Epimers of 1,3,5-Cyclohexanetricarboxylic Acid

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The hydrogenation of the **trimethyl ester** of trimesic acid with Raney nickel catalyst produced mainly *cis*-1,3,5-cyclohexanetricarboxylic acid, since after hydrolysis of the hydrogenated ester and crystallization, only a single compound, mp 216–218°, was isolated.[1,2]

This work reports the hydrogenation of the free acid in an aqueous slurry using palladium on carbon as catalyst. The composition of the product of the hydrogenation of trimesic acid was established indirectly by a procedure which involved first the esterification and then gas chromatographic analysis of the triesters. It was independently verified that no epimerization occurred during the procedure. This procedure leads to the conclusion that the hydrogenation of the acid produced the two possible epimers in 22:78 ratio (in order of elution).

The minor isomer is regarded as having the *trans* configuration (II) with two carboxyls in the equatorial position and one in the axial, while the major isomer is assumed to have all of the carboxyl groups equatorial (I). These assignments are based on the following arguments: (1) three *cis* additions of hydrogen during one act of adsorption on the catalyst producing the *cis* isomer should be more favorable than *cis* addition of hydrogen during successive acts of adsorption leading to the *trans* isomer, and (2) it has already been demonstrated[3] that the *trans*-dimethyl ester of 1,3-cyclohexanedicarboxylic acid appears before the *cis* isomer, and assuming a reasonable correlation of the molecular volumes and order of elution between the 1,3-diester and the 1,3,5-triester the *trans* epimer of the triacid would also be expected to elute before the *cis* epimer.

The pure *cis* epimer (I) of 1,3,5-cyclohexanetricarboxylic acid, mp 218–219° in agreement with the literature value, was isolated by crystallization from ethanol. It was at least 98% pure since the corresponding methyl ester showed this degree of purity by gas chromatography.

The *trans*-tricarboxylic acid could not be obtained in high degree of purity from the initial hydrogenation mixture since the *trans* acid is considerably more soluble than the *cis* isomer which greatly predominated. However, the pure *trans* epimer was isolated by epimerization of the original acid mixture.

It was found possible to effect a nearly complete conversion of the original hydrogenation mixture into pure *trans* epimer (II) by first, heating a solution of the acids in acetic anhydride containing sodium acetate, and then neutralizing the basic epimerization catalyst by refluxing with acetyl chloride, concentrating, and crystallizing from water. The *trans* epimer (II), mp 208–210°, was obtained in 96% purity as analyzed by gas chromatography following esterification. A possible explanation for the unusual selectivity of this epimerization is the conversion of the unstable *cis*(a,a,a) conformer of the triacid into the unstable *cis*-anhydride axial carboxyl followed by sodium acetate catalyzed epimerization into the *trans*-anhydride acid (III), which would undergo hydrolysis to the *trans* (e,a,a) conformer (IV) which equilibrates with the *trans* (a,e,e) conformer (II) (see Scheme I).

Equilibration of the original mixture of 22:78 *trans–cis* mixture of tricarboxylic acid obtained by hydrogenation was conveniently effected by keeping the mixture molten at 240° for 24 hr. The product of this treatment now contained the *trans–cis* acids in the ratio 56:44. The same equilibrium mixture was obtained by the same thermal treatment of the pure *trans* acid and the pure *cis* acid showing that equilibration had been obtained in this treatment.

The main question raised by these experiments concerns the reason for the formation of the equilibration mixture containing 56% *trans* and 44% *cis* isomer at 240°.

Equilibration of the acid isomers by maintaining them in a molten state for an extended period of time might be suspect of giving rise to hydrogen-bonded entities which would disturb the true thermodynamic epimer equilibrium. However, when a sample of mixed isomers of 1,3-cyclohexanedicarboxylic acid was held at 240° for 20 hr the composition became 63.8% *cis*.[4] Calculation of the equilibrium from the conformational free energy of the carboxyl group and applying the entropy of mixing term of $R \ln 2$ (based on the existence of the *trans* isomer as a racemate) favoring *trans* isomer as used by Allinger and Curby[3] gives a theoretical composition of 62% *cis*. Thus it is believed that hydrogen bonding is not significant at the high temperatures used for equilibration. Shifting of the equilibrium does not occur on cooling since the molten samples are shock chilled to their freezing point of 218°.

Calculation of a theoretical epimer equilibrium for 1,3,5-cyclohexanetricarboxylic acid may be made from the conformational free energy of a carboxyl group (1.2 kcal/mol[5] favoring equatorial conformation) by applying a comparatively large entropy term for the free energy of mixing of a compound having a symmetry number of 3 ($T\Delta S = RT \ln 3 = 1.12$ kcal/mol at 240°) which favors the *trans* epimer. This method of calculation predicts a value of 48% *trans* epimer, whereas 56% was found. It is not known why this theoretical treatment is not so applicable to epimerization of tricarboxylic acid systems as it is for dicarboxylic acids. However, the ring inversion forms for *trans*-1,3-cyclohexanedicarboxylic acid (a,e and e,a) are identical whereas the ring inversion form of *trans*-(a,e,e)-1,3,5-cyclohexanetricarboxylic acid (II), namely, *trans*-(a,a,e)-1,3,5-cyclohexanetricarboxylic acid may contribute to the energetics of equilibrium. This conformer is analogous to the diaxial carboxyl conformation of 1-*t*-butyl-3,5-cyclohexanedicarboxylic acid which exists in equilibrium with the diequatorial carboxyl and *trans* (a,e) forms.[6] At 240°, 3.8% of the 1-*t*-butyl-3,5

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[1] J. M. Van der Zanden and G. De Vrees, *Rec. Trav. Chim. Pays-Bas*, **67**, 998 (1948).

[2] M. S. Newman and H. S. Lowrie, *J. Amer. Chem. Soc.*, **76**, 4598 (1954).

[3] N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

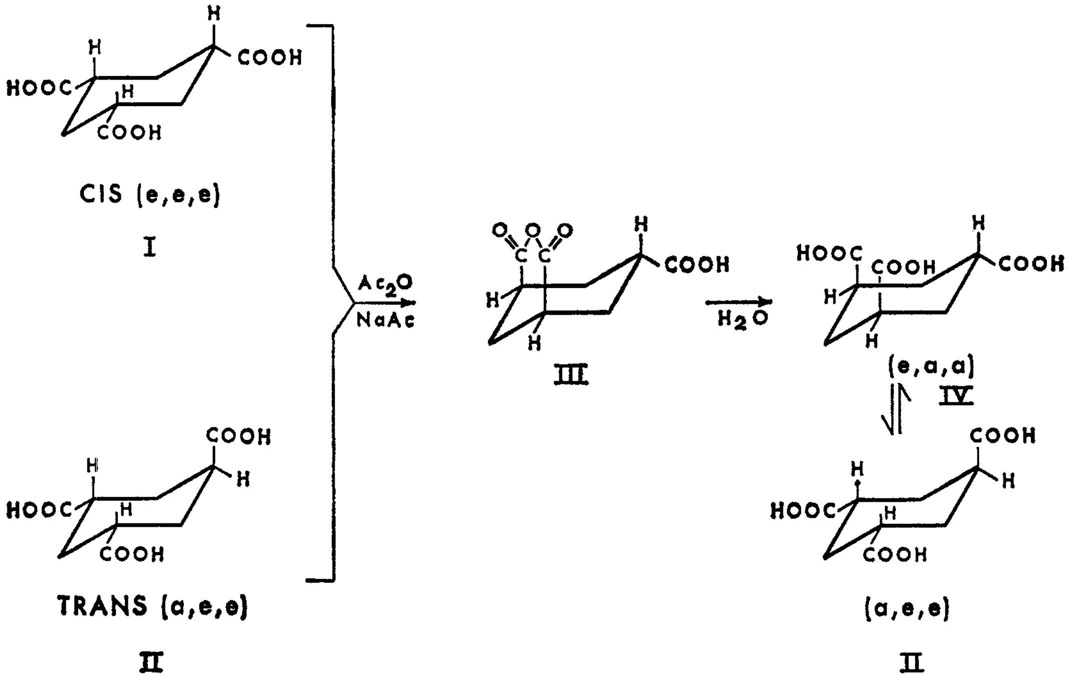
[4] A. Steitz, Jr., *Amer. Chem. Soc., Div. Petrol. Chem., Preprints*, **12**, No. 2, *D*162, 1967.

[5] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965; pp 43–44 and 57.

[6] B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).

SCHEME I

PREPARATION OF *trans*-1,3,5-CYCLOHEXANETRICARBOXYLIC ACID



(a,a)-cyclohexanedicarboxylic acid is formed as shown by gas chromatography of the equilibrated mixture after esterification. Armitage, *et al.*,[6] suggests that this third epimer of 1-*t*-butyl-3,5-cyclohexanedicarboxylic acid assumes the skew-boat conformation.

Experimental Section

Hydrogenation of Trimesic Acid.—A slurry of trimesic acid (three parts) in water (five parts) was hydrogenated at 150° and 1500 psig using as catalyst 5% palladium on carbon in the amount of 5% based on trimesic acid. Hydrogen uptake ceased in 3 hr. Catalyst was filtered from the otherwise homogeneous product. In order to preserve isomer ratio, the total solids (mp 175–206°, acid number 762 (theory 778), were recovered by evaporation of solvent rather than by crystallization. The solids were esterified with diazomethane[3] and analyzed by gas chromatography on a 10-ft column of silicone grease–Carbowax 6000 on Chromosorb W with the temperature programmed from 80 to 210°. The product consisted of 76.6% *cis* isomer, 21.4% *trans* isomer, and 2.0% dibasic acids.

cis-**1,3,5-Cyclohexanetricarboxylic Acid.**—The hydrogenation product was dissolved in the minimum quantity of boiling ethanol, and toluene was added to decrease solubility. The crystals obtained on cooling were washed with chilled ethanol–toluene, and recrystallized in the same manner. The dried crystals melted at 218–219°; analysis showed that the product consisted of 1.5% *trans* isomer, 98% *cis* isomer, and 0.5% dibasic acids.

Anal. Calcd for $C_9H_{12}O_6$: C, 49.9; H, 5.55. Found: C, 50.2; H, 5.58.

trans-**1,3,5-Cyclohexanetricarboxylic Acid.**—The hydrogenation product (5 g) was refluxed with 20 ml of acetic anhydride and 1 g of sodium acetate for 4 hr. The base was removed by refluxing 2 hr with 10 ml of acetyl chloride. Excess acetyl chloride was removed by distillation to an overhead temperature of 132°. The liquid mixture containing some sodium chloride crystals was poured into 400 ml of water. Evaporation to 5 ml and cooling gave a crystal crop, which was recrystallized from water, mp 208–210°. Analysis by esterification and gas chromatography showed 95.9% *trans* isomer, 2.5% *cis* isomer, and 1.7% dibasic acids.

Anal. Calcd for $C_9H_{12}O_6$: C, 49.9; H, 5.55. Found: C, 50.3; H, 5.58.

Thermal Equilibration.—Two-gram samples of the hydrogenation product and each of the pure isomers were heated in test tubes in a thermostatically controlled aluminum block at 240° for 24 hr. The molten samples were rapidly chilled to below their freezing point of 218°. The pulverized products were analyzed by esterification and gas chromatography, all products had substantially the same composition: 54.9 (± 0.3)% *trans* isomer, 43.5 (± 0.6)% *cis* isomer, and 1.6 (± 0.7)% dibasic acids.

Registry No.—I, 16526-68-4; II, 16526-69-5.

Phosphonitrilic Chloride as Activator of Carboxylic Acids. Formation of Amides and Hydrazides[1]

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Considerable advances have been made in the study of the chemical behavior of phosphonitrilic halides during the last decade.[2]

The simplest and best known member of this family of compounds, hexachlorocyclotriphosphatriazene **1**, reacts readily with a variety of compounds, like amines, alcohols, and phenols, to yield substitution products. The high reactivity of the halogen atoms and the observation that the high-temperature reaction of **1** with sodium benzoate resulted in the formation of benzonitrile and benzoic anhydride[3] prompted us to examine the possibility of using **1** or other phosphonitrilic chlorides as activators of carboxylic acids. It was expected that the reaction of an acid or its

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(2) See, for recent surveys, R. A. Shaw, *Chem. Ind.* (London), 1737 (1967); N. L. Paddock, *Quart. Rev.*, **18**, 168 (1964).

(3) I. I. Bezman and W. R. Reed, *J. Amer. Chem. Soc.*, **82**, 2167 (1960).