted too far to the left. [c] Measured by the glc method described in the text. [d] At 20.0° (ref 1). [e] An earlier estimate in the range of 0.5–0.8 (ref 12) is now considered to be wrong. [f] Extrapolated from the values at 20 and 30° (see Table II). [g] Estimated upper limit. [h] Relative configuration established by resolution (see Experimental Section).

solution. Since the solvolysis rate constant is small, the anhydride can be extracted into ether without losses and then analyzed by glpc. Using known values of the first ionization constants of the diacids,[15] the equilibrium constant can be evaluated. Measurements in several buffers of different pH indicated that the method is less accurate than the first-mentioned one; it was reproducible to about ±25%. For the purpose at hand this accuracy is acceptable.

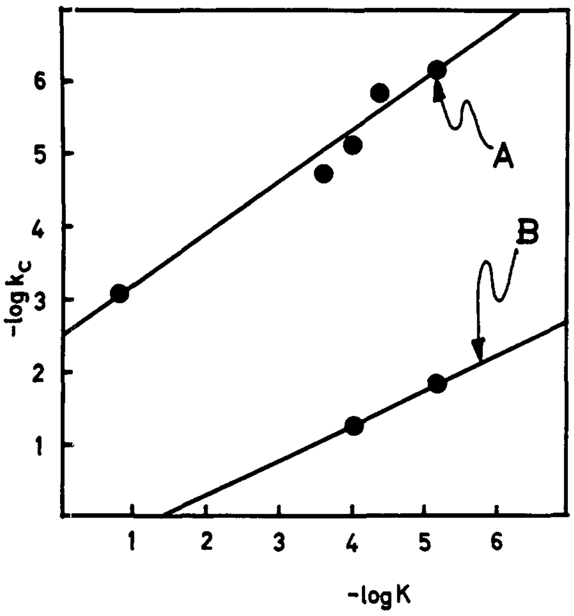

Figure 1. Plot of the logarithm of the rate constants for the intramolecularly catalyzed hydrolysis of succinanilic acids[2] (line A, values at 25.0°), and aryl hydrogen succinates[8] *vs.* log K for the corresponding diacid–anhydride equilibria (see Table I).

Table I gives relevant data for a number of dicarboxylic acids, taken both from the literature[1,2] and from this work. All values have been measured at 60°, except for compounds **12**, **13**, and **14**, which were too reactive to be studied at this temperature. Inspection of Table I reveals that several structural features may lead to high values of K. The *gem*-dialkyl effect[16] operates strongly in the succinic acid series, K changing by a factor of 2.5×10^4 in going from succinic to tetramethylsuccinic acid (**1–6**) and increasing further on successive replacement of the methyl groups by ethyl groups (**7–9**). Also, in certain cases two bulky alkyl groups in the 2,3 positions are sufficient to shift the equilibrium toward the side of the anhydride, as for *dl*-2,3-di-*tert*-butylsuccinic acid (**11**). Looking at the series of maleic acids (**12–16**), it is first necessary to estimate a value of K for maleic acid itself before the data can be discussed. This can be found by extrapolation of known rate data in the following way. Succinanilic acids[14] and *p*-methoxyphenyl hydrogen dicarboxylates[8] are hydrolyzed according to a cyclization mechanism involving formation of the anhydride as an intermediate. For succinanilic acids enough data are available to establish a satisfactory linear correlation between log K for eq 1 and the logarithm of the intramolecular rate constant for hydrolysis of succinanilic acids (line A of Figure 1). If one then uses the two rate constants that have been determined for the hydrolysis of aryl hydrogen succinates[8] (unsubstituted and 2,2-dimethyl-) and assumes that an analogous linear correlation holds in this case too, one obtains the second line (B) of Figure 1. Using the known rate constant for hydrolysis of *p*-methoxyphenyl hydrogen maleate,[8] a K value of approximately 10^{-2} for maleic acid is obtained. Although this value is uncertain,[17]

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(15) P. K. Glasoe and L. Eberson, *J. Phys. Chem.*, **68**, 1560 (1964).

(16) E. E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 196.

(17) This treatment neglects differences in nucleophilicity of the carboxylate ion and reactivity of the ester group between monoaryl

it nevertheless shows that substitution by two alkyl groups greatly increases the equilibrium constant (**12–15**), diisopropylmaleic acid exhibiting the largest K value ever observed. Unfortunately, attempts to synthesize di-*tert*-butylmaleic acid failed, so that data for this interesting compound could not be obtained.

In the series of phthalic acids, only those substituted by alkyl groups in the 3,6 positions showed high K values (**21**, **22**). Chemical evidence indicates that 3,4,5,6-tetramethylphthalic acid has an exceedingly stable anhydride but unfortunately its low solubility makes determinations of K by the methods employed in this investigation impossible. The 3,6-diiode compound **23** with a K value lower than 0.1 is representative of a number of other phthalic acids studied. All of these contained one or two groups other than alkyl in the position(s) adjacent to the carboxyl group(s). These groups were chosen to provide the same or larger steric requirements than the methyl group. However, none of these acids displayed any tendency for ring closure detectable by the method employed. Moreover, their solvolysis rates were much too high to be conveniently followed at 60° and thus had to be determined at lower temperature; this in turn caused solubility problems, so that a medium consisting of 20% dioxane–water (w/w) had to be used. Approximate solvolysis rates of these anhydrides are given in Table II.

Table II. Approximate Rate Constants for Solvolysis of Substituted Phthalic Anhydrides in 20% Dioxane–Water (w/w)

Substituted phthalic anhydride	No.	k_{-1} (min^{-1}) at °C			
		5°	10°	20°	30°
3-Chloro-	**24**			1.0	
3-Bromo-	**25**			0.9	
3-Iodo-	**26**			0.5	
3,6-Dibromo-	**27**		1.0	2.2	
3,6-Diiodo-	**23**			0.8	2.1
3,6-Dimethyl-	**21**				0.065
3-Nitro-	**28**	>7			

For phthalic acid itself a value of K was estimated in the same way as was done for maleic acid,[17] now using line A of Figure 1 and the rate constant for the intramolecularly catalyzed hydrolysis of phthalanilic acid.[18a] This gives a K value for phthalic acid of approximately 10^{-2}. From the excellent log–log correlation between the rate constants for the intramolecularly catalyzed hydrolysis of a series of *o*-hydroxyphenyl hydrogen succinates[18b] (from **1**, **2**, **4**, **5**, and **6**) and the corresponding K values of Table I, a value of approximately 10^{-3} can be estimated.

During the course of this investigation it became apparent that data regarding the interactions between cis 2,3-alkyl groups in the succinic anhydride ring were necessary for the interpretation of the equilibrium data. Therefore, pure *dl* and meso forms of dimethyl-, diethyl-, and diisopropylsuccinic anhydride were equilibrated in dioxane at 170° and the resulting mixtures analyzed by glpc. These results are shown in Table III.

Table III. Equilibrium Constants for the Isomerization *dl*-Anhydride $\rightleftarrows$ *meso*-Anhydride in Dioxane at 170°

Anhydride	% meso form at equilibrium[a]	Equilibrium constant	ΔG, kcal/mol
2,3-Dimethylsuccinic	9 ± 1	0.10 ± 0.01	2.0
2,3-Diethylsuccinic	5 ± 1	0.05 ± 0.01	2.6
2,3-Diisopropylsuccinic	<0.5[b]	$<5 \times 10^{-3}$	>4.7

[a] Determined as the mean value from four runs, approaching equilibrium from both sides. [b] Limit for detection of *meso*-anhydride in mixture with the *dl* form.

Finally, the alicyclic diacids represent cases in which the geometry of the molecule introduces severe nonbonded interactions, as can easily be seen by inspection of models. In these systems the carboxyl groups are situated in the near (**20**) or fully (**17–20**) eclipsed position.

Thus, the common denominator in all cases of high K values studied appears to be the existence of strong nonbonded interactions in the diacid which are relieved in the cyclic anhydride. At first sight it may seem somewhat inconsistent that 3,6-diiodophthalic acid does not show any tendency to cyclize, considering that the steric requirements of the iodo substituent are larger than those of the methyl group. However, the polar effect of the iodo groups increases the rate of solvolysis of **23** by a factor of approximately 30 compared to the dimethyl derivative **21**. Assuming that the rate of ring closure (k_1) is not significantly affected by polar effects it is easily seen that the method employed would not detect any cyclization in the diiodo derivative. In fact, one can allow for a k_1 for **23** of about 2 min^{-1} without coming within the range of applicability of the method.[19]

In some cases it is not *a priori* evident that a rationale based on relief of steric strain in going from the acyclic to the cyclic molecule should obtain. For example, compare the succinic and tetramethylsuccinic acid systems. Assuming a planar or nearly planar anhydride ring,[20a,b] it is not clear why tetramethylsuccinic anhydride, with two eclipsed CH_3–CH_3 interactions, should be so much more stable with respect to the

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maleate (phthalate) and succinate ion due to differences in inductive and conjugation effects. However, a scrutiny of the data on cyclization of monoaryl dicarboxylates[8] shows that differences in nucleophilicity cannot be important, since, *e.g.*, an increase in cyclization rate by a factor of almost 10^3 can be noted for half-esters where a consideration of only nucleophilicity would predict a slight decrease in cyclization rate (*p*-bromophenyl glutarate *vs.* 2,2-dimethylsuccinate with pK_{app} of 6.22 and 5.90, respectively). Likewise, a comparison between the succinate and maleate derivatives ($k_{\text{maleate}}/k_{\text{succinate}} \approx 50$) with p$K_{\text{app}}$ 2.68 and 4.34 indicates that differences in nucleophilicity cannot be important. Similarly, from the rates of the hydroxide ion catalyzed hydrolysis of monoethyl succinate, maleate, and phthalate (relative rate 1.0:0.28:0.14; E. Halonen, *Acta Chem. Scand.*, **9**, 1492 (1955); L. Pekkarinen, *Ann. Acad. Sci. Fenn., Ser. AII*, 85 (1957)) it can be seen that the reactivity differences for attack on the ester group by a nucleophile in these compounds are not large. Moreover, since both the maleate and phthalate hydrolyze at a slower rate than the succinate, a correction for these differences would lead to smaller estimated K values for maleic and phthalic acid and hence the effect of alkyl substituents on K would appear to be even larger.

(18) (a) H. Morawetz and J. Shafer, *J. Amer. Chem. Soc.*, **84**, 3783 (1962); (b) L. Eberson and L.-Å. Svensson, unpublished work.

(19) It has been shown (R. H. Eastman and K. Tamaribuchi, *J. Org. Chem.*, 30, 1671 (1965)) that inductively electron-attracting substituents in 2,2-diethyl-3-(*p*-X-phenyl)succinic acids favor the diacid form. Since the $-I$ effect is known to increase the rate of the solvolysis reaction (k_{-1}), this would actually mean that the $-I$ effect *decreases* the rate of ring closure in this case.

(20) (a) M. Ehrenberg, *Acta Crystallogr.*, **19**, 698 (1965); (b) L. E. Erickson, *J. Amer. Chem. Soc.*, **87**, 1867 (1965); R. J. W. Le Févre and A. Sundaram, *J. Chem. Soc.*, 4009 (1962).

Table IV. Comparison between Experimental and Calculated Free-Energy Differences for Acid–Anhydride Equilibria of Succinic Acids (Eq 1)

	Exptl		Calcd[a]		Calcd[b]			$\Delta\Delta H_{exp}$
Substituent	ΔG	$\Delta\Delta G$	ΔG	$\Delta\Delta G$	ΔG	$\Delta\Delta G$	ΔH_{exp}[c]	corrected[d]
None	7.8	0	2.4	0	2.4	0	11.2	0
CH_3	6.7	1.1	2.0	0.4	1.9	0.5	11.1[e]	−1.0
1,1-$(CH_3)_2$	6.1	1.7	1.3	1.1	−0.3	2.7	11.6[e]	0.6
dl-2,3-$(CH_3)_2$	5.5	2.3	1.4	1.0	−0.5	2.9	7.1	2.1
$(CH_3)_4$	1.3	6.6	2.1	0.3	−3.3	5.9	8.5	3.2

[a] Using a value of 0.8 kcal/mol for all gauche CH_3–CH_3, CH_3–COOH, and COOH–COOH interactions. [b] Using a value of 1.7 kcal/mol for all "strong" gauche CH_3–CH_3, CH_3–COOH, and COOH–COOH interactions, and 0.8 kcal/mol for the "normal" ones. [c] Reference 23. [d] Corrected for the heats of solution of the diacids, using a value of 13.34 kcal/mol for the heat of ionization of water and assuming that heats of ionizations of carboxyl groups are negligible in this connection (J. W. Larson and L. G. Hepler in "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 1). [e] Assuming that the heat of fusion of the anhydride is 2.0 kcal/mol.

parent acid than is succinic anhydride (which has only two eclipsed H–H interactions) with respect to its parent acid. It is therefore necessary to make an at least semiquantitative treatment of the energetics of the anhydride equilibria in the succinic acid systems.

Allinger and Zalkow[21] have demonstrated that there is a simple explanation based on thermodynamics for the *gem*-dialkyl effect. The decrease in the number of gauche interactions between nonbonded groups in going from an acyclic to a cyclic molecule becomes greater with increase in substitution on the carbon chain. This was shown by extensive calculations for a simple reaction involving the formation of a six-membered ring, but the principle was considered applicable to other ring sizes too.

In order to apply this approach to the series of methyl-substituted succinic acids under study it was first assumed that the gauche CH_3–CH_3, CH_3–COOH, and COOH–COOH interactions are identical and equal to the CH_3–CH_3 interaction in gauche butane, 0.8 kcal/mol (for the COOH–COOH interaction, Erickson[20b] used the value 1.0 kcal/mol, but we resorted to the lower value for the sake of simplicity), whereas gauche CH_3–H and H–H interactions were neglected. In the anhydrides the eclipsed H–H and CH_3–H interactions were estimated to be 1.0 and 1.2 kcal/mol, respectively, from the barrier to internal rotation in ethane, 3.0 kcal/mol, and the lower barrier to rotation around the central C–C bond in butane, 3.4 kcal/mol. The eclipsed CH_3–CH_3 interaction was obtained from the enthalpy difference between *dl*- and *meso*-2,3-dimethylsuccinic anhydride (Table III) which was calculated to be 1.7 kcal/mol assuming that only the entropy of mixing of enantiomers contributes to the entropy term and that the enthalpy difference is invariant with temperature. Using these parameters the eclipsed CH_3–CH_3 interaction is calculated to be 3.1 kcal/mol.

Using these parameters it is possible to calculate conformer populations in the diacids **1**–**4** and **6**; these in turn make it possible to estimate the free-energy differences due to nonbonded interactions between diacid and anhydride by the commonly used procedure.[22] The free-energy differences thus obtained are given in the third column of Table IV, together with the experimental free-energy differences in column 1. Columns 2 and 4 gives $\Delta\Delta G$ values using the succinic acid system as a reference. For comparison, ΔH values determined directly by reaction calorimetry[23] are also included in Table IV (column 7). It should be noted that these values apply to the process diacid(s) $\rightleftarrows$ anh(s) + H_2O (eq 1) and therefore are not strictly comparable to our values. However, the trend toward increasing anhydride stability with respect to the diacid as the number of methyl groups increases is the same as for the experimental ΔG values, especially if one corrects for the heat of solution of the diacids (column 8). This correction can be made easily for the diacids using published data[23] but unfortunately not for the corresponding anhydrides.

The calculated $\Delta\Delta G$ values (Table IV, column 4) differ appreciably from the experimental ones (column 2), especially for tetramethylsuccinic acid, the key compound in the series. In fact, the naive calculations based on nonbonded group interactions predict a *decreased* tendency for tetramethylsuccinic to cyclize, as compared to the other methylsuccinic acids studied.

If we examine the assumption on which these calculations are based, the gauche CH_3–CH_3 interaction, 0.8 kcal/mol, taken as the value for the interaction between the methyl groups in gauche butane, may not be the best choice for all compounds studied. In gauche butane, some of the steric strain of the ideal gauche arrangement has been relieved by changes in the dihedral angles around the C–C bonds (cited[24] to be between 65 and 70° instead of 60°). It is not to be expected that the value for the CH_3–CH_3 interaction in gauche butane shall be directly applicable to a molecule like tetramethylsuccinic acid,[25] in which (assuming that CH_3–CH_3, CH_3–COOH, and COOH–COOH interactions are identical) the dihedral angle necessarily must be 60°. Inspection of models shows that the relevant nonbonded H–H distance between the methyl groups in real gauche butane is 2.00 Å, but only 1.85 Å in an ideal gauche conformation. Using Hendrickson's "soft" function for the H–H potential[24] this change in distance corresponds to an increase in the H–H interaction from 0.8 to 1.7 kcal/mol.

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(21) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 23 ff.

(23) J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *J. Amer. Chem. Soc.*, **64**, 1747 (1942).

(24) J. B. Hendrickson, *ibid.*, **89**, 7036, 7043 (1967).

(25) Thermochemical data for tetramethylpentanes (S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969), Table II) indicate that such highly substituted hydrocarbons do indeed possess stronger nonbonded interactions than the usual gauche correction, 0.8 kcal/mol, allows for. Also, electron-diffraction data for hexamethylethane (S. H. Bauer and J. Y. Beach, *J. Amer. Chem. Soc.*, **64**, 1142 (1942)) suggest that this molecule is highly strained in that the central C–C bond is reported to be abnormally long, 1.58 ± 0.03 Å.

A second set of calculations based on this value for the "hard" interactions, *e.g.*, those in conformations in which the dihedral angle must be 60°, between CH_3 and CH_3, CH_3 and COOH, and COOH and COOH, but otherwise the same parameters as in the first set, was then performed with the results shown in Table IV, columns 5 and 6. The comparison with experimental values now is much better and it is especially noteworthy that the strong stabilization of the anhydride in the tetramethylsuccinic acid system is indicated also in the calculated values. Thus, it appears that Allinger's and Zalkow's treatment of the *gem*-dialkyl effect is applicable to five-membered ring systems but additional parameters are required for the highly alkylated systems, in which gauche interactions necessarily must be stronger.[26]

Calculations based on these principles cannot at present be performed for the other alkylated succinic acids of Table I due to the lack of reliable parameters for interactions between alkyl groups other than methyl. However, it should be noted that an increase in alkyl group size leads to an increase in the stability of the anhydride, as would be expected.

For the remaining systems it is evident that similar interpretations can be applied; *i.e.*, the main factor determining the position of the equilibrium is the existence of severe nonbonded interactions in the acyclic molecule which can be effectively relieved in the cyclic form. As an example, X-ray crystallographic studies on maleic acid[27] and maleic anhydride[28] indicate that the C–C–H angle is appreciably larger in the anhydride (128.5°) than in the acid (118°), indicating that the alkyl–alkyl interaction must be smaller in the anhydride than in the diacid. In combination with the fact that the COOH–COOH interaction in the diacid disappears on ring closure, the high stability of the dialkylmaleic anhydrides relative to the corresponding diacids is understandable. The same type of reasoning applies to the alicyclic systems **17–20** and 3,6-dialkyl substituted phthalic (**21, 22**) acids.

As mentioned in the introductory statement, aryl hydrogen dicarboxylates are hydrolyzed *via* intramolecular carboxylate ion attack upon the ester function with formation of an anhydride.[7–10] It has previously been suggested[29] that there should be a linear correlation between the rate constant for this cyclization process and the ΔpK of the corresponding diacid, since the ΔpK of a diacid at least in cases where it is high should be largely determined by the existence of another acyclic–cyclic form equilibrium, namely the formation of an intramolecular hydrogen bond in the monoanion.[30] However, although such correlations do exist in a limited series of diacids,[29] it is evident that they cannot possibly hold for all kinds of diacids, not even within series of compounds of a single type of acid.[31] The reason for this is now obvious.[32] In order for a diacid to possess a very high ΔpK value, its geometry should allow for formation of an internal hydrogen bond of about 2.40 Å with as little change in molecular strain as possible in going from the open-chain to the cyclic form. Typically, this situation prevails in a diacid like 1-cyclobutene-1,2-dicarboxylic acid, a diacid which does not given an anhydride.[33] If, on the other hand, the hydrogen bond in the monoanion can be formed only at the expense of a large increase in strain, the ΔpK of the diacid will be normal. The carboxyl groups will then be so close to each other that the planes that they define must be almost parallel and perpendicular to the planes of the CO–C–C–CO bonds. This situation exists, for example, in **17–20** acids which form anhydrides spontaneously in aqueous medium. Thus, an important requirement for fast cyclization apart from the existence of steric strain in the diacid appears to be that the carboxyl groups be as closely situated as possible.[34a]

On the other hand, log–log correlations between rate constants for processes catalyzed intramolecularly by carboxylate or carboxyl groups and K values of eq 1, such as those referred to above, should have great value as diagnostic tools for finding very fast cases of intramolecular catalysis. In this connection, it is gratifying to see that the rate constant for hydrolysis of the half-amide of dimethylmaleic acid is reported to be exceedingly large[34b] due to intramolecular catalysis.

Experimental Section

The following diacids and the corresponding anhydrides were prepared and purified according to well-established literature procedures: **5**,[35] **6**,[36] **7**[37] (resolution, see below), **8**,[37] **9**,[36] **10**,[36] **11**,[36] **18**,[38] **19**,[39] **20**,[40] **21**,[41] **23**,[42] **24**,[43] **25**,[44] **26**,[45] **27**,[46] and **28**.[47] Two compounds, **16** and **17**, were kindly supplied by Dr. L. L. McCoy[48] (University of Missouri, Kansas City, Mo.). Dioxane (Merck analytical grade) was purified by twofold distillation over sodium.

Resolution of the Low-Melting Form of 2,3-Diethyl-2,3-dimethylsuccinic Acid. Low-melting 2,3-diethyl-2,3-dimethylsuccinic acid[37]

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[26] One factor which has been neglected in the treatment above is the possible role of the solvent water on equilibrium 1 for the structurally flexible diacids. There is no doubt that the entropy effect caused by changes in the water structure around the alkyl groups would favor the form in which the alkyl groups are closer to each other. However, the magnitude of this effect is not known, and we therefore prefer to use the isolated molecule approach.

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(10 g) was dissolved in 80 ml of methanol. Brucine (containing $2H_2O$, 21.3 g) was added and the solution was left overnight, whereby a brucine salt had crystallized. The salt was recrystallized twice from methanol and the diacid liberated by treatment with dilute hydrochloric acid, $[\alpha]_{578}^{20}$ +37.6° (*c* 0.1 ethanol). Two further recrystallizations of the brucine salt from methanol gave diacid samples with $[\alpha]_{578}^{20}$ 39.5 and 38.7°, respectively, showing that the resolution was complete.

Diisopropylmaleic Anhydride (15). *meso*-2,3-Diisopropylsuccinic acid[36] (5 g) was dissolved in acetyl chloride (10 ml) and allowed to stand overnight. Excess acetyl chloride was evaporated and the anhydride was purified by distillation. Bromine (3 g) was then added slowly to the anhydride (3.7 g) at 120°. When the bromine color had disappeared the reaction mixture was dissolved in aqueous sodium hydroxide. The solution was acidified with hydrochloric acid and the resulting precipitate was filtered off and recrystallized from ethanol-water: mp 123–124°; nmr (δ in CCl_4) 3.01 (1, heptuplet, $CH(CH_3)_2$, J = 7.0 Hz), 1.28 (6, d, $CH(CH_3)_2$, J = 7.0 Hz); ir (KBr) 1830, 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.74; O, 26.3. Found: C, 66.0; H, 7.70; O, 26.2.

3,6-Diethylphthalic Anhydride (22). 2,5-Diethylfuran[49] (10 g) was added to a solution of maleic anhydride (7.9 g) in ether (10 ml). After stirring for 4 hr, the mixture was cooled to −20° and the crystals were filtered off. The product (which slowly reverts to starting materials on standing at room temperature) was immediately transferred to a beaker containing 90% sulfuric acid (150 ml) cooled to −5°. The solution was stirred for 30 min at −5 to 0° and then poured onto ice. The precipitate was filtered and dissolved in aqueous sodium hydroxide (6 g in 120 ml of water). Addition of acetic acid (10 ml) precipitated some oily impurities which were filtered off. Final acidification of the filtrate gave the anhydride (12% yield) which was purified by sublimation and recrystallization from hexane, mp 124–125° (lit.[50] 122–125°).

Kinetic Measurements. Rate constants for the solvolysis of anhydrides (k_{-1}) were determined by the pH-stat method used previously.[51] At temperatures ≤30° the Radiometer G 202 B glass electrode was employed, whereas the high-temperature electrode G 202 CH was used at 60°. Rate constants for attaining equilibrium (eq 1) from the diacid side ($k_1 + k_{-1}$) were determined spectrophotometrically (Cary 15 spectrophotometer, with the cuvette housing thermostated by circulating water from an external thermostat). The reaction was followed by a suitable wavelength on a solution prepared by rapid addition of a solution of the salt of the diacid to 0.1 *M* hydrochloric acid.

For systems with difficultly soluble anhydrides (**10** and **11**) the following method was used. An accurately weighed amount (about 10 mg) of the diacid was dissolved in an acetic acid–acetate (0.1 *M*) buffer solution (250 ml) and the solution was kept in a well-stoppered flask at 60.0° for several weeks for equilibration. After this period 100 ml of the solution was withdrawn by a pipet and quickly cooled to about +5° in an ice bath. The solution was neutralized by sodium carbonate (to a pH of 8) and then it was extracted by ether (two 20-ml portions). The amount of anhydride in the ether solution was then determined by glc (internal standard, 2 m × 0.3 mm 10% DC-30 column).

Equilibration of Succinic Anhydrides. Solutions of the anhydrides (20 mg in 1 ml of dioxane) were filled into ampoules and the ampoules were equilibrated in an oven for 2 weeks. The temperature of the oven[52] was kept at 170.0 ± 0.2°. The equilibrium mixture of anhydrides was analyzed directly on a 2 m × 0.3 mm 5% SE-30 on Chromosorb P column. No equilibration took place at the temperatures used (less than 100° on both injector and column) during these analyses.

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Kinetics of Sulfur–Sulfur Bond Cleavage in Methylated Methyl Disulfide by Nuclear Magnetic Resonance

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Abstract: The sulfenyl compound $(CH_3)_2S^+SCH_3BF_4^-$ reacts rapidly and reversibly with both methyl sulfide and methyl disulfide by cleavage of the S–S bond. The rates and activation parameters for these reactions in CH_3NO_2 have been determined by nmr techniques. The position of equilibrium in the reaction $(CH_3)_2S^+SCH_3 + CH_3SSCH_3 \rightleftarrows (CH_3)_2S + CH_3S^+(SCH_3)_2$ has been found to lie far to the left with $K = k_2/k_3 = 7.4 \times 10^{-4}$. Equilibrium is rapidly established ($k_2 = 1.06 \times 10^4$ M^{-1} sec^{-1} and $k_3 = 1.4 \times 10^7$ M^{-1} sec^{-1}) and is responsible for the pronounced catalytic effect observed for $(CH_3)_2S^+SCH_3BF_4^-$ in the interchange of organic disulfides. The enthalpy and entropy of the disulfide–salt equilibrium and the rates of cleavage of $CH_3S^+(SCH_3)_2$ with methyl sulfide and methyl disulfide have been determined. The results indicate that the reactivity of the S–S bond toward nucleophilic attack is enhanced by a factor in excess of 10^6 by methylation and S-methylation at sulfur.

The ease with which the S–S bond of dimethylthiomethylsulfonium salts **1** are cleaved by nucleophilic reagents was first documented by Helmkamp and coworkers in their work on the preparation of **1** and its addition to alkenes and alkynes.[2] These reactions and the related studies of Meerwein[3] indicate that compounds of type **1** may be regarded as sulfenyl derivatives and a potential source of alkylsulfenyl ions,

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