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# Crystal Structure of Diisopropylammonium Hydrogen Maleate

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## To cite this article:

Dame Seye, Assane Toure, Momath Lo, Cheikh Abdoul Khadir Diop, Libasse Diop, David Geiger. Crystal Structure of Diisopropylammonium Hydrogen Maleate. *Science Journal of Chemistry*. Vol. 7, No. 6, 2019, pp. 110-113. doi: 10.11648/j.sjc.2019070612

**Received:** January 7, 2020; **Accepted:** January 29, 2020; **Published:** February 11, 2020

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**Abstract:** Use of salts and co-crystals of active pharmaceutical ingredients (APIs) as a method for tuning their delivery and activity is an area of growing interest. Modifying API properties such as solubility by finding new salts that employ similar hydrogen-bonding have been successful. In an effort to further study the hydrogen-bonding patterns of the maleate ion with other diisopropylammonium we report here the synthesis and diisopropylammonium maleate. The salt was isolated from reaction between diisopropylamine and maleic acid in methanol. The results of elementary analyzes (CHN) showed the presence of the nitrogen atom of diisopropylamine, carbon atoms and hydrogen. The IR spectrum of diisopropylammonium hydrogen maleate, showed the presence of two intense bands due to the vibrations of symmetric and anti-symmetric valence of the carboxylate group and a wide absorption due to the NH<sub>2</sub> groups of the cation. Those which has been confirmed by crystallography. The asymmetric unit contains one diisopropylammonium cation, iPr<sub>2</sub>NH<sub>2</sub><sup>+</sup> and one hydrogen maleate anion. In the structure, anions which present an inner O-H...O hydrogen bond are linked to cations through N-H...O hydrogen bonds leading to infinite chains. Chains are connected to their neighbours through weak C-H...O hydrogen bonds affording a layer. The study of the interactions of diisopropylammonium hydrogen maleate, by the presence of hydrogen bonds leading to supramolecular architectures has shown the possibility of its use in Active Pharmaceutical Ingredients (API).

**Keywords:** Crystal Structure, Diisopropylammonium, Maleate, Hydrogen Bonds, Sheet

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## 1. Introduction

Various ammonium salts of maleic acid have been synthesized and structurally characterized [1-6]. Use of salts and co-crystals of active pharmaceutical ingredients (APIs) as a method for tuning their delivery and activity is an area of growing interest [6]. Modifying API properties such as solubility by finding new salts that employ similar hydrogen bonding have been successful. Maleate derivatives remain among the agents most used in the design of active pharmaceutical ingredients (APIs) because of its power to

give APIs a high solubility. Recently, Timolol maleate has been developed and validated as being safe and effective APIs in the treatment of ocular glaucoma [7, 8]. Enalapril maleate has been successfully designated and evaluated according to the United States Pharmacopoeia (USP) for the treatment of hypertensive diseases [9]. For example, in the context of improving the solubility of this drug, three saccharinate, maleate and oxalate salts of Ethionamide (ETH) have been synthesized [1]. Mechanochemical protocols, confirmed by powder X-ray diffraction, show a more complete solid state characterization for Ethionamide (ETH) maleate [1].

Whenever possible, Active Pharmaceutical Ingredients (APIs) having properties of increasing solubility by the presence of its hydrogen bonds like maleate should be selected for the formation of the optimal salt. In an effort to further study of the hydrogen bonding patterns of the maleate ion with another ammonium counter cation nous avons synthétisé le diisopropylammonium hydrogen maleate. Diisopropylammonium comes from diisopropylamine which was used recently with dichloroacetate as being alleviates liver fibrosis through inhibiting activation and proliferation of hepatic stellate cells [10], we investigated the interactions between diisopropylamine and maleic acid which yielded single crystals of diisopropylammonium hydrogen maleate,  $\{[iPrNH_2]^+ \cdot [HCO_2CH=CHCO_2]^- \}$  whose crystallographic characterization is reported herein.

## 2. Materials and Methods

### 2.1. General

Chemicals were purchased from Sigma-Aldrich (Germany)

Table 1. Results of the elemental analyses of diisopropylammonium hydrogen maleate.

Compound	Chemical formula	Elemental analysis [%]					
		C		H		N	
		Calc.	Found	Calc.	Found	Calc.	Found
A	$\{[iPrNH_2]^+ [HCO_2CH=CHCO_2]^- \}$	72,06	71,80	9,40	8,60	8,85	8,75

## 3. Structure Description

### 3.1. Spectroscopic Study

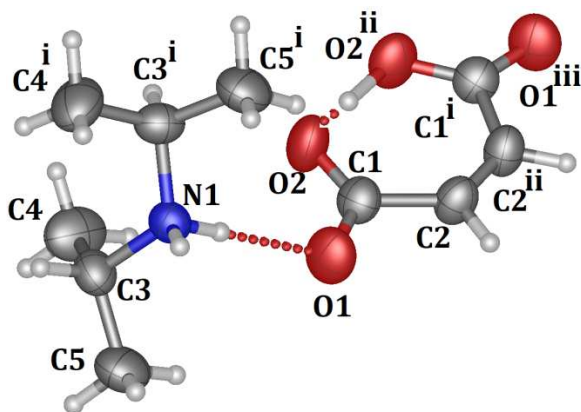


Figure 1. Asymmetric unit of diisopropylammonium hydrogen maleate.

The table 2 shown the Infrared data of diisopropylammonium hydrogen maleate. Compound diisopropylammonium hydrogen maleate was investigated by FT-IR spectroscopy. In the past, several works with FT-IR diisopropylammonium cations, carboxylates anions and multiples other vibration bands investigation have been reported [13]. The infrared spectrum enables to diagnose N–H stretching and bending vibrations at  $3385\text{ cm}^{-1}$ ,  $3251\text{ cm}^{-1}$  and  $11619\text{ cm}^{-1}$ , CO antisymmetric and symmetric vibrations at  $1548\text{ cm}^{-1}$ ,  $1576\text{ cm}^{-1}$  and  $1318\text{ cm}^{-1}$ . The band around  $1619$

and were used without any further purification. Elemental analyses were performed at the Institut de Chimie Moléculaire, Université de Bourgogne Franche-Comté, Dijon, France. The infrared spectra were recorded on a Bruker Vector 22 spectrometer equipped with a Specac Golden Gate™ ATR device. A crystal of dimensions  $0.60 \times 0.32 \times 0.16\text{ mm}$  was used in the data collection. The structure has been resolved and refined using the SAINT V8.37A programs (Bruker AXS Inc., 2015), XT VERSION 2014/5 [11, 12].

### 2.2. Synthesis

All the chemicals were purchased from Aldrich Company (Germany) and used without any further purification. Maleic acid,  $HCO_2CH=CHCO_2H$  (5.00g, 43mmol) was partially neutralized with diisopropylamine,  $iPr_2NH$  (4.38g, 43mmol) in methanol (50 mL). The clear obtained mixture was stirred 2h at room temperature (300 K). Crystals of the title salt suitable for an X-ray diffraction analysis was obtained after a month of a slow solvent evaporation at room temperature (300 K).

$\text{cm}^{-1}$  is due to the anti-symmetrical vibration of the  $NH_2$  group. This shows the presence of a maleate anion and a diisopropylammonium cation, confirmed by data from the asymmetric unit of the molecule shown in the following (figure 1).

### 3.2. Crystallographic Study

The title salt crystallizes in the orthorhombic Pccn space group as colourless plate-like crystals with parameters  $a = 9.6312(16)$ ,  $b = 11.188(2)$ ,  $c = 11.7591(15)$  (table 3). Its asymmetric unit is comprised of one diisopropylammonium cation and one hydrogen maleate (Figure 1). Several crystals of salts containing the diisopropylammonium cation,  $iPrNH_2^+$  are isolated and their structures reported in the literature [14, 15, 16, 17, 18].

In the structure, the acid anions  $H_2OC-CH=CH-CO_2^-$  are linked together by cations via hydrogen bonds  $OH \cdots O$ ,  $NH \cdots O$  giving rise to zigzag chains parallel to  $[010]$  (Figure 2) in which cations and anions alternate.

The geometric parameters (bond lengths and angles) of the  $iPr_2NH_2^+$  cation in the studied salt are well in accordance with those previously reported for other carboxylate salts such as bis(diisopropylammonium) hydrogen 1,2,3,4-butane tetracarboxylate  $[(Hdpa^+)_2 \cdot (H_2Bta^{2-})]$ ,  $H_2Bta^{2-}$  = dihydrogen 1,2,3,4-butane tetracarboxylate] and diisopropylammonium hydrogen 1,2-phenylenediacetate  $[(Hdpa) \cdot (Hpda^-)]$ ,  $Hpda^-$  = hydrogen 1,2-phenylenediacetate [17]. Maleate salts with diverse counter cations are also widely reported in the literature [2, 3, 5]. Bond lengths and angles within the maleate are in the expected range [2, 3, 5].

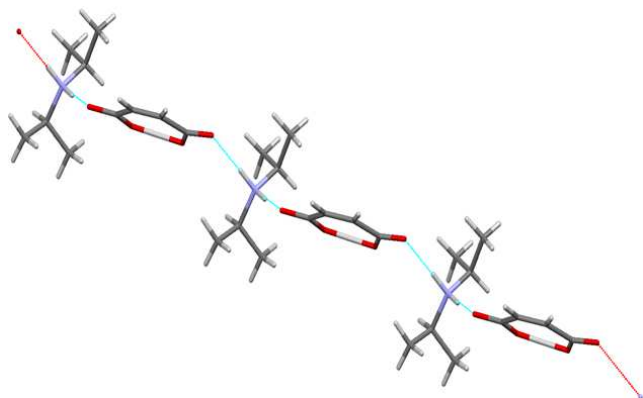


Figure 2. Hydrogen bonds (N-H...O) along axis *a*.

In the structure, the acid anions HO<sub>2</sub>C-CH=CH-CO<sub>2</sub><sup>-</sup> are linked together by cations via hydrogen bonds OH...O, NH...O giving rise to zigzag chains parallel to [010] (Figure 2) in which the cations and anions alternate. If we visualize approximately these interactions along the C axis, we observe a superposition of chains in which the maleates and the diisopropylammonium cations are superimposed between them. The layers interact by Vander Waals type connections (Figure 3).

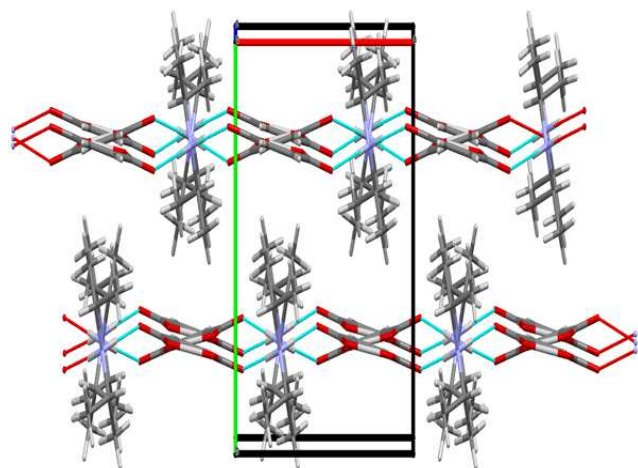


Figure 3. Hydrogen bonds O-H...O, N-H...O seen approximately along the axis *c*.

Table 2. Infrared data of the characteristic bands of diisopropylammonium hydrogen maleate.

Compound	vasCOO-	vsCOO-
[ <i>i</i> PrNH <sub>2</sub> ] <sup>+</sup> [HCO <sub>2</sub> CH=CHCO] <sup>-</sup>	1548(m) 1576(m)	1318(m)

δCOO-	v(NH <sub>2</sub> )	vas(NH <sub>2</sub> )
835(m)	3251(m) 3385(f)	1619(s)

A search of the Cambridge Structural Database (CSD Version 5.41, Update November 2019; Groom *et al.*, 2016) [19], yielded 67 hits for diisopropylammonium salts while more than 80 hits were obtained for the maleate anion. Within the maleate, a strong inner O<sub>2</sub>-H<sub>2</sub>A...O<sub>2</sub><sup>ii</sup> (Table 4) hydrogen bond link the two carboxylates. In the structure

*i*Pr<sub>2</sub>NH<sub>2</sub><sup>+</sup> cations and maleate anions are connected alternately through a N1-H1A...O1 hydrogen bond giving rise to an infinite chain. Weak C4-H4A...O1 (Table 4) link chains leading to a sheet structure (Figure 4).

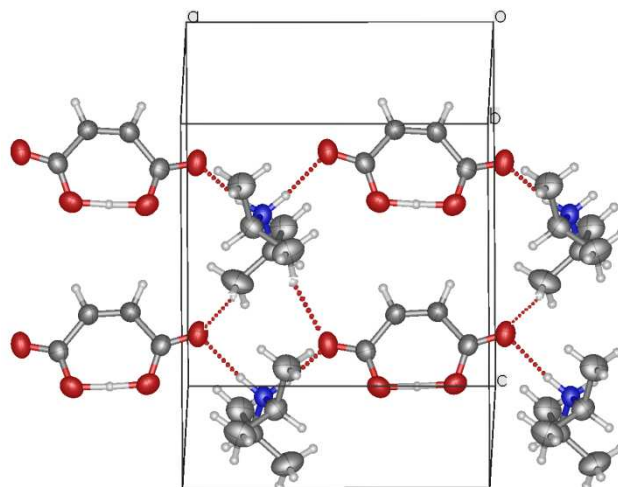


Figure 4. Partial packing diagram showing the hydrogen-bonding interactions.

CCDC 1975887 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

Table 3. Experimental details.

Crystal data	
Chemical formula	C <sub>10</sub> H <sub>19</sub> NO <sub>4</sub>
<i>M</i> <sub>r</sub>	217.26
Crystal system, space group	Orthorhombic, <i>Pccn</i>
Temperature (K)	200
<i>a</i> , <i>b</i> , <i>c</i> (Å)	9.6312 (16), 11.188 (2), 11.7591 (15)
<i>V</i> (Å <sup>3</sup> )	1267.1 (3)
<i>Z</i>	4
Radiation type	λ = 0.71073 Å
μ (mm <sup>-1</sup> )	0.09
Crystal size (mm)	0.60 × 0.32 × 0.16
Data collection	
Diffractometer	
Absorption correction	Multi-scan <i>SADABS2016/2</i> - Bruker AXS area detector scaling and absorption correction
<i>T</i> <sub>min</sub> , <i>T</i> <sub>max</sub>	0.64, 0.99
No. of measured, independent and observed [ <i>I</i> > 2σ( <i>I</i> )] reflections	9187, 1274, 987
<i>R</i> <sub>int</sub>	0.056
(sin θ / λ) <sub>max</sub> (Å <sup>-1</sup> )	0.625
Refinement	
<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )], <i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>S</i>	0.043, 0.117, 1.02
No. of reflections	1274
No. of parameters	78
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δ <sub>max</sub> , Δ <sub>min</sub> (e Å <sup>-3</sup> )	0.13, -0.15

**Table 4.** Hydrogen-bond geometry ( $\text{\AA}$ ,  $^\circ$ ) of diisopropylammonium hydrogen maleate.

$D-H\cdots A$	$D-H$	$H\cdots A$
$O2-H2A\cdots O2^{ii}$	1.21 (1)	1.21 (1)
$N1-H1A\cdots O1$	0.932 (15)	1.894 (15)
$C4-H4A\cdots O1^{iii}$	0.98	2.54
$D\cdots A$	$D-H\cdots A$	
2.413 (2)	177 (3)	
2.8186 (15)	171.5 (13)	
3.494 (2)	164	

Symmetry codes: (ii)  $-x+1/2, -y+1/2, z$ ; (iii)  $x, -y+1/2, z+1/2$ .

## 4. Conclusion

The structure of diisopropylammonium hydrogen maleate studied is an infinite chain deriving from hydrogen bonds of N-H... O and C-H... O type leading to a supramolecular structure. The study of these interactions has shown the possibility of using these salts in active pharmaceutical ingredients (APIs).

## Acknowledgements

The authors gratefully acknowledge the Cheikh Anta Diop University – Dakar (Senegal), the University of Bourgogne Franche-Comté, Dijon (France) and the SUNY-College – Geneseo – NY (USA) for facilities and financial supports.

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