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Synthesis, thermal, mass and ab initio analyses of cyclopropane-1,1,2-tricarboxylic acid

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Abstract

The preparation of cyclopropane-1,1,2-tricarboxylic acid from cyanoacetic acid and 2,3-dibropropionic acid has been done in one-step procedure in alkaline medium. The compound has been characterized, by nuclear magnetic resonance, mass spectrometry, and thermal analyses. The mass spectrum showed the molecular ion peak in the negative mode. The thermal analysis results show that the compound decomposes in three steps, and the second step of decomposition was tentatively assigned to the loss of two carboxylic acid groups. Also, theoretical calculations were made in order to assign vibrations and determine the most stable structure for the compound. © 2004 Elsevier B.V. All rights reserved.

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1. Introduction

The importance of cyclic ligands such as cyclobutane-1,1-dicarboxylate arose in the 1980s when its platinum complex was found to be a cancer therapeutic agent [1]. In addition to their anesthetic and insecticidal properties, cyclopropane derivatives are ideal scaffolds for exploring determinants of ligand-receptors binding, since rigid ring orients the substituents into well-defined and spatially isolated trajectories. In this regard, cyclopropanes with defined stereochemistry have been used in several studies as amino acid mimetics to determine bond peptide conformation [2,3].

Synthesis of cyclopropane-1,1,2-tricarboxylic acid has been previously done using malonic acid esters with a very low yield [4-6]. However, the preparation of cyclopropane-1,1-dicarboxylic acid from cyanoacetate, malononitrile or malonic acid has been attempted but unsuccessfully [7]. It was presumed that, because these alkylation reactions necessitate the formation of an anion, it was very difficult to synthetically generate a usable concentration of a trianion when the starting material was malonic acid. This seems to corroborate with the fact that malonic acid derivatives, other than the ester, have never been considered in the synthesis of cyclopropane-1,1,2-tricarboxylic acid. It is also interesting to note the discrepancy on melting point values of cyclopropane-1,1,2-tricarboxylic acid in literature. The reported values from different studies are 195, 184 and 185-186 °C [4–6].

Since the crystal structure of cyclopropane-1,1,2-tricarboxylic acid is not known up to now, the present study is reporting on its preparation and characterization from 2,3-dibromopropanoic acid and cyanoacetic acid. The thermal and mass spectrometry analyses of obtained compounds were made in order to assess its stability and eventually clarify the melting point ambiguity. Also ab initio calculations of cyclopropane-1,1,2-tricarboxylic acid has been made to determine its structure and also assign the infrared vibrations.

2. Experimental

2.1. Materials

All the chemicals: benzyltriethylammonium chloride (TEBA), sodium hydroxide, cyanoacetic acid (99%), 2,3-dibropropionic acid (98%) and solvents were purchased

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from Sigma-Aldrich and were used without further purification.

Proton nuclear magnetic resonance (¹HNMR) spectra were recorded on a Bruker-300 MHz in D_2O and on a VARIAN INOVA 500 MHz in CDCl₃.

Elementary analysis was performed by the Microanalytical Services at the University of Cape Town (South Africa). The instrument used is Fisons Elemental Analyser 1108 CHNS-O. The calibration compound was acetanilide. The results were obtained in duplicate for consistency.

Fast atom bombardment (FAB) mass spectrum was performed on VG 70 SE spectrometer (Cape Techniknon Research Unit). The calibration compound was perfluorokerosene.

Electrospray mass spectrum was recorded on a VG Quattro triple quadripole spectrometer (University of Stellenbosch, South Africa). Samples were dissolved in 100 l of 50% (v/v) acetonitrile (50% ACN). Ten liters of this solution were diluted to 100 l with 50% ACN. Ten liters of the final solution, were injected in the analyzer, via a Rheodyne injection valve. The carrier solvent was a solution of 50% ACN, at a flow rate of 20 l/min. Spectra were made of an average of 10 scans, and were recorded using a cone voltage of 30 V and a capillary voltage of 3.5 kV. The calibration compound was polyethylene glycol 200.

Differential scanning calorimetric (DSC) analyses were performed on a Perkin–Elmer DSC 7 and thermogravimetric (TG) analyses on a Perkin–Elmer TGA 7, using 5-10 mg powder samples at a heating rate of $5 \text{ }^{\circ}\text{C} \text{ min}^{-1}$ under a nitrogen flow rate of $20 \text{ cm}^3 \text{ min}^{-1}$. For DSC analyses, empty aluminum pans were used as reference.

2.2. Synthesis of cyclopropane-1,1,2-tricarboxylic acid

A mixture of 2,3-dibromopropionic acid (9.30 g, 40 mmol) and cyanoacetic acid (3.40 g, 40 mmol) was placed in a 500ml-flask with a magnetic stirrer. Benzyltriethylammonium chloride (9.10 g, 40 mmol) was added with stirring. The reaction mixture was cooled in an ice-bath while 50% sodium hydroxide (40 ml) with vigorous stirring over a period of 30 min. The light brownish solution was stirred for 1 h at room temperature. The solution was then diluted with 100 ml of water and then extracted with ether $(2 \times 30 \text{ ml})$. The organic phase was discarded and the aqueous layer was acidified with concentrated HCl (50 ml), then extracted with diethyl ether $(3 \times 30 \text{ ml})$. The organic phase was washed with brine, then dried over anhydrous sodium carbonate and was filtered. The filtrate was left in the air for evaporation. The resulting product was 2-bromoacrylic acid (3.66 g, 60%.), m.p. 68-70 °C. Anal. Found %: C, 24.14; H, 1.72. Calcd% for C₃H₃Br: C, 23.87; H, 2.00.

The aqueous phase was concentrated to about 100 ml at 45 $^{\circ}$ C with a rotary evaporator. The residue was cooled to 0 $^{\circ}$ C and acidified to pH 1 with concentrated hydrochloric acid. The solution was subsequently extracted with

diethylether ether $(3 \times 30 \text{ ml})$. The organic layer extracts were combined, dried over anhydrous magnesium sulfate and filtered. The filtrate gave, after a slow evaporation, a white powder: (2.8 g, 40%), m.p. 139 °C. Anal. Found %: C, 30.01; H, 5.40. Calcd% for C₆H₁₃O_{9.5} or C₆H₆O₆·3.5 H₂O (cyclopropane-1,1,2-tricarboxylic acid hydrate): C, 30.39, H, 5.53.

After re-crystallization in ethanol, the decomposition point was found to be 150 °C. The elemental analysis showed the compound to be containing 0.25 molecule of alcohol per formula. Anal. Found%: C, 42.56; H, 4.37. Calcd% for C_{6.5}H_{7.5}O_{6.25} or C₆H₆O₆·0.25 C₂H₅OH: C, 42.05; H, 4.04. The compound still contains traces of alcohol as impurity. This could suggest that the solvent is very important in stabilizing the structure of the compound.

2.3. Theoretical calculations

The reported calculations were carried out at the MP2/ 6-31G(d) [8,9]. Full geometry optimization was carried out after conformational searching with smaller basis sets identified the lowest energy conformation. All stationary points were classified as minima by Hessian matrix calculations. Calculations were performed using GAMESS (March 1997 Version) [10]. Thermodynamic calculations were performed for all stationary points. The frequencies were scaled by a factor of 0.92 [11] for the MP2/6-31G(d) structures. Visualization of vibrational motions derived from the Hessian calculation was accomplished using the MacMOLPLT software package [12].

3. Results and discussion

The TEBA-catalyzed reaction of cyanoacetic acid and 2,3-dibromopropionic acid in 50% sodium hydroxide has been investigated (Scheme 1). Several procedures were tried by changing the temperature, duration of the reaction and the order of addition of reactants in order to increase the yield in cyclopropane-1,1,2-tricarboxylic acid. The best



results gave us the yield of 40% for cyclopropane-1,1,2tricarboxylic acid and 60% for 2-bromoacrylic acid. The production of the latter is not surprising since it is well known that 2,3-dibromopropionic acid reacts with potassium hydroxide in methanol to produce 2-bromoacrylic acid [13]. The percentage yield from previous study was 26% for the cyclopropane-1,1,2-tricarboxylic acid [4]. The melting point measured was 139 °C whereas previous studies have reported 195, 184 and 185–186 °C [4–6].

However, after re-crystallization in ethanol, the melting point was found to be 150 °C.

Moreover, according to the results from previous study on cyclopropane-1,1-dicarboxylic acid, the reaction between cyanoacetic acid and 2,3-dibromopropionic acid should have yielded 1-cyanocyclopropane-1,2-dicarboxylic acid [7]. Physical methods were therefore needed to characterize the obtained compounds.

3.1. NMR spectrometry

The spectrum NMR of cyclopropane-1,1,2-tricarboxylic acid, after re-crystallization in ethanol, is displayed in Fig. 1. There are three cyclopropyl protons (Ha, Hb and Hc), each a doublet-of-doublets, at, respectively, δ 2.40 (*J* 8.2 and 6.6 Hz), 1.70 (*J* 6.2 and 4.8 Hz) and 1.56 (*J* 8.4 and 4.8 Hz). Previous studies have shown the presence of three peaks with similar chemical shifts as the present study [4]. However, there are two small peaks due to the re-crystallization solvent, ethanol.

The spectrum of 2-bromoacrylic acid in CDCl_3 has shown two acrylic protons, each a doublet, at δ 7.10 (*J* 1.6 Hz) and at 6.40 (*J* 1.6 Hz) and a carboxylic acid proton at δ 11.57.

3.2. Mass spectra

The positive mode FAB mass spectrometry (70 eV) of cyclopropane-1,1,2-tricarboxylic acid has failed to produce any data. However, its negative-ion mode FAB mass spectrum was obtained. The principal and molecular peak is at m/z 173.1; corresponding to $(M-H)^-$. The exact mass calculated for $C_6H_5O_6$ is 173.1060. There is no other significant peak present. This could be an indication of instability of the compound that favors the decomposition. These results are completely different from previous study findings. The positive-mode mass spectrum of cyclopropane-1,1,2-tricarboxylic acid at 15 eV showed no molecular ion but peaks due to loss of OH, H₂O, CO₂ were found [4]. This discrepancy may be due to the difference in ionization processes for the instruments used.

Also the positive-mode electrospray mass spectrometry of 2-dibromoacrylic acid gave no results. In the negative-ion mode, however, peaks were found at m/z 148.66 (M–H)⁻, 104.84 (M–COOH)⁻, and 78.74 (Br⁻). Each of them presented the isotopic pattern with equally intense peaks at M and M + 2, characteristic of the presence of one bromine atom in the species (Fig. 2). The fragment found at m/z 174 may be assigned to cyclopropane-1,1,2-tricarboxylic acid as impurity.

3.3. Thermal analysis

The thermal analysis was motivated by the discrepancies in the reported melting points of cyclopropane-1,1,2tricarboxylic acid. The experiment was done on the crude compound to avoid the interference of alcohol in the analysis. The thermogravimetric results are listed in Table 1 and the TGA/DSC traces are shown in Fig. 3. The loss



Fig. 1. NMR spectrum of cyclopropane-1,1,2-tricarboxylic acid in D₂O.



of non-bound water occurs between 26 and 87 °C and represents 3.2% of the total mass. The dehydration of crystal water takes place in one step and corresponds to the first endothermic peak in the DSC curve. It ranges from 87 to 179 °C and represents a total mass loss of 27%, in line with an expected mass loss of 27% for three and half molecules of bound water. This relatively large amount of water can be justified by the presence of three carboxylic acid groups in the molecule. The peak temperature of this step is 139 °C; corresponding to the apparent melting point recorded in our laboratory. The melting process is ruled out due to the broadness of the endothermic peak. In the early thermal analysis of itaconic acid, a di-carboxylate compound, the fusion endotherm is very sharp, and those for dehydration of metal complexes of itaconic were very broad [14]. The second mass loss step ranging from 179 to 250 °C may be due to the decomposition of cyclopropane-1,1,2tricarboxylic acid. The absence of a defined endothermic peak in DSC curve, suggests that there is no clear fusion. The mass loss of 37% could be attributed to the loss of two CO₂ molecules (calculated mass loss of 37%). This possibility can be also justified by the common decarboxylation that occurs when a dicarboxylate is heated above 150 °C. The example is the conversion of 1.1-cyclopropanedicarboxylic acid into cyclopropane-carboxylic acid [15].

 Table 1

 Thermal analysis data for cyclopropane-1,1,2-tricarboxylic acid in nitrogen

Process	Temperature range (°C)	Peak temperature	Mass loss (%)	
		(0)	Calculated	Found
Loss of humidity Loss of bound water Loss of two CO ₂	26–87 87–179 179–226	- 139 201	- 26.6 37.1	3.2 27.0 37.0
Total decomposition	226-580	-	36.3	36.0

The degradation continues up to 580 °C when the sample is fully decomposed. In comparison, the TG curve of itaconic acid showed even more clearly two different steps of mass loss, accompanied by two endothermic peaks in DSC [14]. The results show that the melting points reported in literature (184, 185–186 and 195 °C) [4–6] originated probably to the decomposition of the compound. This could explain the large margin in reported values (around 10 °C), that could be attributed to the fact that the decomposition is so fast; the melting point apparatuses could not pinpoint the start of the process. Also the presence of water of crystallization have contributed to the discrepancy.

In addition, the thermal analysis of 2-bromoacrylic acid has been done in comparison with the above cyclic compound. The TGA/DSC data are displayed in Fig. 4. The results show a sharp endothermic peak at 70 °C without mass loss, which corresponds to the melting point of the compound. The decomposition of the sample takes place in one step, starting at 100 °C and finishing at 170 °C. These results could indicate that a molecule with one carboxylic acid tends to disintegrate in one single step. In case of



Fig. 3. TGA and DSC curves for cyclopropane-1,1,2-tricarboxylic acid.

Τź



Fig. 4. TGA and DSC curves for 2-bromoacrylic acid.

multiple carboxylic groups, there could be more than one decomposition processes [14].

3.4. Theoretical and infrared analyses

Since the crystal structure of cyclopropane-1,1,2tricarboxylic acid is not known, we were interested in determining the most stable geometry, and assigning the bands of infrared absorption, using ab initio calculations MP2/6-31G. The selected calculated structural parameters of cyclopropane-1,1,2-tricarboxylic acid are shown in Scheme 2. The optimized geometry is a C_1 structure with R conformation. The C3C2C4 bond angle is the biggest of the ring with 61.20°, whereas the two others are around 59.00°. Also, the C3C4 bond length is the greatest with 1.527 Å, while C3C2 and C2C4 bond lengths are about



Table 2					
Observed	and	calculated	frequencies	for	cyclopropae-1,1,2-tricarboxylic
acid in the	e 400	00-500 cm	⁻¹ region		

Vibration number	Fundamental	Ab initio	IR (KBr)
	OU stastsk	2410	
ν_1	OH stretch	3412	2262
ν_2	OH stretch	2269	2205
ν_3	OH stretch	3308	3205
ν_4	CH ₂ stretch	3061	3022
ν_5	CH stretch	3022	3005
ν_6	CH ₂ stretch	2956	2855
ν_7	C=O stretch	1708	1710
ν_8	C=O stretch	1692	1700
ν_9	C=O stretch	1690	1692
ν_{10}	Ring stretch	1408	1420
ν_{11}	C-C strech	1373	1380
ν_{12}	C-C stretch	1334	1300
ν_{12}	C–C stretch	1303	1280
ν_{13}	Ring breathing	1248	
ν_{14}	CH in-plane bend	1213	1210
ν_{15}	C–O stretch	1155	1190
ν_{16}	C–O stretch	1105	
ν_{17}	C–O stretch	1087	
ν_{18}	C-H out-of plane bend	1069	
ν_{19}	CH ₂ wagging	1041	
ν_{20}	CH ₂ wagging	1022	
ν_{21}	Ring breathing	963	963
ν_{22}	Ring breathing	952	
ν_{23}	Ring breathing	884	880
ν_{24}	Ring breathing	865	
ν_{25}	Ring-C in-plane bend	787	
25 V26	Ring-C in-plane bend	733	
V27	Ring-C out-of plane bend	696	
ν_{29}	Ring-C out-of plane bend	695	
V20	Ring-CO bend	665	670
V20	OH out-of plane bend	618	600
· 50	OH out-of plane bend	590	590
V 22	OH out-of plane bend	587	570
· 52	OH out-of plane bend	560	

1.50 Å. Similar studies on cyclopropane rings, with less substitution, showed bond lengths very close to 1.50 Å and bond angles very similar and close to 60.00° [16,17]. Therefore, this ring structure allows the two carboxylate groups to be far from each other.

Moreover, Table 2 shows the comparison between the calculated and obtained spectra using KBr pellet on FTIR instrument. The calculated values have been adjusted with a factor of 0.92. The assignment of bands has been made using the animation program, MacMOLPLt. For the majority of vibrations, calculated frequencies are very close to those found. Some calculated vibrations were not found, due to the solid state of the sample. The main infrared features are the OH stretching bands found around 3300 cm^{-1} , the three C=O vibrations, around 1700 cm^{-1} . and the C–O stretching vibrations at around 1100 cm^{-1} . Minor bands, due to OH deformation and ring breathing, were, respectively, observed at about 600 and 950 cm^{-1} . Previous results showed a band at 1665 cm^{-1} for C=O stretching [4].

4. Conclusion

The synthesis of cyclopropane-1,1,2-tricarboxylic acid has been synthesized in one-step procedure using cyanoacetic acid and 2,3-dibromopropionic acid with a relatively better yield that the previous studies. The mass spectrometry and thermal analyses confirmed the structure of the compound and its chemical and thermal stability. The study has also calculated structural parameters, and vibrational frequencies that could be used for assignment. The next step of our work would be the resolution of this chiral compound in its optical isomers for possible platinum coordination and eventually for determination of anticancer properties of the complexes.

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