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1:1 crystal complexes of 2′,6′-dimethoxyflavone with trichloroacetic and chloroacetic acids. Correlation between pK_a values and x-ray hydrogen bond data

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epoc ABSTRACT: The structures of two solid inclusion compounds with the 2′,6′-dimethoxyflavone host molecule (**1**) were investigated by single-crystal x-ray analysis. Both compounds, **1**·trichloroacetic acid (1:1) and **1**·chloroacetic acid (1:1) crystallize in non-centrosymmetric groups $Pna2_1$ and $P2_12_12_1$, respectively. The complexation involves an intermolecular hydrogen bond between the oxygen of the carbonyl group of the flavone and the acidic hydrogen of the substituted acetic acid. The results were used to improve a previous relationship between O···O distances and pK_a values. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: 2′,6′-dimethoxyflavone–trichloroacetic acid complex; 2′,6′-dimethoxyflavone–chloroacetic acid complex; crystal structure; pK_a values; hydrogen bond

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INTRODUCTION

The synthesis of new host molecules that form crystalline host–guest inclusion compounds is a topic of increasing attention.[1] They have applications in molecular recognition[1,2] and solid materials.[3] Good host molecules should pack with voids and contain appended sensors to bind with guest molecules.[4] One of the most important types of formation is through hydrogen bonding. In 2′,6′-dimethoxyflavone, the dimethoxyphenyl ring is situated approximately perpendicular to the γ-benzopyrone moiety. Such a conformation favours the formation of cavities that can include appropriate guest molecules. It has been known for a long time that flavones have basic properties. They form crystalline compounds with a wide variety of acids, giving with the stronger ones flavylium cations whose structure has been the subject of controversy.[5]

We have already reported the ability of the 2′,6′-dimethoxyflavone to form host–guest complexes. Brønsted acid molecules are hydrogen bonded to the carbonyl of the flavone[6–10] and Lewis acids form adducts.[11]

We describe in detail two new inclusion compounds with Brønsted acids having the same stoichiometry.

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EXPERIMENTAL

Preparation of crystalline inclusion compounds. The crystalline inclusion compound with $CHCl_2COOH$ was prepared by dissolving the host molecule, 2′,6′-dimethoxyflavone (**1**), in dichloroacetic acid. The resulting solution was allowed to stand for a few days to deposit crystals of a 1:1 inclusion compound which seemed suitable for x-ray analysis.

Crystalline inclusion compounds **1**·$CH_2ClCOOH$ and **1**·CCl_3COOH were prepared by dissolving equimolar amounts of the respective acid and the host molecule, **1**, in ethanol. The solution was allowed to evaporate at room temperature and after a few days crystals of 1:1 inclusion compounds were obtained.

The host–guest stoichiometry ratios were determined by ^{1}H NMR integration for **1**·$CH_2ClCOOH$ and **1**·$CHCl_2COOH$. For **1**·CCl_3COOH, elemental analysis was used. Analysis: calculated for $C_{19}H_{15}O_6Cl_3$, C 51.16, H 3.36; found, C 50.96, H 3.39%. Crystal data and selected experimental details are given in Table 1.

Structure analysis and refinement. The structure of **1**·$CH_2ClCOOH$ was solved without difficulty. For the structure of **1**·CCl_3COOH, we observed a large decay of the intensity standards during data collection (34.9%) which was definitively linear and from the results obtained adequately corrected. The structure of **1**·$CHCl_2COOH$ could not be solved owing to a strong

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Table 1. Crystal data, summary of intensity data collection and structure refinement for the compounds **1**·CCl_3COOH and **1**·$CH_2ClCOOH$

Parameter	**1**·CCl_3COOH	**1**·$CH_2ClCOOH$
Crystal data:		
Compound	$C_{17}H_{14}O_4 \cdot C_2HO_2Cl_3$	$C_{17}H_{14}O_4 \cdot C_2H_3O_2Cl$
Colour/shape	Pale yellow/parallelepiped	Colourless/parallelepiped
Formula weight	445.66	376.78
Space group	$Pna2_1$	$P2_12_12_1$
$F(000)$	912	784
Cell constants:		
a (Å)	6.790(2)	5.237(1)
b (Å)	28.060(4)	17.649(1)
c (Å)	10.356(1)	19.327(3)
V (Å^3)	1973.1(6)	1786.4(5)
Z	4	4
D_c (g cm^{-3})	1.500	1.401
μ(cm^{-1})	4.98	2.47
Crystal dimensions (mm)	0.56 × 0.12 × 0.10	0.58 × 0.20 × 0.17
Intensity measurements:		
Diffractometer/scan	Enraf-Nonius CAD-4/$\omega - 2\theta$	
Radiation, λ (nm)	Mo Kα (0.71069 Å)	
Temperature (K)	293(2)	293(2)
Reflections measured	1980	2999
Range of 2θ(°)	2.10–25.62	1.56–29.97
Range of h,k,l	0 to 8, 0 to 34, −12 to 0	0 to 7, 0 to 24, 0 to 27
No. of standard reflections	3	3
Interval between the standards (min)	60	60
Max. decay correction (linear)	1.238	1.038
Structure refinement		
No. of reflections included	1980	2999
No. of refined parameters	260	286
$R(F)$	0.0421	0.0688
Weights	$w = 1/[\sigma^2(F_o^2) + (aP)^2$ with $P = [F_o^2 + 2F_c^2]/3$	
	$a = 0.0633$	$a = 0.0302$
$wR(F^2)$	0.0953	0.0896
Goodness of fit	0.908	0.812
Weighted agreement factor including all unique non-zero reflections wR_{tot}	0.1199	0.1162
Final $\Delta\rho_{max}/\Delta\rho_{min}$ (e$^-$Å^{-3})	0.259/−0.247	0.262/−0.218

decay of the crystal by x-ray irradiation during data collection.

Structures were determined by direct methods with SHELXS-86[12] and refined by full-matrix least-squares on F^2 with SHELXL-97.[13] All non-hydrogen atoms were refined anisotropically. In **1**·CCl_3COOH, hydrogen atoms were introduced in calculated positions and refined riding on their bonded atom with global isotropic temperature factors except for H121. In **1**·$CH_2ClCOOH$, H atoms were found by difference Fourier synthesis and refined with their temperature factors fixed to 1.2 times the U_{eq} value of their corresponding bonded atoms. Pluton-93 was used for structure drawings.[14]

RESULTS AND DISCUSSION

Perspective views of **1**·CCl_3COOH and **1**·$CH_2ClCOOH$ with their crystallographic numbering scheme are shown in Fig. 1(a) and (b), respectively.

Molecular structure

In **1**·CCl_3COOH, H121 was located by difference Fourier synthesis and was refined isotropically. Results of this refinement confirmed that trichloroacetic acid, which is a strong acid ($pK_a = 0.70$), is non-ionized in the present crystal (Table 2). This is consistent with three structural data from the literature: the pure acid,[15] the complex with triphenylphosphine oxide[16] and the trichloroacetate anion of a pyrilium salt.[17] The trichloroacetate anion is characterized by similar carbon–oxygen bond distances associated with a larger O—C—O bond angle. In the non-ionized forms of trichloroacetic and chloroacetic

Table 2. Geometry of intermolecular hydrogen bonds (eds in parentheses)[a]

Compound	Distance (Å) D·A	Distance (Å) D—H	Distance (Å) H···A	Angle D—H···A (°)
1·CCl_3COOH	2.527(6)	1.01(8)	1.57(8)	156(8)
1·$CH_2ClCOOH$	2.589(5)	0.79(6)	1.84(6)	159(7)

[a] D—H···A is O121—H121···O4. Symmetry code: **1**·CCl_3COOH, *x,y,z*; **1**·$CH_2ClCOOH$, $x + 3/2$, $-y + 1/2$, $-z$.

acid,[18–20] carbon–oxygen bond distances of the carboxyl group are well differentiated (Table 3).

Correlation of d(O···O) versus pK_a

The previous relationship of pK_a vs x-ray hydrogen bond data that we had proposed was established in a short range of pK_a and we included the pK_a value of orthophosphoric acid.[10] Now the stoichiometry in the flavone–orthophosphoric acid complex is 1:2. Since the orthophosphate anion that is bound to the flavone is also H-bonded to another orthophosphoric acid molecule, the latter molecule may help in the ionization of the former. Accordingly, the structure with orthophosphoric acid must be excluded of the data to keep only host:guest stoichiometric ratio equal to one. To support this assertion, we note that in the urea–orthophosphoric acid (1:1) complex the urea carbonyl is not ionized and the acid hydrogen atom involved in the hydrogen bond is nearly centred.[21–23] With these new experimental results, a polynomial regression was applied to the data in Table 4. The curve giving the variation d(O···O) versus pK_a is represented in Fig. 2. The regression is $dO\cdots O = 0.0033pK_a^2 + 0.0089pK_a + 2.520$ with a correlation coefficient $r^2 = 0.9249$. The precision of this structural approach is lower than that of the method associated with

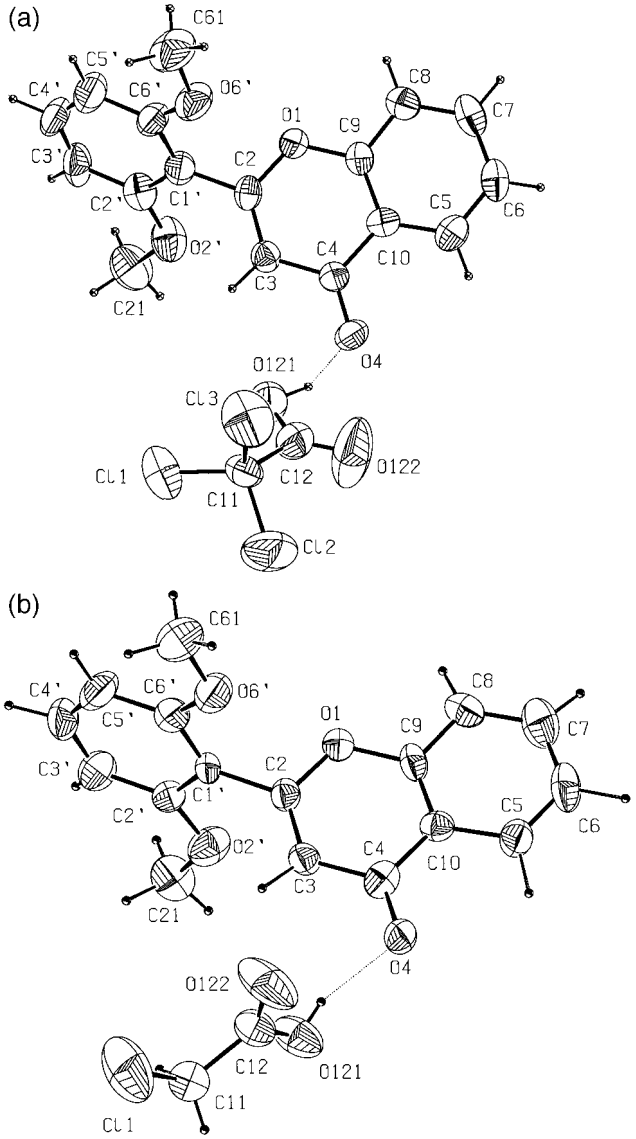

Figure 1. ORTEP drawings of the molecules with the atom-labelling schemes for the compounds (a) **1**·CCl_3COOH and (b) **1**·$CH_2ClCOOH$. The thermal ellipsoids are drawn at 50% probability

Table 3. Bond distances (Å) and bond angles (°) for trichloroacetic and chloroacetic acids and their acetate anions

Compound	Distance (Å) C—C	Distance (Å) C=O	Distance (Å) C—O	Angle O=C—O (°)	Ref.
CCl_3COOH	1.539(4)	1.205(4)	1.290(4)	125.9(3)	15
TPPO·CCl_3COOH[a]	1.554(4)	1.185(4)	1.292(4)	127.8(3)	16
1·CCl_3COOH	1.533(9)	1.179(9)	1.267(9)	125.9(8)	This work
CCl_3COO^-	1.579(7)	1.225(6)	1.233(6)	131.0(5)	17
$CH_2ClCOOH$-α[b]	1.502(5)	1.201(4)	1.316(5)	124.3(3)	18
	1.501(5)	1.199(5)	1.315(4)	123.8(3)	
$CH_2ClCOOH$-β	1.508(8)	1.212(6)	1.297(5)	124.9(5)	19
$CH_2ClCOOH$[c]	1.524(10)	1.196(9)	1.309(8)	125.5(5)	20
$CH_2ClCOOH^{-c}$	1.520(10)	1.239(8)	1.254(8)	126.4(5)	20
1·$CH_2ClCOOH$	1.502(9)	1.180(7)	1.307(7)	123.1(7)	This work

[a] TPPO = triphenylphosphine oxide.
[b] Two independent molecules in the asymmetric unit.
[c] From the structure of adeninium chloroacetate–chloroacetic acid solvate.

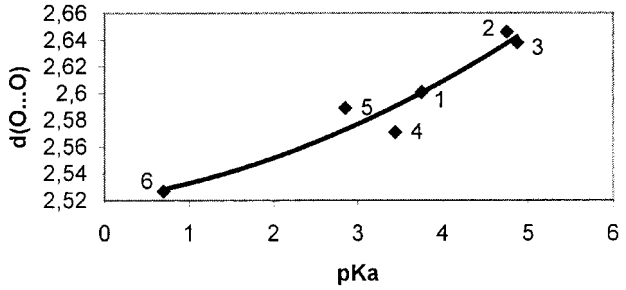

Figure 2. Dependence of hydrogen-bond distances on pK_a values

Table 4. pK_a values and hydrogen bond distances used in the regression for the different complexes

Acid in the complex	No.	pK_a	d(O···O)	Ref.
Formic	1	3.75	2.601(6)	7
Acetic	2	4.75	2.646(6)	6
Propionic	3	4.87	2.638(4)	7
2,6-Dimethoxybenzoic	4	3.44	2.571(2)	10
Chloroacetic	5	2.85	2.589(5)	This work
Trichloroacetic	6	0.7	2.527(6)	This work

a free energy relationship owing to the relatively large errors in the measurement of bond distances. In addition, the introduction of the data related to the 2,6-dimethoxybenzoic acid complex is questionable since the pK_a value of this acid (which is poorly soluble in water) is not definitely known. Experimental pK_a values are 3.44 by a titration procedure[24] and 3.60 obtained potentiometrically from dioxane–water mixtures by extrapolation to 0% dioxane.[25] Calculated values are 3.31 using ionization data for 2,4,6-trimethoxybenzoic acid and *p*-methoxybenzoic acid[24] and 3.99 using ionization data for benzoic acid and *o*-methoxybenzoic acid.[24] This curve (Fig. 2) should reach a limit at a d(O···O) characteristic of the basicity of the flavone. From the empirical equation, one can deduce the coordinates of the minimum value of the curve that would correspond to a symmetric O···H···O hydrogen bond. In that case the acid should have a pK_{a_0} of *ca* −1.3 and the hydrogen bond length should be 2.51 Å. The shortest d(O···O) hydrogen bonds found in crystals are around 2.39 Å.[26]

Probably with stronger acids, protonation of the carbonyl oxygen would occur. Corresponding data would lie on the left part of the curve with respect to the minimum value.

This hypothesis could be confirmed with stronger acids such as nitric or sulphuric acid. We have already reported the structure of the complex with perchloric acid,[9] but in this case a water molecule was involved in the hydrogen bond. For this reason, it was not included in the present data. Work is in progress in order to improve the correlation and confirm our results.

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