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Structural, spectroscopic and computational studies of the 2:1 complex of nipecotic acid with squaric acid

Elżbieta Bartoszak-Adamska, Zofia Dega-Szafran *, Anna Komasa, Mirosław Szafran

Faculty of Chemistry, Adam Mickiewicz University, Umultowska 89b, 61-614 Poznań, Poland

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ABSTRACT

The 2:1 centrosymmetric complex of protonated (*R*) and (*S*)-nipecotic acids (piperidinium-3-carboxylic acid) with the squarate dianion (3,4-dihydroxy-3-cyclobuten-1,2-dione) (**1**), has been synthesized and characterized by single-crystal X-ray analysis, FTIR and NMR spectroscopy. Crystals are monoclinic, space group $C2/c$, $Z' = 0.5$. The squarate dianion lays at the center of symmetry. It is surrounded by six stereoisomers of (*R*) and (*S*)-nipecotinium acid cations. The molecules are linked by N–H···O and COOH···O hydrogen bonds of 2.759(2) and 2.619(2) Å, respectively. The piperidine ring adopts a chair conformation with the carboxylic group in equatorial position. The FTIR spectrum shows a broad and intense absorption in the 3400–2000 cm^{-1} region, typical of medium–strong N–H···O and O–H···O hydrogen bonds. The ^{1}H and ^{13}C NMR spectra of the investigated complex confirm the structure of **1** in aqueous solution. Two models of the isolated 2:1 complexes (**2** and **3**) have been optimized at B3LYP/6-311G(d,p) level of theory to predict the more energetically stable structure. In **2** the molecules are linked by the O–H···N and O–H···O hydrogen bonds, while in **3** by the N–H···O and O–H···N hydrogen bonds.

1. Introduction

The relationships between molecular structure and its expressed physicochemical properties have been of long-standing interest to chemists and pharmacists. Nipecotic acid (piperidine-3-carboxylic acid) is a GABA-related compound (γ-aminobutyric acid), which has been widely used as an inhibitor of neuronal GABA uptake. GABA is the major inhibitory neurotransmitter in the mammalian central nervous system [1–7]. N-alkylated nipecotic acid and its derivatives are frequently used as building blocks in many compounds of pharmacological interest, e.g. with antiviral, antiepileptic, anticonvulsant or antihistaminic activities [8,9]. Nipecotic acid is a zwitterionic β-amino acid with the chiral center at C(3) (Fig. 1). As a zwitterion, it has two interacting centers, the proton-donor $N^{+}H_2$ group and the proton-acceptor COO^{-} group with pK_a values of 10.20 and 3.45, respectively [10]. In the crystals of nipecotic acid the carboxylate group is in equatorial position [11]. A similar conformation has been found in its hydrogen-bonded crystals with hydrochloric [12] and L-tartaric acids [13]. However, in the complexes of nipecotic acid with p-hydroxybenzoic [14] and salicylic acids [15] the carboxyl group is in the axial position.

To better understand the activity of nipecotic acid, as an important compound in the scientific research, we have synthesized a complex of (*R*/*S*)-nipecotic acid with squaric acid (3,4-dihydroxy-3-cyclobuten-1,2-dione, H_2SQ) (Fig. 1), which is a reagent for chemical synthesis, used for instance to make photosensitive squarate dyes [16,17] inhibitors of protein tyrosine phosphatases and squaraine-modified DNA [18]. The structure of squaric acid is not a perfect square [19–23]. The high acidity of H_2SQ with $pK_1 = 1.5$ for the first proton and $pK_2 = 3.4$ for the second one [24–26], is attributable to resonance stabilization of the anion [27]. H_2SQ in the presence of proton-acceptor can lose one or two protons, generating the hydrogen squarate anion, HSQ^{-}, or the squarate dianion, SQ^{2-} (Fig. 1) [28–32]. An interesting point of this study is the interaction between nipecotic acid which has one proton-donor and one proton-acceptor centers and squaric acid with two proton-donors. Thus the structure of the crystalline complex of dinipecotinium acid squarate (**1**) was determined by X-ray diffraction and the compound was characterized by FTIR and NMR spectroscopies. The geometry parameters of the optimized structures of the 2:1 complexes, by the B3LYP/6-311G(d,p) approach, support the information on the N–H···O and O–H···O hydrogen bonds in the isolated molecules and evaluate the relative stability of the 2:1 complex of nipecotic acid with squaric acid.

* Corresponding author. Tel.: +48 61 8291216; fax: +48 61 8291555.
E-mail address: degasz@amu.edu.pl (Z. Dega-Szafran).

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Table 1
Crystal data and structure refinement for the 2:1 complex of *R*/*S*-nipecotic acid with squaric acid (**1**).

Empirical formula	$C_{16}H_{24}N_2O_8$
Formula weight	372.37
Temperature	130(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	*C*2/*c*
Unit cell dimensions	a = 24.048(2) Å b = 6.3649(4) Å c = 12.4806(10) Å β = 117.363(11)°
Volume	1696.6(2) Å^3
Z	4
Calculated density	1.458 g/cm^3
Absorption coefficient	0.998 mm^{-1}
F(000)	792
Crystal size	0.22 × 0.18 × 0.08 mm
θ range for data collection	4.14–74.94°
Limiting indices	$-29 \leqslant h \leqslant 30$ $-7 \leqslant k \leqslant 7$ $-15 \leqslant l \leqslant 15$
Reflections collected/unique	10694/1731 [*R*(int) = 0.0513]
Completeness to θ = 74.94	99.2%
Max. and min. transmission	0.9244 and 0.8104
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1731/0/167
Goodness-of-fit on F^2	1.165
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0372, *wR*2 = 0.1047
R indices (all data)	*R*1 = 0.0417, *wR*2 = 0.1207
Extinction coefficient	0.0008(4)
Largest diff. peak and hole	0.312 and −0.247 e.Å^{-3}

2. Experimental

2.1. Synthesis

Nipecotic acid and squaric acid were purchased from Aldrich Chemical Co. To a solution of 1.044 g nipecotic acid in 1 mL of water, 0.47 g of squaric acid dissolved in 1 mL of water was added. The solvent was evaporated and the residue was recrystallized from a mixture of methanol–water (3:1), m.p. 188–189 °C. Elemental analysis for $C_{16}H_{24}N_2O_8$; calc.: %C, 51.61; %H, 6.50; %N, 7.52; found: %C, 51.47; %H, 6.55; %N, 7.45.

2.2. Measurements

X-ray diffraction data of the complex **1** were collected on a Super Nova Diffractometer. The structure was solved by direct methods using SHELXS-97 and refined on F^2 by the full-matrix least-squares with SHELXL-97 [33]. The crystal data, details of data collection and structure refinement are given in Table 1 and the final atomic coordinates in Table S1 (Supplementary material). The crystallographic and structural data in CIF format are available from the Cambridge Crystallographic Database Centre (CCDC 997665).

FTIR spectra were measured in Nujol and Fluorolube suspensions between KBr plates using a Bruker IFS 66v/S instrument, with the resolution of 2 cm^{-1}. Each spectrum was accumulated by acquisition of 64 scans.

The NMR spectra were recorded on a Bruker Advance DRX spectrometer operating at 599.93 and 150.85 MHz for ^{1}H and ^{13}C, respectively. The 2-D spectra were obtained with the standard Bruker software. The spectra were measured in D_2O relative to an internal standard of 3-(trimethylsilyl)propionic-d_4 acid sodium salt.

Elemental analysis was made using an Elemental Model Vario EL III.

2.3. Computational details

The DFT calculations were performed with the GAUSSIAN 09 program package [34]. The calculations employed the B3LYP exchange-correlation functional, which combines the hybrid exchange functional of Becke [35,36] with the gradient-correlation functional of Lee et al. [37] and the split-valence polarized 6-311G(d,p) basis set [38]. All calculated IR frequencies are positive and confirmed that the optimized structures corresponded to a minimum energy.

3. Results and discussion

3.1. Crystal structure

(*R*/*S*)-nipecotic acid (piperidine-3-carboxylic acid) forms a stable crystalline complex at the 2:1 ratio with squaric acid (3,4-dihydroxy-3-cyclobuten-1,2-dione), **1**. Compound **1** crystallizes in monoclinic *C*2/*c* space group with four molecules per unit cell, therefore the asymmetric unit contains a half of the 2:1 complex. The labeling of atoms is shown in Figs. 1 and 2 and S1 (Supplementary material). The full list of the bond lengths, bond and torsion angles is given in Table S2 (Supplementary material).

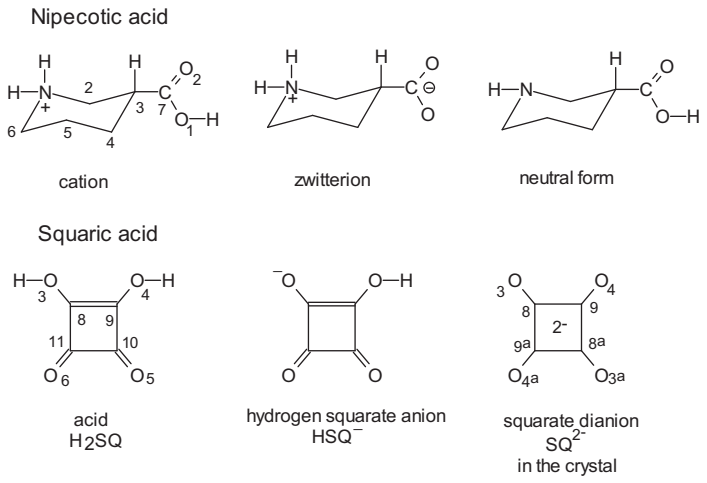

Fig. 1. Chemical structures and atoms labeling for nipecotic acid, squaric acid and their ions. ([a]symmetry code: $-x$, $-y-1$, $-z$).