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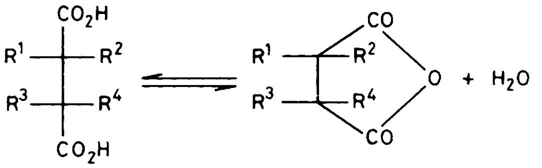
Quantitative Evaluation of the *gem*-Dimethyl Effect on the Succinic Acid $\rightleftharpoons$ Anhydride Equilibrium. Conformations of the Acids and Anhydrides by Empirical Force Field Calculations

Petko M. Ivanov and Ivan G. Pojarlieff *
Institute of Organic Chemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

In order to evaluate quantitatively the *gem*-dimethyl effect on the succinic acid $\rightleftharpoons$ anhydride equilibrium, the conformations of succinic acid and its 2-methyl-, racemic 2,3-dimethyl-, tetramethyl-, and racemic 2,3-di-t-butyl-derivatives have been calculated by means of Allinger's 1977 empirical force field. An extension of the field was developed to calculate the conformations of the respective anhydrides. The calculated preferred conformations compare well with existing experimental data. No low-energy hydrogen-bonded minima for the acids were obtained. Increased substitution in the acids caused conformational changes facilitating ring closure: smaller torsion angles of conformations with *gauche* carboxy groups, favourable bond length and angle deformations, and a reduced number of preferred conformations. In the anhydrides, substitution leads to a twist around the C(2)–C(3) bond of the ring. The $\Delta\Delta H$ values estimated for the diacid $\rightleftharpoons$ anhydride equilibria agree well with experimental data in water indicating that the main cause of the observed *gem*-dimethyl effect in the anhydrides is relief of intramolecular strain arising on substitution in the acids.

In recent years considerable progress has been made in the understanding of the nature of the *gem*-dimethyl effect.[1] However, little success has been achieved in its quantitative prediction. For systems not involving special strain effects, as are encountered in small rings or ground-state strained compounds such as lactones with a trimethyl lock,[2-4] Allinger and Zalkow [5] outlined a simple quantitative approach. This consisted in taking into account the *gauche* interactions in the open and ring compounds and the assumption of a small constant decrease of entropy for each branch in the open chains. The free energies of the formal equilibria of hexane $\rightleftharpoons$ cyclohexane cyclizations were reasonably well predicted, which at the same time indicated the origin of the effect. In the general case of cyclization to heterocyclic compounds the approach never had any real success because the *gauche* interactions in the open-chain compounds are usually unknown, non-additive, and change from compound to compound. Thus Eberson and Welinder [6] could bring the predictions and experimental results in line for the succinic acid $\rightleftharpoons$ anhydride equilibria only by assuming, somewhat arbitrarily, two kinds of methyl-methyl interactions: soft, 3.3 kJ mol^{-1}, and hard, 7.1 kJ mol^{-1}, the latter in the persubstituted compounds. Another early attempt was to seek linear free-energy correlations with Taft's steric constants; Bruice and Bradbury [7] thus correlated the effect of substituents in position 3 in the solvolysis of mono-*p*-bromophenyl glutarates. To our knowledge this could be done for one further series.[8] A much wider scope of reaction series could be correlated linearly, as shown by Blagoeva *et al.*,[9] if instead of steric constants, the steric strains between appropriate fragments of the open-chain molecules are used, which can be assessed from the enthalpies of formation of homomorphic hydrocarbons by means of an additive scheme. In some cases the approach failed and this was attributed to unrelated strains introduced by the substituents in the ring forms. The best solution is of course to estimate the strains both in the open and in the ring forms and this has become possible largely by means of molecular mechanics.[4,10a] Recently this was further demonstrated by DeTar and Luthra [10b] who linearly correlated the free energies of the rates of ring closure of branched ω-bromoalkylamines with the steric-energy differences between the open chains and models of the transition state, estimated with an extension of Schleyer's force field.



(I)

Acid	R^1	R^2	R^3	R^4	Anhydride
(1)	H	H	H	H	(6′)
(2)	Me	H	H	H	(7′)
(3)	Me	H	H	Me	(8′)
(4)	Me	Me	Me	Me	(9′)
(5)	Bu^t	H	H	Bu^t	(10′)

In order to assess the more general applicability of empirical force field calculations to the quantitative evaluation of the *gem*-dimethyl effect we used the same strategy in an attempt to estimate the effect of alkyl substituents on the succinic acid $\rightleftharpoons$ anhydride equilibrium. This has been studied in water by Eberson and Welinder [6] who found that the equilibrium constants vary over a range of 10^6. As regards the computations, an equilibrium series has the advantage that no assumptions on the geometry of the transition state have to be made. This reaction series has been correlated by the approach used by Blagoeva *et al.*[9] and molecular mechanics were anticipated to give some insight into the nature of strain release accompanying the ring closure of substituted succinic acids.

The conformations of the succinic acids and their anhydrides will be discussed briefly because of continued interest and some controversies in the recent literature. The MM2 scheme in its original version [11] was adopted for the conformational calculations of the open-chain compounds. For the treatment of the succinic anhydrides an extension of Allinger's 1977 force field was developed (see Appendix).

Compounds (1)—(5) and (6′)—(10′) and equilibria (I) were considered.

Results and Discussion

Conformations of Succinic Acids.—The designation of the conformations of the substituted succinic acids are shown on Figure 1.

Some selected data from the empirical force field (EFF)

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Table 1. Torsion angles and relative energies of the lowest energy conformations of substituted succinic acids

Conformation [a]	Torsion angles [a] (°) C(1)–C(2)–C(3)–C(4)	O(6)–C(1)–C(2)–C(3)	C(2)–C(3)–C(4)–O(5)	ΔE^{strain} [b]/ kJ mol^{-1}	Number [c] of conformers	Population [d] Lowest minimum	Total
Succinic acid (1), $E_g^{strain} = -6.48$ kJ mol^{-1}							
sc	65.4	9.0	7.9	0.63	5	0.42	0.61
ap	180.0	−1.3	−0.3	0.00	5	0.27	0.39
Methylsuccinic acid (2), $E_g^{strain} = -4.32$ kJ mol^{-1}							
+*sc*	62.7	13.6	8.7	0.00	9	0.28	0.49
ap	169.7	9.4	−12.4	3.01	5	0.08	0.21
−*sc*	−56.1	131.0	3.0	3.59	11	0.07	0.30
racemic 2,3-Dimethylsuccinic acid (3), $E_g^{strain} = 2.80$ kJ mol^{-1}							
+*sc*	56.6	19.3	19.7	0.00	5	0.21	0.45
ap	174.8	120.8	120.9	1.04	6	0.14	0.33
−*sc*	−60.9	−0.6	−0.2	3.68	7	0.05	0.22
Tetramethylsuccinic acid (4), $E_g^{strain} = 29.09$ kJ mol^{-1}							
sc	55.2	91.0	91.0	0.42	6	0.17	0.77
ap	156.1	−109.3	−109.3	0.00	4	0.10	0.23
racemic 2,3-Di-t-butylsuccinic acid (5), $E_g^{strain} = 53.46$ kJ mol^{-1}							
−*sc*	−26.6	83.0	83.0	0.00	3	0.56	1.00

[a] Designations are shown on Figure 1. [b] $\Delta E_g^{strain} = E_l^{strain} - E_g^{strain}$ where l and g refer to the strain energies of the local and global minima, respectively. [c] Number of conformations of the same type with $\Delta E^{strain} < 13$ kJ mol^{-1}. [d] At 300 K.

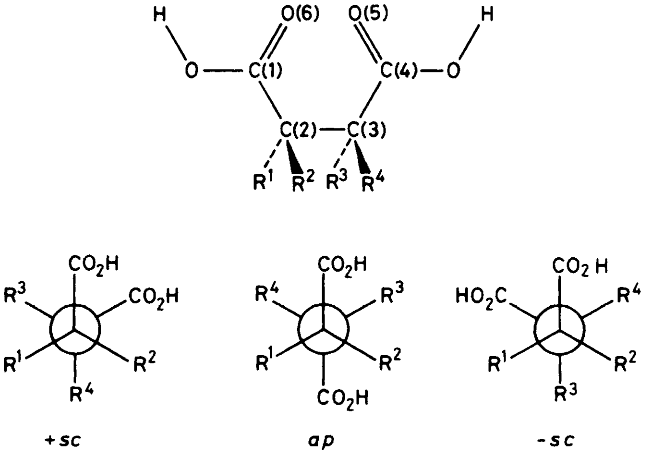

Figure 1. Designation of conformations and numbering scheme for definition of torsion angles

calculations are presented in Table 1. Data on the torsion angles, energies and dipole moments of all local minima up to 13 kJ above the global one are available as Supplementary Publication No. SUP 23763 (5 pp.).*

The calculated data refer to the un-ionized acids.

For the lowest members of the series, nine local energy minima with $\Delta E^{strain} > 13$ kJ mol^{-1} were found for succinic acid and 24 for methylsuccinic acid. The conformations with *gauche* carboxy groups are preferred, in agreement with recent n.m.r. results by Nunes *et al.*[12] and Retey *et al.*[13] who corrected previous erroneous assignments of vicinal couplings.[14] For a solution of succinic acid in water, 83% of the *sc* conformation is estimated [12] against 61% from the EFF calculations, and for methylsuccinic acid the figures for the (+)-*sc* conformation are 69 and 49%, respectively. The latter n.m.r. result [13] was obtained by Snyder's method, which neglects the participation of the (−)-*sc* conformation with the three groups *gauche* to each other. This conformation is calculated, however, to be even more favoured than the *ap* conformation (Table 1). The EFF calculations support the interpretation [13] of a negative Cotton effect at *ca.* 207 nm observed with (*S*)-methylsuccinic acid at low pH as being due to eclipsed C=O and C(2)–C(3) bonds. Such conformations comprise 58% of the calculated populations while the alternative ' chiral ' conformations with eclipsed C=O and C–CH$_3$ bonds amount to only 22%. No conformations with OH ⋯ O=C contacts that would be suitable for hydrogen bonding were calculated. This agrees with the small Δ*pK* values upon ionization [15] and the similarity of the *J* values observed for the diesters of (1) and (2).[14] The physical reasons for the preference of the synclinal arrangement of the carboxy groups in these compounds are not clear.[13] Extra stabilization of the synclinal arrangement as the more polar form in water appears unlikely as succinic acid showed the same *J* values in less polar solvents.[12] In order to obtain some information concerning the reasons for the observed preferences, a detailed analysis of the intramolecular interactions in the most populated local minima for the (+)-*sc*, *ap*, and (−)-*sc* conformations was attempted. It is helpful at this stage to introduce group interactions: E_{gem}^{23}, between substituents at C(2) and C(3), E_{vic}^{g}, *gauche*-vicinal interactions between the substituents at C(2) and the substituents at C(3), and E_{vic}^{t}, the respective *trans*-vicinal interactions. The interaction energy between group A and group B is defined to include not only the non-bonded energy term but also the electrostatic and torsional contributions from bonds adjacent to C(2)–C(3). The data for compounds (1)—(4) are shown in Table 2. For succinic acid (1), the three types of sums of group interactions are well balanced with each other in the two local minima, similar to the small difference in the total energies calculated for the two conformations (Table 1). With (2), E_{gem}^{23} and E_{vic}^{t} only slightly change with conformation and the energy separation between the

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Table 2. Total sums of group interactions in the most populated local minima of methyl-substituted succinic acids (kJ mol^{-1})

Compound	(1)		(2)			(3)			(4)	
Conformation [a]	*sc*	*ap*	+*sc*	*ap*	−*sc*	+*sc*	*ap*	−*sc*	*sc*	*ap*
$E_{gem}^2 + E_{gem}^3$	2.5	2.4	4.6	4.8	5.4	8.0	9.8	9.9	22.5	21.1
E_{vic}^g	4.3	4.4	4.4	6.4	6.6	6.4	7.5	9.9	16.6	16.7
E_{vic}^t	−1.1	−1.0	−1.7	−1.3	−1.3	−2.2	−0.9	−0.7	−2.7	−0.8

[a] Designations are shown in Figure 1.

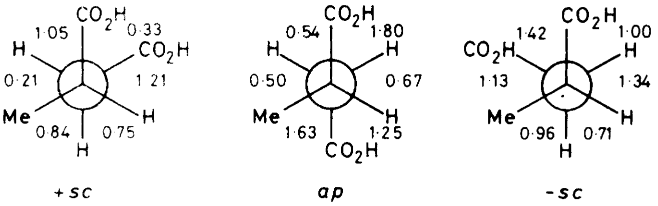
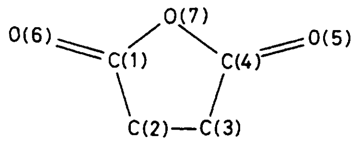


Figure 2. Group-interaction energies (kJ mol^{-1}) for the most populated local minima of methylsuccinic acid

three local minima originates from the differences in the sums of the *gauche*-vicinal group interactions which increase from 4.35 kJ mol^{-1} in the (+)-*sc* conformation to 6.35 and 6.56 kJ mol^{-1} for and *ap*- and (−)-*sc* conformations. As can be seen from Figure 2, there is no additivity in the *gauche* group interactions, *e.g.*, the CO_2H–CO_2H interaction changes from 0.33 in the (+)-*sc* to 1.42 kJ in the (−)-*sc* conformation; CO_2H–H, CH_3–H, and even H–H interactions in some cases are comparable in magnitude with CO_2H–CO_2H and CO_2H–CH_3. This analysis rules out any speculations based on additive *gauche* group interactions in conformationally mobile systems.[6] Figure 2 illustrates how even for a simple molecule, such as methylsuccinic acid, the group interactions depend on their disposition with respect to other portions of the molecule as well as on their mutual orientation. Thus the difference in CO_2H–CO_2H in (+)-*sc* and (−)-*sc* of (2) is due to the electrostatic contributions changing from 0.21 in the (+)-*sc* to 1.55 kJ mol^{-1} in the (−)-*sc* conformation as a result of the different orientations of the bond dipole moments.

The introduction of a second methyl group in racemic 2,3-dimethylsuccinic acid (3) only slightly changes the calculated conformational equilibrium. The (+)-*sc* conformation with *gauche* carboxy groups and *anti* hydrogen atoms is the most populated, in agreement with the ^{1}H n.m.r. study of Paolillo and Temusi[16] (60% in water and 48% in acetone recalculated with the more realistic J^t and J^g values of 2 and 12 Hz). The (−)-*sc* conformation, which has been favoured from general considerations[17] and recent interpretation of ^{13}C chemical shifts,[18] is, in contrast, calculated as being the least populated. As indicated by the values in Table 2 this is due to an unfavourable change in all the separate energy terms. The substitution with four methyl groups in (4) enhances the population of conformations with *gauche* carboxy groups (77%). The energy difference between the lowest energy local minima for the *sc* and *ap* conformations is negligibly small, only 0.42 kJ mol^{-1}. Almost 90% of the calculated population pertains to seven local minima within the energy limits of 3 kJ mol^{-1}. Four of them are with *gauche* carboxy groups almost parallel to each other and perpendicular to the planes of the OC–C–C–CO bonds. The *gauche* CO_2H–CO_2H torsion angle ranges from 32.7 to 55.2° while in (1) and (2) the average is around 60°. The limited number of orientations for the carboxy groups result from the increased geminal and vicinal group interactions (Table 2) with respect to the compounds considered previously. For the racemic 2,3-di-t-butylsuccinic acid (5) even more locked structures were calculated: only three local minima with *trans* Bu^t groups and the CO_2H–CO_2H torsion angle ranging from −26.6 to −41.2°. In all cases the carboxy groups are almost perpendicular to the planes of the OC–C–C–CO bonds.

Table 3. Observed (reference 22) and calculated geometry parameters in tetramethylsuccinic anhydride (9)



Bond	Observed [a]	Calculated
C(1)–C(7)	1.396(4) Å	1.397 Å
C(1)–C(2)	1.524(6) Å	1.522 Å
C(2)–C(3)	1.567(15) Å	1.544 Å
C(2)–Me	1.537 Å	1.537 and 1.542 Å
C(1)–O(6)	1.192 Å	1.199 Å
O(7)–C(1)–C(2)	109.2(4)°	109.8°
C(1)–C(2)–C(3)	100.9(4)°	102.0°
C(1)–O(7)–C(4)	109.6(5)°	109.2°
O(7)–C(1)–O(6)	121.0(4)°	119.3°
Me–C(2)–Me	109.1(8)°	108.8°
C(4)–O(7)–C(1)–C(2)	10.8(6)°	9.0°
O(7)–C(1)–C(2)–C(3)	26.5(13)°	22.5°
C(1)–C(2)–C(3)–C(4)	30.4(16)°	25.8°

The standard deviations (in parentheses) refer to the last digit.

It is worth noting the excellent correlation between the calculated (averaged over the populations of the individual local minima) and experimental dipole moments[19] for succinic acid and the racemic di-t-butyl derivative: 2.06 and 2.53 D (calculated) *versus* 2.08 and 2.53 D (experimentally), respectively. There are also experimental data[19] for several tetra-alkyl-substituted succinic acids varying between 2.39 and 2.60 D. Our estimate for the averaged dipole moment of tetramethylsuccinic acid is 2.40 D.

There is no firm experimental indication for the existence of intramolecular hydrogen bonds in the free acids in solution except for Eberson's i.r. data for (5) in methanol.[20] Nevertheless, it is surprising that no contact suitable for hydrogen bonding was calculated in all cases. Our treatment was based on the assumption of a synperiplanar O=C–O–H conformation, which is the commonly observed case. The antiperiplanar O=C–O–H conformation is, however, found[21] when a carboxylic acid forms an intramolecular OH · · · O bond. We studied this possibility by repeating the calculations for the synclinal conformations of compounds (1)—(5) with all combinations of synperiplanar and antiperiplanar O=C–OH fragments. These yielded only a limited number of high, energy hydrogen-bonded minima with CO · · · HO contacts of 2.12—2.45 Å. If these conformations exist in solution they

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Table 4. Torsion angles in substituted succinic anhydrides (degrees), atom numbering as in Table 3

	Compound				
Bond	(6)	(7)	(8)	(9)	(10)
O(5)–C(4)–O(7)–C(1)	−179.6	−175.6	−175.1	−173.9	−176.1
C(4)–O(7)–C(1)–C(2)	0.8	5.9	6.5	9.0	6.1
O(7)–C(1)–C(2)–C(3)	−2.0	−14.6	−16.3	−22.5	−15.3
C(1)–C(2)–C(3)–C(4)	2.3	16.8	18.9	25.8	17.5

Table 5. Calculated relative enthalpy differences (kJ mol^{-1}) and equilibrium constants for the reaction $HO_2C{\cdot}CR^1R^2{\cdot}CR^3R^4{\cdot}CO_2H \rightleftharpoons \overline{O{\cdot}CO{\cdot}CR^1R^2{\cdot}CR^3R^4{\cdot}CO}$

	Equilibrium				
Parameter	(1) $\rightleftharpoons$ (6)	(2) $\rightleftharpoons$ (7)	(3) $\rightleftharpoons$ (8)	(4) $\rightleftharpoons$ (9)	(5) $\rightleftharpoons$ (10)
$-\Delta\Delta H$	0.00	5.35	16.01	30.26	37.03
$K_{calc.}$[a]	1	6.6	2.8×10^2	4.2×10^4	4.6×10^5
$K_{obs.}$[b]	1	6.0	0.36×10^2	2.4×10^4	8.6×10^5

[a] At 340 K. [b] From ref. 6.

are probably stabilized by solute–solute or solute–solvent interactions. Alternatively, this result could originate from the inadequacy of the empirical force field used to account for intramolecular hydrogen bond interactions.

Conformations of Succinic Anhydrides.—Experimental data on the conformations of the anhydrides considered in this paper are available only for succinic anhydride (6) and tetramethylsuccinic anhydride (9). The latter was found [22] to be considerably twisted, according to electron diffraction in the gaseous phase, while (6) is essentially planar both in the crystalline [23] and in the gaseous state.[24] Our extention of Allinger's MM2 empirical force field reproduced quite satisfactorily the geometry of tetramethylsuccinic anhydride, as demonstrated in Table 3. In a discussion of the c.d. spectra of mono- and di-substituted succinic anhydrides, Sjöberg and Obenius [25] have recently assumed that methyl- and racemic dimethylsuccinic anhydrides, (7) and (8), are twisted around the C(2)–C(3) bond. As shown in Table 4, the calculated geometries fully support this hypothesis.

Estimation of the gem-*Dimethyl Effect on the Succinic Acid* $\rightleftharpoons$ *Anhydride Equilibrium.*—As discussed above, increased substitution in the acids creates better conditions for ring closure: a smaller CO_2H–CO_2H torsion angle, CO_2H groups almost perpendicular to the planes of the CO–C–C–CO bonds, and increased repulsive vicinal and geminal interactions producing a limited number of locked conformations with *gauche* CO_2H groups. The shortest O=C···O contacts, 2.91—2.95 Å, were calculated for compounds (4) and (5). For succinic acid (1) the shortest one is 3.16 Å. The increase in substitution is also accompanied by a lengthening of the C(2)–C(3) and C(1)–C(2) bonds from 1.537 and 1.519 Å in (1) to 1.567 and 1.537 Å, respectively, in tetramethylsuccinic acid (4), and a corresponding diminution of the adjacent valence angle C(1)–C(2)–C(3) from 113.4 to 110.0°.

In order to evaluate the changes in the enthalpies of the acid $\rightleftharpoons$ anhydride equilibria upon substitution the following procedure was used. In as much as our extension of Allinger's 1977 force field (Appendix) is not calibrated to calculate heats of formation of dicarboxylic acid anhydrides, we were not able to estimate the enthalpy changes in the anhydride series, (6)—(10), and hence of the separate equilibria. Using double differences of the calculated steric energies, SE, however, we can calculate the variation of the enthalpy difference for acid–anhydride with substitution with respect to the enthalpy difference for succinic acid–succinic anhydride being taken as zero, equation (1).

$$\Delta\Delta H = \Delta H^{nm} - \Delta H^{(6)(1)} = (SE_{anhydride}{}^{n} - SE_{acid}{}^{m}) - (SE^{(6)} - SE^{(1)}) \quad (1)$$

Relationship (1) is valid because the various unknown but constant contributions are cancelled in the double substraction. The same results are obtained if the strain instead of the steric energies are used. The latter for the acids were corrected in two respects. The admixture of higher energy conformations was accounted for by calculating the enthalpy at 340 K (the experimental temperature [6]) as described in refs. 11*b* and 26. To these quantities corrections for the torsional flexibility (1.51 kJ mol^{-1} for one degree of torsional freedom [11*b*,26]) around the C(2)–C(3) bond in (3), (4), and (5) were added. In the case of (5) corrections for the torsional motions around the C–Bu^t bonds were also included. In this way the substituted diacids (2)—(5) were calculated to be of, respectively, 3.26, 11.83, 36.83, and 64.08 kJ mol^{-1} higher enthalpy than succinic acid.

The results obtained for the $\Delta\Delta H$ values and the calculated equilibrium constants ratios are presented in Table 5. Bearing in mind that steric effects of a reaction in water are considered, the predictions are unexpectedly good. With the only exception of (3), the $K_{calc.}$ values agree with the observed ones within a factor of 2. DeTar and Luthra [10*b*] have pointed out that such correlations will hold when other effects, *e.g.* polar and solvation, remain constant throughout the series and cancel out in the double differences. They obtained ΔΔSE values for ring-closure rates of substituted ω-bromoalkylamines proportional to the changes in the free energies of activation by a scaling factor depending on the model of the transition state. The common case of a linear free energy relationships is, however, a compensation effect of several factors, particularly for reactions in solution. The large effective molarities observed in ring-closure of heavily alkylated dicarboxylic acids have been discussed by Kirby [1] as possibly being enhanced by hydrophobic forces better accommodated by the more compact hydrocarbon part of the anhydride. The previous correlation of this reaction with steric-strain estimates [9] suggested, however, that this may not be important for tetramethylsuccinic acid (4).[1] The fact that the $\Delta\Delta H$ values, estimated here, not only correlate, but also agree in magnitude with the observed changes in the free energies of the diacid $\rightleftharpoons$ anhydride equilibria, prompts us to

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believe that these are correctly predicted by the procedure used and hence the main cause for the observed equilibrium shifts is relief in the anhydrides of intramolecular strain brought about by substitution in the diacids. As noted already by Eberson and Welinder,[6] this relief of strain is not *a priori* evident. Why should, for example, tetramethylsuccinic anhydride (9) with two eclipsed Me-Me interactions be so much more stable with respect to the parent acid (4) than is succinic anhydride with respect to (1)? The H atoms in succinic anhydride are almost eclipsed (2.9° torsion angle) and their interactions amount to 7.1 kJ mol^{-1} including the respective torsional terms. The same energy, 7.5 kJ mol^{-1}, is calculated for the Me—Me interactions in (9) as a result of the greater torsion angle, 31.7°, and an opening of the C(2)–C(3)–Me angles to 114—115 °C. On the other hand, the vicinal interactions (Table 2) are >10 kJ mol^{-1} more unfavourable in tetramethylsuccinic acid than in (1). Additional stabilization, *ca.* 20% of the total, comes from favourable valence bond and angle deformations. The previous correlation [9] of the succinic acid $\rightleftharpoons$ anhydride equilibria is not directly comparable with the present results as it involved a linear relationship between the free energies and the strains arising between one of the carboxy groups and the rest of the diacid molecule, estimated from the enthalpies of formation of model hydrocarbons.

Appendix

Although the carboxylic acid portion of the empirical force field adopted here [11] is not so well developed as its hydrocarbon part, it was considered that the error involved is hardly likely to exceed that originating from estimation of the intramolecular electrostatic interactions. No explicit account of the hydrogen bond interactions is included in the force field and the solving of this problem is still at a preliminary stage in the framework of full-relaxation molecular mechanics schemes. In order to avoid partly the deficiencies of our calculational scheme we carried out a parallel treatment with the potential-energy functions of Momany *et al.*[27] which are calibrated to account for intramolecular hydrogen-bond type interactions (see ref. 28). The local minima obtained from the first stage of minimization with the potential functions of Momany–Scheraga (only torsion angles as variables) served as starting conformations for the MM2 calculations. This allowed a more thorough examination of the conformational space available for the molecules, at less expense. The electrostatic interactions were estimated in the point charge (Momany–Scheraga) and the dipole (MM2) approximations, respectively. Partial atomic charges were estimated from CNDO/2 calculations and an 'effective' dielectric constant of 4.0 was used in the estimation of the electrostatic interactions.

In order to generate an extension of Allinger's 1977 force field suitable for cyclic dicarboxylic acid anhydrides, the following strategy was adopted. The hydrocarbon part of the force field was kept constant and only the new additional parameters necessary for considerations of the anhydrides were calibrated with respect to geometry (*X*-ray) data for appropriately selected compounds. The bond stretching and bond angle bending force constants were held fixed at the values incorporated in MM2,[11b] and for the only missing bending force constant for angle type 3–6–3 (for atom-type designation see ref. 11*b*) a value of 0.75 mdyn Å rad^{-2} was ascribed. Making the additional assumptions $V_3 = 0$ for 1–3–6–3, and $V_1 = V_3 = 0.0$ for 7–3–6–3, only nine parameters remained to be optimized: two minimum-energy bond lengths, l_0(3–6 and 3–7), four minimum-energy bond angles, θ_0(1–3–6, 1–3–7, 6–3–7, and 3–6–3) and the torsional parameters V_1 and V_2 for 1–3–6–3 and V_2 for 7–3–6–3. The set of geometry data used in the calibration comprises 21 values for valence bonds, 28 values for valence angles, and 28 values for torsional angles selected from *X*-ray data for succinic anhydride,[23,24] bicyclo[2.2.2]octene-2,3-*endo*-dicarboxylic anhydride,[29,30] and bicyclo[2.2.1]hept-5-ene-2,3-*exo*-dicarboxylic anhydride.[31] The following values for the optimized parameters were obtained: l_0(3–6) 1.375 Å, l_0(3–7) 1.195 Å, θ_0(3–6–3) 108.4°, θ_0(6–3–7) 117.5°, θ_0(1–3–6) 110.0°, θ_0(1–3–7) 129.4°, V_1(1–3–6–3) -13.79 kJ mol^{-1}, V_2(1–3–6–3) 16.7 kJ mol^{-1}, and V_2(7–3–6–3) 66.9 kJ mol^{-1}. A satisfactory reproduction of the *X*-ray geometries of bicyclo[2.2.1]hept-5-ene-2,3-*endo*-dicarboxylic anhydride,[31] *anti*-tricyclo[4.2.2.0]deca-3,9-diene-7,8-*endo*-dicarboxylic anhydride,[32] and cantharidine [33] was achieved. Although geometry data alone are not sufficient for a proper calibration of the extention of the 1977 MM2 force field, it is suitable forthe energy considerations in our case, which are based on a relative scale.

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