Attempted Synthesis of Esters of Tricarballylic Acid and 3,5-Dibromosalicylic Acid. Structure and Properties of Tricarballylic Acid, its Anhydrides and Some of their Derivatives, and an Investigation of the Reaction Pathways of Anhydride Formation by ^{1}H NMR Spectroscopy, MNDO and Molecular Mechanics Methods

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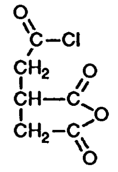
Reactions ordinarily leading to the formation of esters of carboxy acids afford, in the case of tricarballylic acid, the cyclic anhydride. A comparison of the experimental and simulated ^{1}H NMR spectra reveals that the product contains a five-membered ring structure. To explain the experimental findings, theoretical calculations were performed at the level of molecular mechanics and MNDO methods, in order to obtain information on the structure and thermodynamic stability of various substrate conformations and reaction products, as well as on the reaction pathways of anhydride formation. Theoretical predictions reveal that the formation of the five-membered ring structure is preferred in the case of tricarballylic acid anhydride.

To our knowledge there are few reports regarding the chemistry of tricarballylic acid. They concern mostly the complexation ability of the compound. Thus, Vijverberg *et al.*[1] studied gadolinium(III) complexes of the acid using NMR spectroscopic techniques. They examined the Gd^{III}-induced relaxation rate enhancements of the ^{13}C nuclei of the ligand. NMR spectroscopic studies have also been carried out by Salnikov *et al.* on complexes of various trivalent metal ions.[2] The formation constants for complexes of tricarballylic acid with several bivalent metal ions, as well as the effect of temperature and pH on their stability, have been examined by titrimetric and potentiometric methods.[3,4] Applying a radioactive tracer method, Lengyel studied the thermodynamic properties of europium–tricarballylate complexes.[5] The interaction of the uranyl ion with tricarballylic acid has also been investigated by means of IR and ^{13}C NMR spectroscopy.[6]

Parellel studies concerned the occurrence and biological activity of the tricarballylic acid molecule.[7] It has been established that the title compound is produced by rumen bacteria and that it influences ruminant tissue metabolism.[8,9]

Our preliminary studies revealed that specific esters of tricarballylic acid can bind stereospecifically to proteins. A family of salicylate derivatives has been developed by Klotz *et al*, which can react preferentially with certain protein amino acid residues.[10,11] Such a procedure could, therefore, be a means of protein modification. In order to obtain substrates for such a modification we attempted to synthesise some mono-, di- and tri-esters, formed with tricarballylic acid and 3,5-dibromosalicylic acid by classical methods. Unexpectedly, in all cases almost all of the tricarballylic acid was transformed into its anhydride.

The aim of the present study was to develop methods of synthesis of esters of tricarballylic acid and 3,5-dibromosalicylic acid, as well as to examine why, under experimental conditions, typical for classical esterification, the anhydride is formed preferentially. For this latter purpose we have employed ^{1}H NMR spectroscopy, molecular mechanics and the semi-empirical MNDO method.



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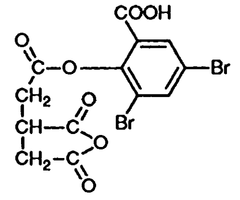

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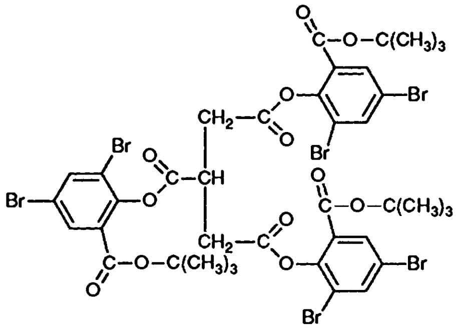

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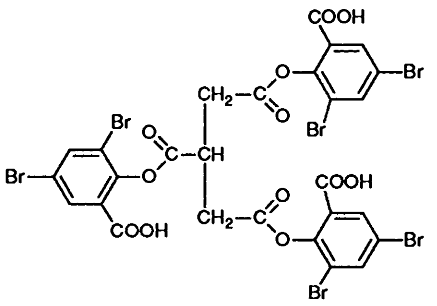

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Experimental

Synthesis.—All reagents and solvents were obtained from Aldrich and were used without further purification, except when drying was necessary.

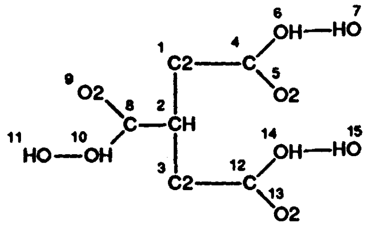

Fig. 1 Numeration and types of atoms in the tricarballylic acid molecule used in the molecular-mechanics calculations

Table 1 The charges of the tricarballylic acid molecule used in the molecular mechanics calculations

Atom[a]	Charge (q/e)	Atom[a]	Charge (q/e)	Atom[a]	Charge(q/e)
C2(1)	−0.026	O2(5)	−0.500	HO(7)	0.350
CH(2)	−0.026	OH(6)	−0.460	HO(11)	0.350
C2(3)	−0.026	O2(9)	−0.500	HO(15)	0.350
C(4)	0.636	OH(10)	−0.460		
C(8)	0.636	O2(13)	−0.500		
C(12)	0.636	OH(14)	−0.460		

[a] For numbering see Fig. 2.

M.p.s were determined on a hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer IR spectrophotometer (Model 283). ^{1}H NMR spectra were run on a General Electric QE-300 FT (Fourier Transform) instrument which was also used to obtain the simulated spectra. All ^{1}H NMR spectra were derived from [$^2H_6$]DMSO (dimethyl sulphoxide) solutions using a $(CH_3)_4Si$ (TMS) internal standard. Elemental analyses were performed by Atlantic Microlab Inc. in Georgia (USA).

Tricarballylic Acid 1,2-*Anhydride* (*Propane*-1,2,3-*tricarboxylic Acid* 1,2-*Anhydride*).—Tricarballylic acid (0.01 mol) was dissolved in acetic anhydride (0.02 mol). The mixture was stirred overnight at room temperature, then excess acetic anhydride was removed under reduced pressure and the product was recrystallised twice from ethyl acetate. The title compound had m.p. = 132–134 °C; ν_{max}/cm^{-1} 1750, 1774 and 1820 (C=O); δ_H [See Fig. 2(*b*)] 2.72–3.04 (4 H, m, 2 × CH_2), 3.41 (1 H, m, CH) (Found: C, 45.55; H, 3.9; O, 50.5. Calc. for $C_6H_6O_5$: C, 45.58; H, 3.83; O, 50.59%).

1-*Chloroformylpropane*-2,3-*dicarboxylic Anhydride* (**1**).—Tricarballylic acid (0.01 mol) was refluxed with $SOCl_2$ (1 mol) for 48 h. The $SOCl_2$ was evaporated and the residue distilled under reduced pressure. The fraction collected at b.p. 132–136 °C (1.5 mmHg) constituted the product which crystallised at room temperature, m.p. 98 °C; ν_{max}/cm^{-1} 1760 and 1835 (C=O); δ_H 2.73–3.12 (4 H, m, 2 × CH_2), 3.47 (1 H, m, CH) (Found: C, 40.85; H, 2.85; Cl, 20.0; O, 36.3. Calc. for $C_6H_5ClO_4$: C, 40.82; H, 2.85; Cl, 20.08; O, 36.25%).

1-(2,6-*Dibromo*-2-*carboxyphenoxy*)*formylpropane*-2,3-*dicarboxylic anhydride* (**2**).—3,5-Dibromosalicylic acid (0.01 mol) and *N*,*N*-dimethylaniline (DMA) (0.02 mol) were suspended in dry benzene. Tricarballylic anhydride monochloride (0.01 mol) was dissolved in dry benzene (10 cm^3) and the mixture was then added dropwise to the suspension. The resulting solution was stirred overnight at room temperature. The solvent was removed under reduced presure, the residue dissolved in ethyl acetate, and extracted three times with cold HCl (2 mol dm^{-3}) and several times with cold water. The extract was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product which was recrystallised twice from ethyl acetate; m.p. 212–214 °C; ν_{max}/cm^{-1} 1682, 1718, 1744 and 1770 (C=O); δ_H 2.77–3.26 (4 H, m, 2 × CH_2), 3.67 (1 H, m, CH), 8.05 (1 H, d, arom.) and 8.30 (1 H, d, arom) (Found: C, 35.85; H, 1.6; Br, 36.7; O, 25.75. Calc. for $C_{13}H_7Br_2O_7$: C, 35.89; H, 1.62; Br, 36.74; O, 25.75%).

Tris-[(2,4-*dibromo*-6-tert-*butoxycarbonyl*)*phenyl*]-*propane*-1,2,3-*tricarboxylate* (**3**).—Tricarballylic trichloride (0.01 mol) in dry tetrahydrofuran (THF) (10 cm^3) was added dropwise to three equiv. of *tert*-butyl 3,5-dibromosalicylate, which had previously been treated with a stoichiometric amount of NaH in THF.[12,13] The mixture was stirred for 5 h at room temperature and the solvent was then removed under reduced pressure. The residue was dissolved in diethyl ether and extracted several times with water. The extract was dried ($MgSO_4$), filtered and concentrated. Recrystallisation from ethanol gave a pure product; m.p. 100–102 °C; ν_{max}/cm^{-1} 1716 and 1765 (C=O); δ_H 1.52 (27 H, s, CMe_3), 3.23–3.62 (4 H, m, 2 × CH_2), 3.97 (1 H, m, CH) and 7.80–8.05 (6 H, m, arom.) (Found: C, 39.8; H, 3.15; Br, 40.7; O, 16.3. Calc. for $C_{39}H_{38}Br_6O_{12}$: C, 39.79; H, 3.25; Br, 40.69; O, 16.30%).

Tris-(3,5-*dibromosalicyl*)-*tricarballylate*. (*Tris*-[(2,4-*dibromo*-6-*carboxy*)*phenyl*]*propane*-1,2,3-*tricarboxylate*) (**4**).—The above compound **3** (2 mmol) was dissolved in anhydrous trifluoroacetic acid (10 cm^3) and allowed to stand at room temperature. After 30 min the solvent was removed under reduced pressure and the precipitate recrystallised from trifluoroacetic acid; m.p. 186 °C; ν_{max}/cm^{-1} 1700 and 1760 (C=O); δ_H 3.11–3.19 (2 H, m, CH_2) 3.39–3.47 (2 H, m, CH_2), 3.75 (1 H, m, CH), 8.06 (3 H, d, arom.) and 8.27 (3 H, d, arom.).

Calculations.—The geometries and energies (enthalpies of formation) of tricarballylic acid, some of its derivatives and its five- and six-membered ring anhydrides were obtained using a semiempirical MNDO method[14] (with the BFGS energy minimisation procedure[15]) using the MOPAC (version 4.0) program package.[16,17] The starting geometries for the minimisation process were created following chemical intuition and taking mean values of bond lengths, planar angles and dihedral angles characteristic of organic molecules.[18] Using the same program package and the MNDO method, examinations of geometries and energies of molecules in the transition state (in the saddle point) for chosen processes were carried out.[17,19,20] They were combined following three procedures: the saddle point geometry estimation,[19,20] gradient minimisation in the saddle point (NLLSQ)[17] and evaluation of the force constants,[17] and always afforded a single negative frequency for the molecule in the transition state.

For the conformational analysis we used molecular mechanics calculations (see Fig. 1). For this purpose the force field of Weiner in united-atom approximation was used.[21] Owing to the similarity of the results obtained using all- and united-atom approximations it did not seem necessary to use the former as well.

In our calculations all degrees of freedom were allowed to be relaxed. The Lennard-Jones (6–12) potential was used for all the van der Waals (VDW) interactions except for those describing H-bonds. In the latter case the potential was of the 10–12 type which prevented unreasonable lengthening of the H-bond distance.

According to Weiner[21] the 1,4 electrostatic and VDW interaction energies were scaled down by a factor of 0.5.

All the molecular-mechanics parameters except for the charges were taken from the work of Weiner.[21] The charges on the carboxy group were estimated on the basis of the MNDO net atomic charges for acetic acid, introducing corrections which reproduce the tendency to parametrisation of the carb-

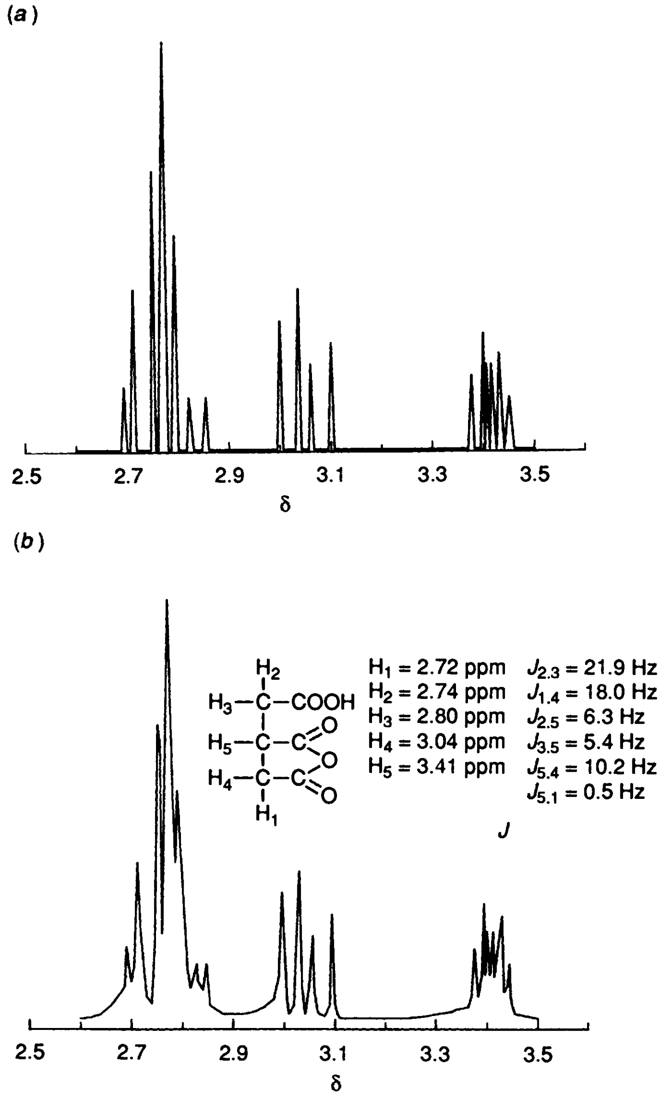

Fig. 2 (*a*) The simulated and (*b*) experimental ^1H NMR spectra of five-membered ring tricarballylic 1,2-anhydride.

Table 2 Enthalpies of formation of tricarballylic acid anhydride in various five- and six-membered ring conformations.

Type of anhydride	Conformation	Enthalpy of formation (ΔH_f)/ kcal mol^{-1})
Five-membered ring	Planar	−210.9
Six-membered ring	Sofa	−208.5
	Boat	−207.2
	Twist	−207.1
	Chair	−208.0

oxylic acid group in Weiner's work. Because of the very low values of the charges on the carbon atoms in the propane chain of the tricarballylic acid molecule we simply distributed these charges on the respective pseudo-atoms so that the total charge of the system was zero. All the charges are collated in Table 1.

To perform the molecular-mechanics calculations we have used a modification[22] of Allinger's MM2 program[23] with a DFP minimisation procedure.[24] The basic geometry of tricarballylic acid was taken from the work of Barnes *et al.*[25]

Results and Discussion

Synthetic Problems.—The primary aim of this work was to synthesise mono-, di- and tri-esters of tricarballylic acid and 3,5-dibromosalicylic acid which we expected to be useful in protein modification. We thought that classical methods would be adequate for this purpose. At the first attempt the esterification was carried out using tricarballylic acid in which the carboxy groups had been activated with DCC (1,3-dicyclohexylcarbodiimide) or BOP (benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate) but in 3,5-dibromosalicylic acid the carboxy group was blocked by the *tert*-butyl group. Unexpectedly, in all cases the main reaction product was tricarballylic 1,2-anhydride. This was proved by comparison of ^1H NMR (Fig. 2) and IR spectra, as well as the results of elemental analyses of the product with those of the original substance. The latter was prepared, independently, by mixing tricarballylic acid with acetic anhydride at ambient temperature (refluxing the substrates affords the bislactone[26]). Further support for the above conclusion was provided by the fact that the simulated ^1H NMR spectrum of the tricarballylic 1,2-anhydride molecule is identical with the experimental spectra of both the synthesised sample and the esterification reaction product (Fig. 2).

The next attempt at synthesising the 3,5-dibromosalicylic esters of tricarballylic acid led to acid chlorides of the latter compound. Typically $SOCl_2$ is used to place chloride instead of hydroxy in the carboxy group.[27] However, after many hours of heating the tricarballylic acid with $SOCl_2$, the main substance formed was 1-chloroformylpropane-2,3-dicarboxylic anhydride **1**. The product was untypical but, nevertheless, we decided to use it for the synthesis of esters. Thus, to obtain mono-, di- or tri-esters mixtures of molar ratio, **1** to 3,5-dibromosalicylic acid to *N*,*N*-dimethylaniline (DMA), 1:1:2, 1:2:3 and 1:3:4, respectively, were prepared and were kept at room temperature. In all cases a monoester of tricarballylic-1,2-anhydride **2** was found as a main product. It is noteworthy that the product again contains the five-membered ring structure which is maintained unchanged under the experimental conditions which accompany synthesis (see Experimental section). We therefore attempted to open the ring in basic media, *i.e.* sodium acetate or sodium hydrogen carbonate solutions in an acetone–water mixture, and next to esterify the remaining two carboxy groups of the tricarballylic acid. Unfortunately, under these conditions hydrolysis of the esters accompanying the release of 3,5-dibromosalicylic acid occurs much faster then ring opening.

Instead of $SOCl_2$ we next used PCl_5 to obtain acid chlorides of tricarballylic acid. Indeed, at the first stage the reaction led to the formation of tricarballylic trichloride. However, the subsequent esterification process carried out with the participation of 3,5-dibromosalicylic acid and in the presence of DMA did not afford a triester with a satisfactory yield. Again, as side products, substances containing a five-membered anhydride ring were formed.

We finally found a method of synthesising tris-(3,5-dibromosalicyl)tricarballylate **4** which requires intermediate preparation of **3**. This method led to the formation of a pure triester in a satisfactory yield (see Experimental section).

Aims of the Theoretical Examinations.—Preparative studies carried out in this work revealed that the tricarballylic acid and its derivatives are characterised by a high tendency towards transformation into cyclic anhydrides. Moreover, in all cases these anhydrides contain a five-membered ring structure. The question, therefore arises, as to why, under various experimental conditions, a five-membered ring structure is preferred over a six-membered one. Quantum chemistry and molecular-mechanics calculations were performed to investigate this matter.

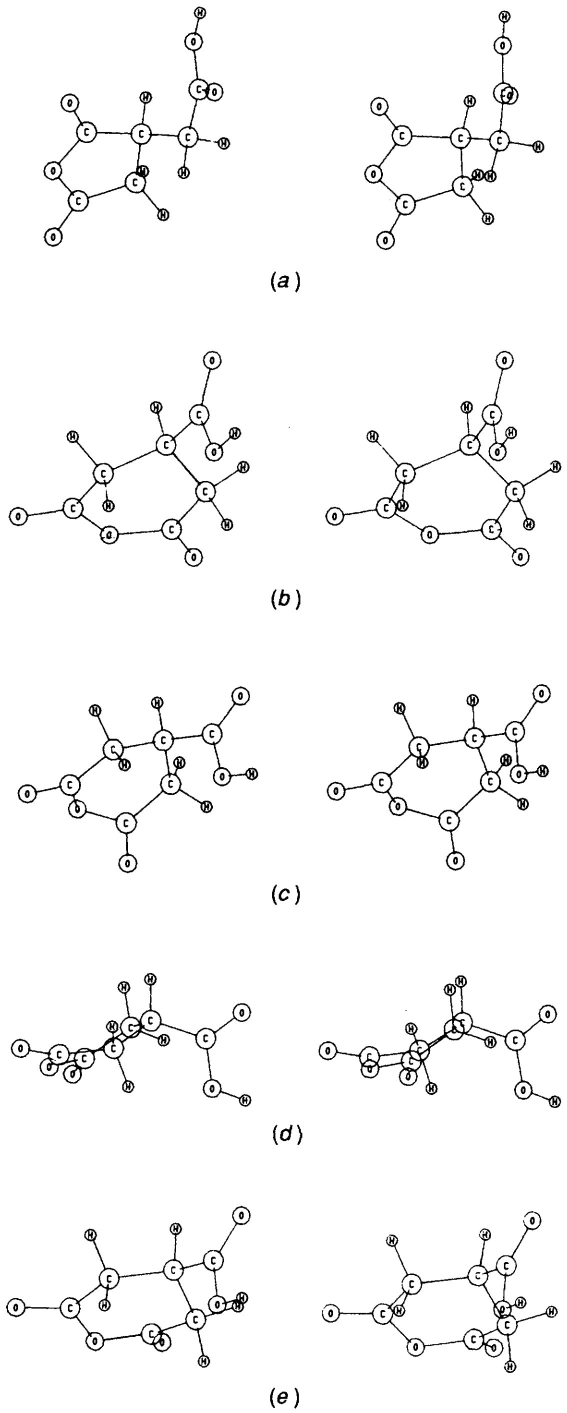

Fig. 3 Stereoviews of the lowest energy conformations of five- (*a*) and six-membered (*b*, *c*, *d*, *e*) ring anhydrides calculated by the MNDO method (*b*, *c*, *d* and *e* indicate sofa, boat, twist and chair conformations, respectively)

Structure and Stability of Tricarballylic Acid Anhydride.— Full geometry optimisation carried out on the level of the MNDO method revealed that the lowest energy conformation of the tricarballylic 1,2-anhydride molecule is almost planar. Two possible enantiomers resulting from the configuration of the CO_2H group at C-2 characterise the same value of the enthalpy of formation (shown in Table 2). This lowest energy structure, in configuration *S* is presented in Fig. 3(*a*).

Tricarballylic 1,3-anhydride is formally a symmetrical molecule which does not exhibit optical activity. The initial structures of this molecule, for the geometry optimisations, were modelled taking into account that a six-membered ring system would have to be planar in fragments holding carbonyl groups and neighbouring C atoms. Considering this fact and the relative arrangement of the C2 atom with the CO_2H group attached to it and the O atom of the anhydride bridge one can select three boundary conformations, namely 'chair', 'boat' and 'sofa'. The fourth conformation, named 'twist', was disclosed by twisting the carbonyl groups and CH_2 fragments along the CH–O (from anhydride bridge) axis in opposite directions. The lowest energy structures corresponding to these conformations, determined by full geometry optimisation with MNDO, are shown in Fig. 3; in Table 2 are presented their thermochemical characteristics. The structures exhibited in Fig. 4. show that the CO_2H group at C-2 can be situated in an axial or an equatorial position to the ring. MNDO calculations revealed that the latter is always energetically favourable.

The formation of a six-membered ring structure is generally preferred to that of a five-membered one. This is not confirmed by present studies. The data in Table 2 indicate that the five-membered ring structure is 2.7 kcal mol^{-1} * more stable than the six-membered one, in the lowest energy conformation (sofa). Although this result should be considered with some reservations it correlates well with our experimental findings. The data in Table 2 shows that the sofa arrangement, with five of the ring atoms of the six-membered ring system almost in plane (except for C-2) is somewhat more stable than the chair, twist or boat conformations. Although it is not easy to explain such a result it seems probable that the conjugative effect of the carbonyl groups in which the O atom of the anhydride bridge participates, is stronger than the strain forces of the ring.

Possible Pathways of Tricarballylic Anhydride Formation.— The ΔH_f values in Table 2 reveal that the five-membered ring anhydride is thermodynamically more stable than is the six-membered one. This information, although correlating with experimental findings does not, however, provide any information about the kinetics, which is the main factor determining the direction of the processes occurring. To shed more light on this latter problem we have considered three reactions, namely: (i) dehydration of the neutral tricarballylic acid molecule; (ii) dehydration of the protonated tricarballylic acid molecule; and (iii) dehydrochlorination of tricarballylic chloride. In addition, the two-step reaction of tricarballylic acid with $SOCl_2$ leading to tricarballylic chloride was investigated.[28] All three processes were examined by considering the involvement of functional groups either in positions 1 and 2, leading to the five-membered ring anhydride, or in positions 1 and 3, leading to the six-membered ring anhydride. For all the reactions, the structures of molecules in the transition states and in the lowest energy conformations, as well as corresponding ΔH_f values, were determined on the level of the MNDO method. These are demonstrated in Figs. 4–7. This information enabled the evaluation of the enthalpy change (ΔH_r) and kinetic activation barrier (ΔH_a) for reactions examined.

The formation of anhydrides through direct dehydration of tricarballylic acid requires the very high activation barriers which are comparable to the energies of the strongest chemical bonds (Fig. 4) to be overcome. It is, therefore, unlikely that anhydrides are created by such a pathway. Nevertheless, it was observed that the formation of the anhydride is an endothermic process and that both ΔH_r and ΔH_a are somewhat higher in the case of the creation of the six-membered ring anhydride than the five-membered one.

The MNDO method predicts that protonation of the carbonyl oxygen of the carboxy group in position 1 is

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* 1 cal = 4.184 J.

exothermic by 190.1 kcal mol^{-1}, whereas that in position 2 is exothermic by 193.2 kcal mol^{-1} (assuming $\Delta H_f[H^+] = 367.1$ kcal mol^{-1} [29]). Therefore, the protonation of this latter group is thermodynamically preferred. On the other hand, the proton affinity of the oxygen atom of OH group is *ca.* 25 kcal mol^{-1} lower, which means that protonation of this atom is rather unlikely. The above information implies that cationic forms should occur in moderately acidic conditions, *e.g.* created by tricarballylic acid itself. As the above data reveal, protonation at the carbonyl group of the CO_2H group in position 2 is preferred over protonation in position 1. This could be how a suitable precursor only for 1,2-anhydride is formed. However, the activation barrier for the dehydration of this latter species is 67.4 kcal mol^{-1} and exceeds the ΔH_a value if the CO_2H group in position 1 is protonated (Fig. 5). Therefore, only the involvement of a CO_2H group in position 1 is subsequently considered. Dehydration of protonated tricarballylic acid (Fig. 5) proceeds with a lower activation barrier than dehydration of the neutral molecule (Fig. 4). The kinetic activation barrier is 0.6 kcal mol^{-1} lower for the formation of the five-membered ring anhydride than the six-membered one. The elimination of both H_2O and H_3O^+ is always endothermic. Endothermicity is lower for the H_3O^+ elimination towards the five-membered ring anhydride than the six-membered one. In the case of the elimination of H_2O the dependency is reversed. The elimination of either H_2O or H_3O^+ from protonated tricarballylic acid seems to be the most feasible process of anhydride formation. The lower activation barrier for the creation of the five-membered ring anhydride corresponds well to the experimental findings.

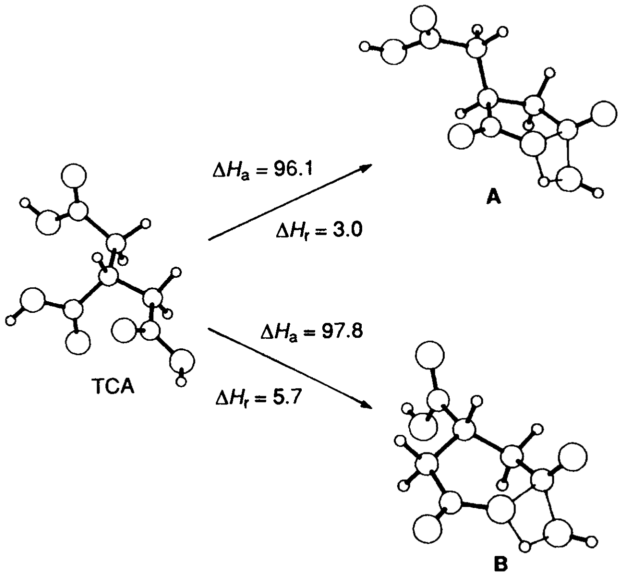


Fig. 4 The structures of the tricarballylic acid molecule in the lowest energy conformation (TCA) and in the transition state for the H_2O elimination towards five- (A) and six-membered ring (B) anhydrides. ΔH_f, ΔH_r and ΔH_a denote, respectively (in kcal mol^{-1}): enthalpy of formation of a given species; enthalpy of reaction equal to the enthalpy difference between reaction products [*i.e.* H_2O and five-(5-TCAN) or six-membered (6-TCAN) ring anhydrides] and substrate (TCA); and enthalpy of activation equal to the enthalpy difference between ΔH_f values of the molecule in the transition state and in the lowest energy conformation; $\Delta H_f[H_2O] = -60.9$; $\Delta H_f[\text{5-TCAN}] = -210.9$; $\Delta H_f[\text{6-TCAN}] = -208.2$; $\Delta H_f[\text{TCA}] = -274.8$. In the transition state structure thin lines bond atoms directly involved in the reaction (reaction centre) and thick lines other atoms. The size of atoms decreases in the following order: O > C > H.

A rather unusual experimental result concerning reaction of TCA with $SOCl_2$ is explained by Figs. 6 and 7. The formation of tricarballylic chloride, considered as a two-stage consecutive process,[28] requires a barrier higher by *ca.* 7 kcal mol^{-1} than that characteristic for the dehydration of a protonated tricarballylic acid molecule to be overcome. Moreover, the overall process of tricarballylic chloride formation is endothermic by 80.7 kcal mol^{-1} which means that it can be realized under specific experimental conditions. Thus, it seems unlikely that tricarballylic chloride is the precursor of the anhydride. The activation barriers for HCl elimination (Fig. 7) are comparable to those for dehydration of protonated tricarballylic acid, however, formation of acid chloride is neither energetically or kinetically favourable. It seems therefore, that heating the tricarballylic acid in the presence of $SOCl_2$, the anhydride is formed primarily and then the non-engaged CO_2H group becomes substituted by Cl giving the acid chloride **1**.

Conformations of Tricarballylic Acid at the Initial Stage of Dehydration.—The skeleton of the tricarballylic acid molecule

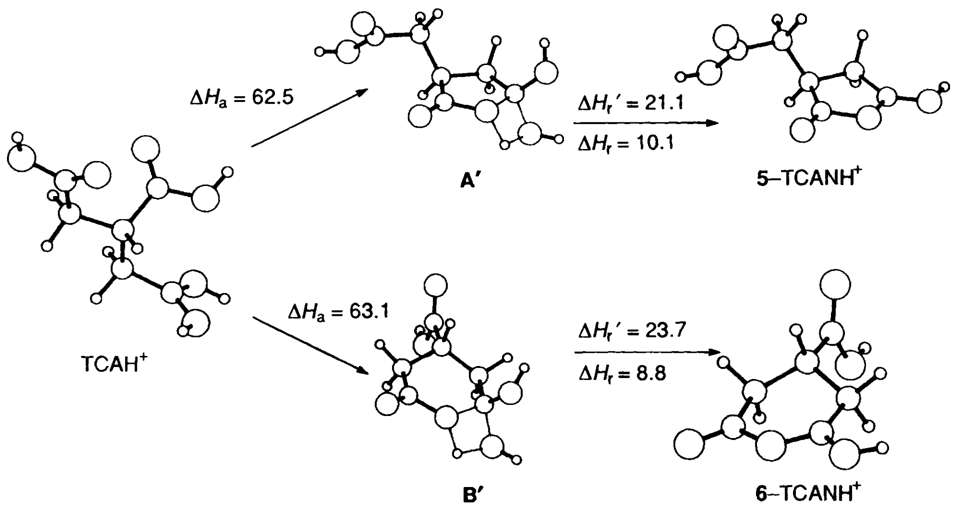


Fig. 5 The structures of the protonated tricarballylic acid molecule in the lowest energy conformation (TCAH$^+$), in the transition states for the H_2O elimination towards protonated five- (A') and six-membered ring (B') anhydrides, and protonated five- (5-TCANH$^+$) and six-membered ring (6-TCANH$^+$) anhydrides. ΔH_f, ΔH_r, $\Delta H_r'$ and ΔH_a denote, respectively (in kcal mol^{-1}): enthalpy of formation of a given species; enthalpy of reaction: $TCAH^+ \rightarrow TCANH^+ + H_2O$ ($TCAH^+ \rightarrow TCAN + H_3O^+$) and enthalpy of activation (for more details see legend to Fig. 4); $\Delta H_f[H_3O^+] = 134.2$; $\Delta H_f[\text{5-TCANH}^+] = -26.8$; $\Delta H_f[\text{6-TCANH}^+] = -28.1$ (for ΔH_f of H_2O, 5-TCAN, and 6-TCAN see legend to Fig. 5). In the transition-state structure thin lines bond atoms directly involved in the reaction (reaction centre) and thick lines other atoms. The size of atoms decreases in the following order: O > C > H.

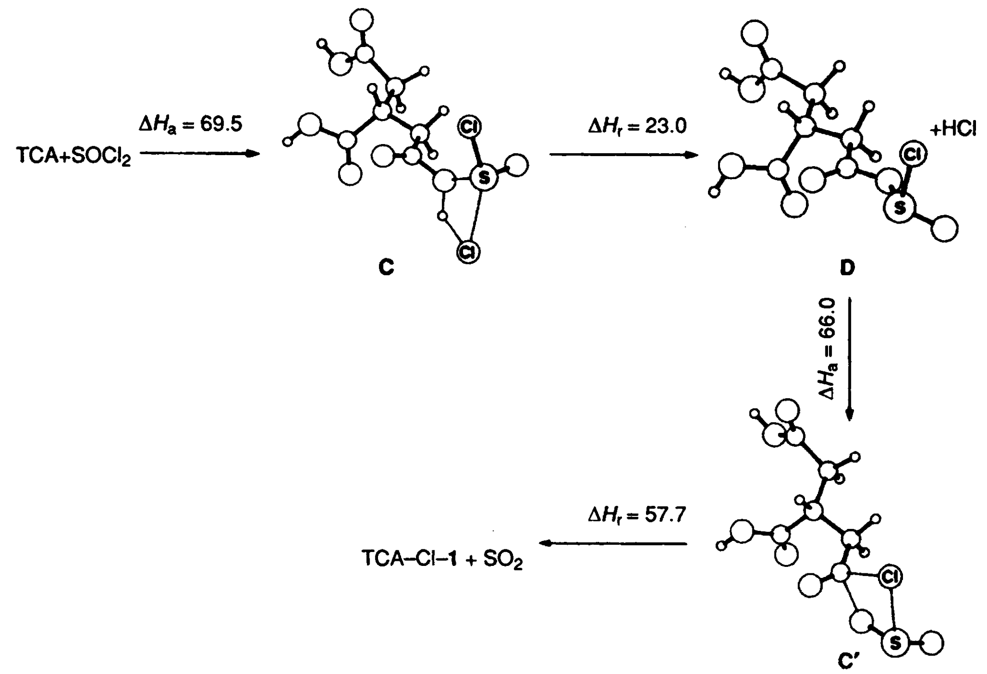


Fig. 6 The structures of molecules in the transition states (C and C′) and in the intermediate state (D) in the two-stage reaction of tricarballylic acid (TCA) with $SOCl_2$ towards tricarballylic chloride-1 (TCA-Cl-1). ΔH_f, ΔH_r and ΔH_a denote, respectively (in kcal mol^{-1}): enthalpy of formation of a given species; enthalpy of reaction and enthalpy of activation; $\Delta H_f[HCl] = -15.3$; $\Delta H_f[SO_2] = 27.6$; $\Delta H_f[SOCl_2] = -22.2$; $\Delta H_f[C] = -227.5$; $\Delta H_f[D] = -258.7$; $\Delta H_f[C'] = -192.7$; $\Delta H_f[TCA\text{-}Cl\text{-}1] = -228.6$ (for $\Delta H_f[TCA]$ see legend to Fig. 4). In the transition-state structure thin lines bond atoms directly involved in the reaction (reaction centre) and thick lines other atoms. S and Cl atoms are labelled; the size of others decreases in the following order: O > C > H.

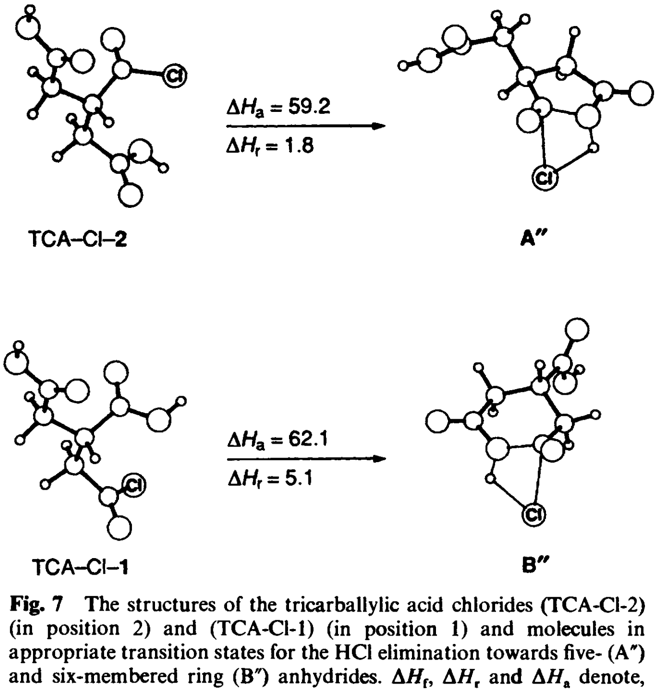


Fig. 7 The structures of the tricarballylic acid chlorides (TCA-Cl-2) (in position 2) and (TCA-Cl-1) (in position 1) and molecules in appropriate transition states for the HCl elimination towards five- (A″) and six-membered ring (B″) anhydrides. ΔH_f, ΔH_r and ΔH_a denote, respectively (in kcal mol^{-1}): enthalpy of formation of a given species; enthalpy of reaction equal to the enthalpy difference between reaction products (*i.e.* HCl, 5-TCAN or 6-TCAN) and substrates [TCA-Cl-2 ($\Delta H_f = -228.0$) or TCA-Cl-1]; and enthalpy of activation equal to the enthalpy difference between ΔH_f values of the molecules in the transition states and in the lowest energy conformations. For other details see Figs. 4 and 6. In the transition-state structure thin lines bond atoms directly involved in the reaction (reaction centre) and thick lines other atoms. Cl atoms are labelled; the size of others decreases in the following order: O > C > H.

makes a three-centre aliphatic chain which, owing to its ability to rotate, allows the whole molecule to admit a certain number of conformations. The arrangement of the molecule is predominantly affected by the large dimensions of the carboxy group and the possibility of its participation in the hydrogen bond interactions. Only some of these conformations may be thought to be important at the initial stage of the dehydration process.

There is a great number of possible conformations of the tricarballylic acid molecule. To simplify the problem we chose only some of them for further consideration. Firstly, it may be assumed that the formation of hydrogen bonds leads to energetically favourable conformations and that the appearance of many hydrogen bonds brings about a deeper stabilisation of the system. For this reason the conformations with two or three hydrogen bonds were considered first of all. Modelling conformations can further distinguish the types of atoms involved in the hydrogen bond formation. Generally, hydrogen bonds of two categories can be expected, namely: –O–H ••• O= and –O–H ••• OH–, which in molecular-mechanics notation can be described as OH–HO–O2 and OH–HO–OH, respectively (see Fig. 1). When conformations with multiple H-bonds were generated we noticed that the hydroxy from one carboxy group can occupy two distinctive positions against the plane allocated to the other carboxy group.

Following the above considerations we generated 32 conformations which are listed in Table 3. The number of conformations is actually doubled due to the symmetry of the molecule (for each chosen conformation its mirror image can be constructed). Such pairs of conformations exhibit, however, the same stability, *i.e.* steric energy value. To reveal structural, as well as energetic, features of these selected conformations we carried out molecular-mechanics calculations (MNDO fails when applied to systems involving hydrogen bonds[30]). The results are compiled in Table 3 and chosen structures are shown in Fig. 8.

Generally, hydrogen bonds can be formed with the participation of two CO_2H groups in either 1, 2 or 1, 3 positions, which results in seven- or eight-membered ring systems,

Table 3 Conformational anlaysis data for tricarballylic acid involved in the hydrogen bonds

	Structural information							H-bond characteristics					
Entry	Type of ring formed[a]	Dihedral angle,[b] α_i/°						Atoms involved[c]	Distance[d]/Å		Energy of electrostatic interaction[e]		Steric energy (E/kcal mol^{-1})
		α_1	α_2	α_3	α_4	α_5	α_6		C↔O	O···H	C↔O	O···H	
1[f]	7	173.0	−17.0	125.7	83.6	−178.6	−81.4	O2(5)-HO(11)	3.17	1.81	−9.7	−17.7	−34.0
	7							O2(9)-HO(15)	3.11	1.83	−10.0	−17.4	
2	7	171.1	−19.8	129.8	83.3	55.8	79.0	O2(5)-HO(11)	3.38	1.81	−8.5	−17.7	−33.5
	7							O2(9)-HO(15)	3.16	1.79	−9.7	−18.2	
3	7	−67.7	−61.1	131.9	16.8	81.4	82.0	O2(5)-HO(11)	3.23	1.81	−9.3	−17.7	−31.2
	7							O2(9)-HO(15)	3.13	1.83	−9.9	−17.3	
4	7	173.2	160.5	125.5	83.9	−179.0	−81.9	OH(6)-HO(11)	3.11*	1.87*	−10.0*	−15.3*	−30.8
									3.15**		−9.8**		
	7							O2(9)-HO(15)	3.15	1.83	−9.8	−17.3	
5	7	171.5	157.3	129.7	84.0	55.4	77.9	OH(6)-HO(11)	3.15*	1.88**	−9.8*	−15.2*	−30.1
									3.15**		−9.8**		
	7							O2(9)-HO(15)	3.38	1.79	−8.5	−18.2	
6	7	−53.0	−42.0	134.5	−49.5	−169.7	16.3	O2(5)-HO(11)	3.10	1.76	−10.1	−18.8	−30.1
	7							O2(9)-HO(15)	3.31	1.81	−8.9	−17.7	
7	7	−72.3	95.0	127.6	31.8	−162.7	−84.3	HO(7)-OH(10)	3.13*	1.94*	−9.9*	−14.2*	−28.9
									3.11**		−10.1**		
	7							O2(9)-HO(15)	3.36	1.80	−8.6	−17.9	
8	7	174.0	163.3	125.4	82.4	−179.4	−82.8	HO(7)-OH(10)	3.19*	1.87*	−9.5*	−15.2*	−28.7
									3.15**		−9.8**		
	7							O2(9)-HO(15)	3.12	1.84	−10.0	−17.1	
9	7	172.8	159.7	129.6	82.7	55.5	77.2	HO(7)-OH(10)	3.19*	1.88*	−9.5*	−15.2*	−28.0
									3.15**		−9.8**		
	7							O2(9)-HO(15)	3.36	1.79	−8.6	−18.1	
10	7	−73.9	97.8	128.4	34.4	−160.2	−82.8	OH(6)-HO(11)	3.09*	1.91*	−10.2*	−14.6*	−27.3
									3.17**		−9.7**		
	7							O2(9)-HO(15)	3.36	1.79	−8.6	−18.1	
11	7	−83.0	100.8	133.5	35.2	69.4	65.0	HO(7)-OH(10)	3.11*	1.92*	−10.1*	−14.6*	−27.2
									3.13**		−9.9**		
	7							O2(9)-HO(15)	3.16	1.80	−9.7	−17.9	
12	7	−66.7	132.8	132.2	12.0	84.0	82.6	OH(6)-HO(11)	3.21*	1.87*	−9.4*	−15.4*	−27.2
									3.04**		−10.5**		
	7							O2(9)-HO(15)	3.10	1.85	−10.1	−17.0	
13	7	172.2	161.2	130.4	97.4	71.5	−60.5	OH(6)-HO(11)	3.23*	1.91*	−9.3*	−14.6*	−26.9
									3.07**		−10.3**		
14	7	173.5	160.6	126.1	90.4	−63.4	−97.2	OH(6)-HO(11)	3.21*	1.90*	−9.4*	−14.8*	−24.8
									3.09**		−10.2**		
15[f]	8	51.9	−80.2	125.7	151.5	63.8	−88.2	O2(5)-HO(15)	3.50	1.81	−8.1	−17.8	−29.3
16	8	52.6	97.8	125.6	147.7	64.3	−86.3	OH(6)-HO(15)	3.47*	1.86*	−8.1*	−15.4*	−26.1
									3.39**		−8.5**		
17	8	63.4	−75.1	124.2	116.4	−96.8	100.3	O2(5)-HO(15)	3.31	1.80	−8.9	−17.8	−24.4
18	8	65.8	90.6	123.5	116.5	−86.9	101.4	OH(6)-HO(15)	3.24*	1.90*	−9.2*	−14.8*	−20.8
19	8	62.0	−107.8	126.2	115.2	−57.2	116.3	O2(5)-HO(15)	3.24	1.94	−9.2	−15.4	−20.6
	8							HO(7)-O2(13)	3.25	1.96	−9.2	−15.1	
20[f]	7	−88.9	−81.3	131.8	41.8	69.4	86.7	O2(5)-HO(11)	3.16	1.82	−9.7	−17.5	−33.7
	8							HO(7)-O2(13)	3.25	1.81	−9.2	−17.7	
	7							O2(9)-HO(15)	3.29	1.83	−9.0	−17.3	
21	8	−85.2	−80.4	131.8	67.8	62.4	82.6	HO(7)-O2(13)	3.18	1.82	−9.6	−17.6	−33.1
	7							O2(9)-HO(15)	3.39	1.81	−8.4	−17.6	
22	8	58.2	89.3	127.1	64.1	56.7	88.0	HO(7)-O2(13)	3.44	1.80	−8.2	−17.9	−32.1
	7							O2(9)-HO(15)	3.36	1.82	−8.6	−17.5	
23	8	56.4	−74.0	132.5	−73.1	53.8	—102.0	O2(5)-HO(15)	3.51	1.81	−7.9	−17.7	−30.7
	7							HO(11)-O2(13)	3.21	1.78	−9.5	−18.3	
24	7	−104.4	−81.9	134.8	53.3	72.5	124.3	O2(5)-HO(11)	3.13	1.83	−9.9	−17.4	−30.1
	8							HO(7)-O2(13)	3.51	1.79	−7.5	−18.1	
25	8	−100.0	−88.0	132.2	−110.0	70.0	112.0	HO(7)-O2(13)	3.17	1.82	−9.7	−17.5	−29.2
	7							OH(10)-HO(15)	3.47*	1.88*	−8.1*	−15.1*	
									3.01**		−10.7**		
26	8	57.8	88.5	128.1	−124.1	57.0	90.1	HO(7)-O2(13)	3.44	1.80	−9.7	−17.9	−28.5
	7							OH(10)-HO(15)	3.40*	1.89*	−8.4*	−14.9*	
									3.02**		−10.7**		

Table 3 (*continued*)

	Structural information							H-bond characteristic					
		Dihedral angle,[b]/α_i[b]/°							Distance[d]/Å		Energy of electrostatic interaction[e]		
Entry	Type of ring formed[a]	α_1	α_2	α_3	α_4	α_5	α_6	Atoms involved[c]	C↔O	O···H	C↔O	O···H	Steric energy (E/kcal mol^{-1})
27	8	57.8	106.0	132.0	−70.3	54.0	−101.8	HO(11)-O2(13)	3.20	1.78	−9.5	−18.3	−27.1
	7							OH(6)-HO(15)	3.52*	1.87*	−7.8*	−15.2*	
									3.27**		−9.1**		
28	8	−83.1	−78.4	137.7	−100.3	59.8	84.0	HO(7)-O2(13)	3.15	1.84	−9.8	−17.7	−26.2
	7							HO(11)-OH(14)	3.48*	1.84*	−8.0*	−15.9*	
									3.16**		−9.7**		
29	8	58.4	89.0	132.3	−107.7	55.3	89.2	HO(7)-O2(13)	3.44	1.81	−8.2	−17.8	−25.9
	7							HO(11)-OH(14)	3.11*	1.84*	−10.0*	−15.8*	
									3.48**		−8.0**		
30	8	−81.0	−79.6	138.9	−96.3	61.5	−98.1	HO(7)-OH(14)	3.13*	2.01*	−9.9*	−13.2*	−25.9
									3.36**		−8.6**		
	7							HO(11)-O2(13)	3.19	1.78	−9.5	−18.3	
31	8	60.4	92.9	132.1	−77.0	53.3	−95.7	HO(11)-O2(13)	3.17	1.78	−9.7	−15.5	−25.8
	7							HO(7)-OH(14)	3.41*	1.86*	−8.4*	−18.2*	
									3.47**		−8.1**		
32	7	−111.9	−81.8	135.4	58.6	74.3	−40.8	O2(5)-HO(11)	3.11	1.84	−10.1	−17.1	−25.4
	8							HO(7)-OH(14)	3.74*	1.86*	−6.9*	−15.5	
									3.20**		−9.5**		

[a] 7 Denotes a seven-membered H-bond ring (interaction of 1, 2 type); 8 denotes an eight-membered H-bond ring (interaction of 1, 3 type). [b] Dihedral angles α_i denotes the following: α_1 = C(4)C2(1)CH(2)C2(3); α_2 = O2(5)C(4)C2(1)CH(2); α_3 = C(8)CH(2)C2(1)C2(3); α_4 = OH(10)C(8)CH(2)C2(1); α_5 = C(12)C2(3)CH(2)C2(1); α_6 = OH(14)C(12)C2(3)CH(2); [c] For numbering see Fig. 1. [d] Distances between carbon and oxygen (C↔O) and oxygen and hydrogen (O··· H) atoms of two of the carboxy groups involved in hydrogen bonding (see Fig. 9). [e] Electrostatic interaction energy between the atoms distinguished in footnote *d*. (Fig. 9). [f] For structure of conformations see Fig. 8.

respectively. It may be thought that the involvement of carboxy groups from neighbouring 1, 2 positions favour the formation of a five-membered ring anhydride, while the interactions between carboxy groups in 1, 3 positions should lead to the six-membered ring anhydride. For simplicity the H-bonds or interactions will be named subsequently as the 1, 2 or 1, 3 type, respectively.

The conformations considered (Table 3) can be categorised into three groups. To the first group belong conformations in which only seven-membered H-bond ring structures, with interactions of the 1, 2 type occur (entries 1–14). The second group holds conformations resulting from the interactions of the 1, 3 type, *i.e.* those in which exclusively eight-membered H-bond ring structures occur (entries 15–19). Finally, to a third group belong conformations which produce simultaneously seven- and eight-membered H-bond ring structures (entries 20–32).

Model analysis revealed that 12 conformations with two seven-membered H-bond rings (of the 1, 2 type) can be envisaged considering the various structural options. They are listed in Table 3 in sequence of decreasing steric energy (entries 1–12). The number of conformations of the tricarballylic acid holding one seven-membered hydrogen bond ring system is several times higher than the number of conformations discussed above. This results from the fact that the carboxy group not involved in the H-bond can rotate around the C2–C3 bond occupying at least two stationary positions. Since the steric energy of such conformations is higher than that of the double H-bond ones, only two of them are listed in Table 3, as examples, under entries 13 and 14. They are related to entry 4 and were obtained after breaking one H-bond.

The possible conformations with one or two eight-membered H-bond ring systems are listed in Table 3 under entries 15–19. Only one conformation was found in which the carboxy groups from positions 1 and 3 are simultaneously engaged in two H-bonds, however this conformation characterises relatively high steric energy. The conformations of a single eight-membered H-bond ring system are more stable. All conformations resulting from the 1, 3 type of interaction, however, exhibit lower stability in comparison with that from the 1, 2 type of interaction. What is also interesting is that the formation of two H-bonds of the 1, 3 type is not as energetically favourable as that in the corresponding 1, 2 type H-bond systems.

The third group constitute conformations with H-bonds of both 1, 2 and 1, 3 types. They are listed in Table 3, in order of decreasing steric energy, under entries 20–32. The unique structure among these conformations with two seven- and one eight-membered H-bond ring systems characterises the lowest steric energy (entry 20). Other conformations belonging to this group always contain one seven- and one eight-membered H-bond ring system. Their steric energies are somewhat higher than is the case for the double seven-membered ring systems but much lower than those characteristic of systems with the 1, 3 type of H-bonds.

As the data in Table 3 reveal, the participation of the carboxy groups of tricarballylic acid in hydrogen bond interactions lowers the steric energy of the molecule. Furthermore, the deeper the stabilisation of the system observed, the greater the number of the H-bonds formed. However, formation of seven-membered ring systems involving CO_2H groups in positions 1 and 2 is energetically preferred to the formation of eight-membered ring systems in which carboxy groups in positions 1 and 3 are engaged. Involvement of CO_2H groups in H-bond interaction brings both groups closer, which should, undoubtedly, facilitate the dehydration process and thus anhydride formation. The energetic factor favours formation of seven-membered ring H-bond conformations which may be thought to be the precursors of the five-membered ring

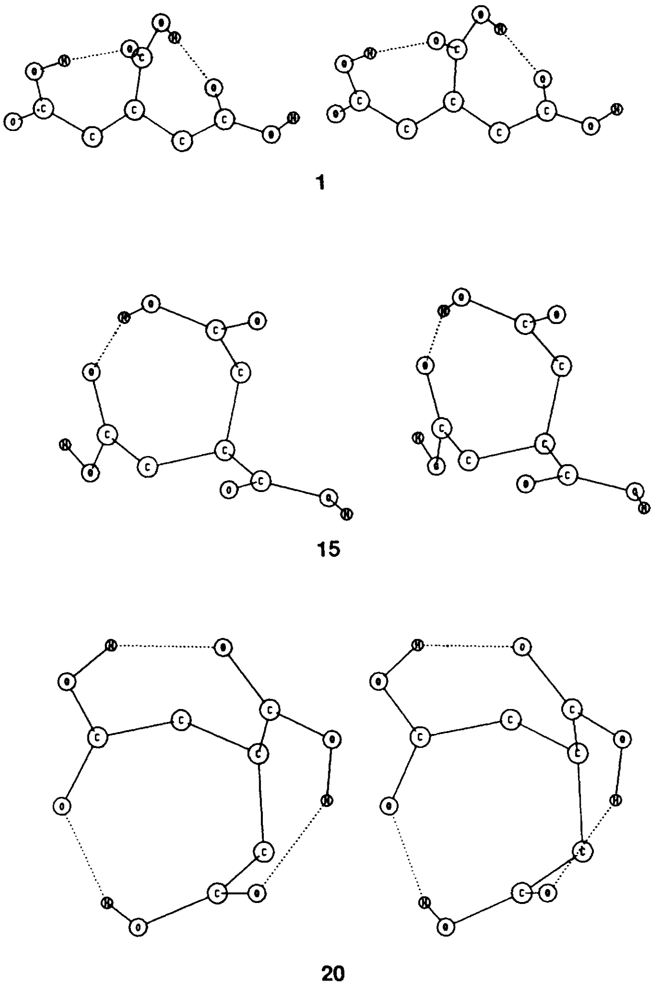
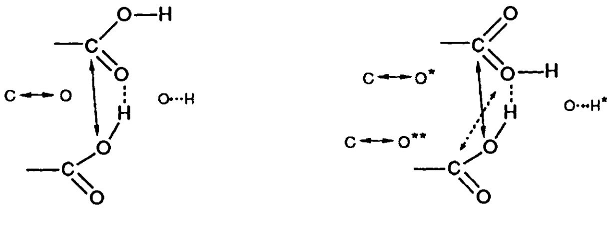


Fig. 8 Examples of conformations (stereoviews) of the tricarballylic acid molecule (for numbers see Table 3)



(*a*) (*b*)

Fig. 9 Schematic representation of interactions within two carboxy groups involved in the hydrogen bond

anhydride. Therefore one can expect that the latter anhydride will predominate in the products of the H_2O elimination process. Indeed this is observed experimentally.

The carboxy groups engaged in an H-bond can interact through two OH fragments or by the involvement of carbonyl and OH residues (Fig. 9). The latter type of interaction always characterises a deeper stabilisation of the system (a lower steric energy value; Table 3). On the other hand, the -OH ··· OH- type of bond creates a very favourable arrangement for the direct elimination of the H_2O molecule, owing to the closeness and direct involvement in bonding of one O and two H atoms. A phenomenological approach to the mechanism of the anhydride formation of carboxylic acids assumes a primary nucleophilic attack by the oxygen atom of hydroxy of one CO_2H group on the carbon atom of another carboxy group (Fig. 9).[28] If the process were initiated by these means one would expect that it would be greatly facilitated by interaction between the O and H atoms directly involved in the hydrogen bond and between the O and C atoms believed to participate in the nucleophilic substitution. Table 3 demonstrates that electrostatic interaction between O and H atoms is always stronger in the -OH ··· O= type of H-bond [O ··· H; Fig. 9(*a*)] than in the -OH ··· OH- one [O ··· H*; Fig. 9(*b*)]. The energy of the Coulombic interaction between the O and C atoms, which can potentially form the oxygen anhydride bridge, (C ↔ O; C ↔ O*; C ↔ O**; Fig. 9) is influenced by the type of H-bond (*i.e.* O ··· H or O ··· H*; Fig. 9). Generally, however, these interactions are stronger in seven-membered H-bond ring systems than in eight-membered systems. This latter finding would suggest that molecules with a multiple H-bond ring system of the 1, 2 and 1, 3 types should, with a greater probability, undergo H_2O elimination resulting in the formation of a five-membered ring anhydride.

The above analysis does not concern protonated forms which, as MNDO mechanistic calculations reveal, may actually be expected as precursors of carballylic acid anhydrides. It can, however, be easily recognized that the formation of a hydrogen bond leads, in fact, to partial 'protonation' of an oxygen atom involved. Therefore, if a tricarballylic acid molecule is simultaneously engaged in multiple internal H-bonds, one of them may play the role of a reaction centre and another may provide a proton to the CO_2H group involved in both.

Examination of the data in Table 3 reveals that there is a greater number of energetically favourable seven-membered ring conformations than eight-membered ones. Furthermore, the number of conformations not exhibited in Table 3 with a single 1, 2 hydrogen bond exceeds by many times the number of conformations with a single 1, 3 H-bond. If the creation of each such conformation had the same probability one could also say that the probability factor prefers the formation of the five-membered ring anhydride.

Conclusions.—The results of the MNDO calculations reveal that the five-membered ring anhydride of tricarballylic acid is thermodynamically more stable than the six-membered one. A similar conclusion results from the mechanistic calculations which also predict a lower kinetic barrier for the formation of the five-membered ring anhydride than the six-membered one. Furthermore, conformational analyses performed on the parent molecule indicate that H-bond interactions resulting in the five-membered ring anhydride are favoured in view of energetic and entropy factors. These facts explain why, under suitable experimental conditions, reactions in which tricarballylic acid or its derivatives participate, produce a five-membered ring anhydride. The theoretical approach actually concerns the gaseous phase. It is, therefore, difficult to say how far the results obtained would apply to the liquid phase. Nevertheless, even the simple approach presented in this paper gives an insight into the behaviour, energetics and reactivity of tricarballylic acid and its anhydride and explains several experimental findings.

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