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NH···O and OH···O interactions of glycine derivatives with squaric acid†

Michalina Anioła, Zofia Dega-Szafran,* Andrzej Katrusiak and Mirosław Szafran

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Four new hydrogen-bonded complexes of a simple amino acid glycine (GLY) and its methyl derivatives – sarcosine (*N*-methylglycine, SAR), dimethylglycine (DMG) and betaine (*N*,*N*,*N*-trimethylglycinium, BET) with squaric acid (3,4-dihydroxy-3-cyclobuten-1,2-dione, H_2SQ) are synthesized and characterized by X-ray diffraction, FTIR and NMR spectroscopy. The complexes differ in stoichiometry, interaction with H_2SQ and the hydrogen-bonding system. Methylation of glycine gradually reverses the dissociation of squaric acid in co-crystals. This process is correlated with the number of N–H···O bonds to the squaric acid oxygens and the N–H donor capability of glycine derivatives. The effect of the presence of methyl groups on the proton and carbon-13 chemical shifts is studied. The DFT calculations are performed for one unit of complexes and stable zwitterionic structures of SAR, DMG and BET in complex with H_2SQ, except the GLY unit, are suggested, which appears as an uncharged (neutral) form. The experimental and computed vibrational spectra of complexes studied are reported.

1. Introduction

Glycine, GLY, is the simplest protein structure unit and the smallest achiral amino acid that can act as a neuroinhibitor in the mammalian center nervous system.[1] Sarcosine, SAR, is the *N*-methyl derivative of glycine and belongs to a group of biologically important compounds containing a carbon atom participating in transmethylation reactions. In nature, it occurs in starfish, sea urchins and in the antibiotic actinomycin.[2] *N*,*N*-Dimethylglycine, DMG, is a sweet-tasting substance classified as a nutrient. It has been presumed to be a key ingredient of vitamin B-15 or pangamic acid. In the living cell, DMG is present as a product of the metabolism pathway of choline and methionine. DMG has been used in the treatment of mental disturbance conditions, like autism and epileptic seizures. DMG is a popular ingredient of supplementary diet tablets and energetic drinks for sportsmen.[2,3] Betaine, BET, trimethylglycinium, is a zwitterion containing an anionic carboxylate group and a positively charged quaternary ammonium group. Betaine is a biological oxidation product of choline and it is widely distributed in plants, algae and animal tissues, where it serves as a methyl transfer agent important in amino acid syntheses.[4] GLY,[5] SAR,[6] DMG[7] and BET[8] form crystalline adducts mainly with inorganic acids as well as with some organic acids.[7b,9] Some of them display interesting physical properties exhibiting phase transitions leading to ferroelectric, antiferroelectric and ferroelastic phases as well as phases with commensurate and incommensurate superstructures.[10] The *N*-alkylation of amino acids is known to increase the population of neutral tautomers in solution.[11]

Since amino acids and their complexes are of considerable chemical and biological interest we have undertaken a systematic investigation of several squaric acid complexes with the simplest amino acid glycine and its *N*-methyl derivatives, sarcosine, dimethylglycine and betaine (Fig. 1). Squaric acid, H_2SQ, is a reagent for chemical synthesis, used for instance to make photosensitive squarate dyes,[12] inhibitors of protein tyrosine phosphatases and squaraine-modified DNA.[13] The structure of squaric acid is not a perfect square.[14] The high acidity of H_2SQ with $pK_1 = 1.5$ for the first proton and $pK_2 = 3.4$ for the second one[15] is attributable to resonance stabilization of the anion.[16] The conjugate base of squaric acid is the hydrogen squarate anion, HSQ^-, whereas the conjugate base of the hydrogen squarate anion is the divalent squarate anion, SQ^{2-} (Fig. 1).[17]

The proton transfer belongs to the most frequent transformations in Nature, however this process is still not well understood. Squaric acid and amino acids are ideal for investigating the proton transfer. Some earlier papers of the groups of Kolev *et al.* concern complexes of amino acids and their derivatives with H_2SQ.[18] In the present work we report on the synthesis of four new complexes of H_2SQ with glycine, GLY, and its methyl derivatives, sarcosine (*N*-methylglycine, SAR), dimethylglycine (DMG), and betaine (trimethylglycinium, BET). The main aim of this work is investigation of the interaction between the zwitterionic compounds and the proton-donor. These complexes differ in their X-ray data, FTIR and NMR spectra. The differences

Faculty of Chemistry, Adam Mickiewicz University, Umultowska 89b, 61-614 Poznań, Poland. E-mail: degasz@amu.edu.pl; Fax: +48-61-8291555; Tel: +48-61-8291216

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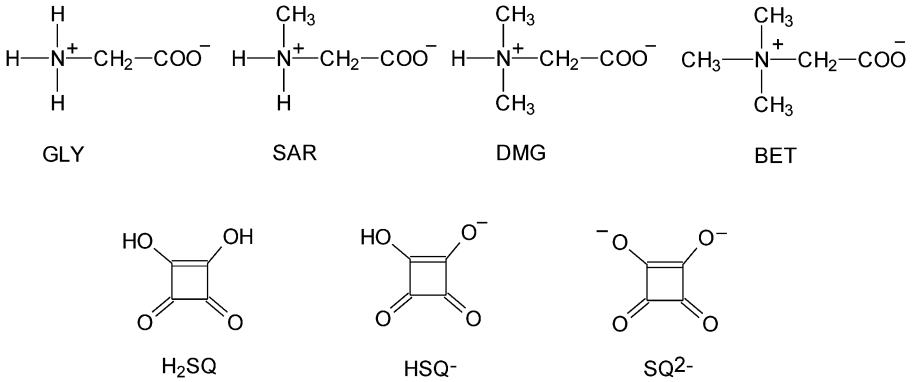


Fig. 1 Molecular structures of glycine (GLY), sarcosine (SAR), dimethylglycine (DMG), betaine (BET), squaric acid (H_2SQ), hydrogen squarate anion (HSQ^-) and squarate dianion (SQ^{2-}).

are caused by the presence of different number of acidic protons and methyl groups attached to the nitrogen atoms. From the point of view of materials science, the information on the formation of crystal structures of the complexes of glycine and its methyl derivatives with squaric acid is essential for understanding the role of hydrogen bonds and other intermolecular forces in the association of ions in the crystalline state. Quantum chemical calculations have been performed for one unit of all complexes to study their structures in the isolated molecules and their IR frequencies.

2. Results and discussion

GLY, SAR, DMG and BET form stable, crystalline complexes with H_2SQ. Their structures are studied by the single-crystal diffraction method, while the molecular structures of the isolated unit of complexes, without any interactions with the neighboring molecules, have been optimized by the B3LYP/6-311G(d,p) approach. The experimental and calculated bond lengths, bond and torsion angles are given in Tables S1 and S2, respectively (ESI†), while the selected ones are listed in Table 1. The hydrogen bond geometries, calculated energies (HF) and dipole moments are listed in Table 2.

2.1. Crystal (1) and optimized (1a) structures of the 2 : 1 complex of glycine with squaric acid

Glycine, GLY, is a non-essential, neutral amino acid without a center of chirality.[2,19] In an aqueous solution of pH ~ 7 GLY exists as a zwitterion with the positively charged amino group and the negative carboxylate group. Binding of proton to glycine is shown in Scheme 1.[20] The K_1 and K_2 constants reflect the intrinsic properties of the amino and carboxyl groups and their interactions on protonation (pK(COOH) = 2.35 and pK(NH_3^+) = 9.78).

GLY with H_2SQ forms a crystalline adduct, **1**, at a ratio 2 : 1. Both OH groups of H_2SQ are engaged in the short, asymmetric and non-equivalent hydrogen bonds, O(5)–H(3)···O(3) and O(5′)–H(4)···O(4) of 2.444(2) and 2.571(2) Å, respectively. Both O–H protons from H_2SQ are transferred to GLY, generating a squarate dianion, SQ^{2-}, and two glycinium cations (Fig. 2a, Table 2). Unlike in the crystal of GLY,[21] the glycine units in the complex exist in the cationic forms. A similar arrangement of the base and SQ^{2-} is observed in the known complexes of H_2SQ with bases.[17h,22] However, the optimized structure of the 2 : 1 complex, **1a**, is more symmetric than the crystal one, and H_2SQ interacts with two uncharged (neutral) forms of GLY units, with the O(3)–H(3)···O(5) and O(4)–H(4)···O(5′) lengths of 2.644 and 2.648 Å, respectively (Fig. 2b, Table 2). The COOH groups in GLY units in **1a** have *trans* conformations. In **1a** there are the O(6)–H(N1)···N(1) and O(6′)–H(N1′)···N(1′) intramolecular contacts between the carboxylic protons and the nitrogen atoms of GLY moieties, of 2.588 and 2.574 Å, respectively (Table 2), while in the crystal of **1** the N–H atoms form several short N–H···O contacts with the squarate dianions of the neighboring molecules. Aggregates of bonded molecules are shown in Fig. 3. The structure of the squarate dianion in **1** is almost square and planar. The C–C–C bond angles vary from 89.3(1)° to 91.2(1)°, whereas the C–C–C–C torsion angles are equal ±0.4(1)° (Table 1).

2.2. Crystal (2) and optimized (2a) structures of the complex of sarcosine with squaric acid and water

Sarcosine, also known as *N*-methylglycine, is an intermediate and by-product in glycine synthesis and degradation.[2]

SAR forms a hydrated complex with H_2SQ at a ratio SAR : H_2SQ : 0.5H_2O (**2**). One proton from squaric acid is transferred to sarcosine and the hydrogen squarate anion, HSQ^-, interacts with water (Fig. 4a). The protonation at O(5) is reflected in the C(5)–O(5) bond length of 1.314(1) Å, compared with the C(5)–O(6) bond of 1.201(1) Å. These bond lengths in pure sarcosine are 1.271(2) and 1.239(2) Å.[23] The geometry of the HSQ^- anion shows that the hydroxyl group is located at the O(4) atom, which is confirmed by (i) the C(4)–O(4) bond length of 1.308(1) Å is much longer than the other ones and (ii) the C(3)–C(4)–C(1) bond angle of 93.4(1)° is more open than the other three ones. The HSQ^- anion insignificantly deviates from planarity, as illustrated by the O–C–C–O torsion angles varying from −3.1(1)° to 3.1(1)° (Table 1).

The O(1W) oxygen atom of the water molecule is located on a two-fold axis, hence only H(1W) of the water molecule is

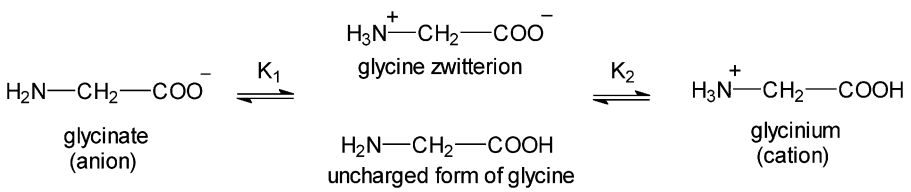
Table 1 Selected experimental and calculated bond lengths (Å), bond and torsion angles (°) for complexes of squaric acid with glycine (**1**, **1a**), sarcosine (**2**, **2a**), dimethylglycine (**3**, **3a**) and betaine (**4**, **4a**) by X-ray diffraction (**1**, **2**, **3**, **4**) and by the B3LYP/6-311G(d,p) approach (**1a**, **2a**, **3a**, **4a**)

	1		**1a**		**2**	**2a**	**3**		**3a**		**4**		**4a**	
Parameters	A[a]	B[b]	A[a]	B[b]			A[a]	B[b]	A[a]	B[b]	A[a]	B[b]	A[a]	B[b]
Bond lengths														
O(1)–C(1)	1.242(2)		1.215		1.250(1)	1.208	1.236(2)	1.235(2)	1.219	1.212	1.207(4)	1.216(4)	1.210	1.217
O(2)–C(2)	1.251(2)		1.201		1.215(1)	1.219	1.218(2)	1.223(2)	1.201	1.220	1.248(4)	1.240(4)	1.227	1.227
O(3)–C(3)	1.265(2)		1.305		1.247(1)	1.296	1.287(2)	1.258(2)	1.309	1.302	1.314(4)	1.304(4)	1.303	1.302
O(4)–C(4)	1.249(2)		1.322		1.308(1)	1.323	1.300(2)	1.318(2)	1.317	1.305	1.240(4)	1.250(4)	1.285	1.285
O(5)–C(5)	1.295(2)	1.312(2)	1.215	1.217	1.314(1)	1.247	1.266(2)	1.305(2)	1.229	1.242	1.298(4)	1.305(4)	1.262	1.262
O(6)–C(5)	1.211(2)	1.197(2)	1.320	1.324	1.201(1)	1.251	1.245(2)	1.213(2)	1.267	1.255	1.207(4)	1.185(4)	1.233	1.233
Bond angles														
C(1)–C(2)–C(3)	89.9(1)		86.67		87.7(1)	88.5(1)	87.7(1)	88.5(1)	86.56	87.91	88.3(3)	88.9(3)	88.33	88.37
C(2)–C(3)–C(4)	91.2(1)		92.86		89.4(1)	89.7(1)	91.4(1)	89.6(1)	92.50	92.10	93.3(3)	93.2(3)	92.74	92.73
C(3)–C(4)–C(1)	89.7(1)		93.02		93.4(1)	94.2(1)	91.9(1)	94.2(1)	92.74	92.97	89.9(3)	89.1(3)	91.39	91.38
C(4)–C(1)–C(2)	89.3(1)		87.45		89.4(1)	87.6(1)	89.0(1)	87.6(1)	88.16	87.01	87.9(3)	88.7(3)	87.54	87.55
Torsion angles														
C(1)–C(2)–C(3)–C(4)	−0.4(1)		0.16		−1.3(1)	−0.15	1.0(1)	0.8(1)	0.42	−0.31	−0.1(3)	−1.8(3)	0.19	0.19
C(2)–C(3)–C(4)–C(1)	0.4(1)		−0.17		1.3(1)	0.16	−1.1(1)	−0.9(1)	−0.43	0.32	0.1(3)	1.8(3)	−0.19	0.19
C(3)–C(4)–C(1)–C(2)	−0.4(1)		0.16		−1.3(1)	−0.15	1.0(1)	0.9(1)	0.42	−0.30	−0.1(3)	−1.7(3)	0.19	−0.19
C(4)–C(1)–C(2)–C(3)	0.4(1)		−0.15		1.3(1)	0.14	−1.0(1)	−0.8(1)	−0.39	0.28	0.1(3)	1.7(3)	−0.18	0.18
O(5)–C(5)–C(6)–N(1)	169.1(1)	170.4(1)	−176.42	−160.34	178.0(1)	143.51	161.8(1)	−166.4(1)	−176.36	−174.04	−168.3(3)	167.2(3)	170.91	−170.90
O(6)–C(5)–C(6)–N(1)	−11.8(2)	9.2(2)	4.05	20.24	−0.5(2)	34.03	−21.4(2)	15.4(2)	4.18	4.54	−10.7(6)	−13.9(6)	−8.03	8.04

[a] Part A - the positions denoted by the unprimed atomic labels. [b] Part B - the positions denoted by the primed atomic labels.

Table 2 Experimental and calculated geometry of the hydrogen bonds for complexes of squaric acid with glycine (**1**, **1a**), sarcosine (**2**, **2a**), dimethylglycine (**3**, **3a**) and betaine (**4**, **4a**) by the B3LYP/6-311G(d,p) approach, as well as calculated energies (HF, a.u.) and dipole moments (μ, D)

	D–H···A	D–H	H···D	D···A	∠DHA	
X-Ray						Symmetry code
1	O(5)–H(3)···O(3)	1.00(2)	1.46(2)	2.444(2)	167(2)	—
	O(5′)–H(4)···O(4)	0.80(2)	1.77(2)	2.571(2)	175(3)	—
	N(1′)–H(2′N)···O(2)	0.93(2)	1.90(2)	2.815(2)	139(1)	$1.5 - x, 0.5 + y, 1.5 - z$
	N(1′)–H(3′N)···O(5)	0.85(2)	2.11(2)	2.805(2)	133(1)	$2 - x, y, 1.5 - z$
	N(1)–H(2N)···O(1)	0.87(2)	2.08(2)	2.916(2)	157(2)	$2 - x, 2 - y, 2 - z$
	N(1)–H(2N)···O(6′)	0.89(2)	2.72(2)	2.828(2)	88(2)	$2 - x, 2 - y, 2 - z$
2	O(5)–H(3)···O(3)	0.92(2)	1.70(2)	2.612(1)	171(2)	—
	O(1W)–H(1W)···O(3)	0.85(2)	2.00(1)	2.849(1)	173(5)	$-x, y, 1.5 - z$
	O(4)–H(4)···O(1)	0.96(2)	1.60(2)	2.528(1)	161(2)	$0.5 + x, 0.5 - y, 2 - z$
	N(1)–H(2N)···O(1)	0.91(2)	2.09(2)	2.924(1)	152(1)	$-0.5 + x, 0.5 - y, -0.5 + z$
	N(1)–H(1N)···O(1W)	0.97(1)	1.90(2)	2.867(1)	173(2)	$-0.5 + x, 0.5 + y, z$
3	O(3)–H(3)···O(5)	0.82	1.65	2.444(2)	163	—
	O(4)–H(4)···O(6)	0.88(2)	1.66(2)	2.527(2)	170(2)	—
	O(4′)–H(4′)···O(1)	0.94(2)	1.68(2)	2.624(2)	176(2)	—
	O(5′)–H(3′)···O(3′)	0.93(2)	1.59(2)	2.514(2)	174(2)	—
	N(1)–H(1)···O(1′)	0.90(2)	2.16(2)	2.870(2)	136(1)	$1 - x, 1 - y, 1 - z$
	N(1′)–H(1′)···O(2)	0.92(2)	1.94(2)	2.803(2)	157(2)	$-x, 1 - y, -z$
	N(1′)–H(1′)···O(6′)	0.92(2)	2.55(2)	3.035(2)	114(1)	$-x, -0.5 + y, -0.5 - z$
4	O(5)–H(4)···O(4)	0.82	1.76	2.559(4)	164	—
	O(3)–H(3)···O(2′)	0.97(4)	1.55(4)	2.503(4)	167(4)	—
	O(3′)–H(3′)···O(2)	0.90(4)	1.61(4)	2.501(4)	166(3)	—
	O(5′)–H(4′)···O(4′)	0.82	1.73	2.546(4)	178	—
B3LYP/6-311G(d,p)						Energy/μ
1a	O(3)–H(3)···O(5)	0.997	1.648	2.644	176.57	−1023.673350/8.574
	O(4)–H(4)···O(5′)	0.995	1.658	2.648	172.63	
	O(6)–H(1N)···N(1)	0.990	1.862	2.588	127.64	
	O(6′)–H(1N′)···N(1′)	0.991	1.865	2.574	125.89	
2a	O(3)–H(3)···O(5)	1.023	1.518	2.537	173.67	−854.906921/7.001
	O(W)–H(1W)···O(6)	0.973	1.868	2.815	163.74	
	N(1)–H(2N)···O(2)	1.030	1.783	2.722	149.71	
3a	O(3)–H(3)···O(5)	0.987	1.693	2.671	170.46	−1635.534053/25.829
	O(4)–H(4)···O(6)	0.993	1.673	2.658	171.35	
	O(4′)–H(4′)···O(1)	0.999	1.646	2.643	175.80	
	O(3′)–H(3′)···O(5′)	1.013	1.561	2.570	172.69	
	N(1)–H(N1)···O(6)	1.064	1.669	2.495	130.49	
	N(1′)–H(N1′)···O(6′)	1.094	1.556	2.460	135.60	
4a	O(4)–H(4)···O(5)	1.052	1.427	2.473	171.72	−1714.166126/0.003
	O(3)–H(3)···O(2′)	1.000	1.600	2.591	169.85	
	O(3′)–H(3′)···O(2)	1.000	1.601	2.591	169.87	
	O(4′)–H(4′)···O(5′)	1.052	1.427	2.473	171.71	



Scheme 1 Binding of protons to glycine.[20]

symmetry independent. The water molecule links complexes of $SARH^{+}{\cdot}HSQ^{-}$ into two cyclamers, R_5^3 (16),[24] through four hydrogen bonds: O(5)–H(3)···O(3), O(1W)–H(1W)···O(3), O(4)–H(4)···O(1) and N(1)–H(2N)–O(1) of 2.612(1), 2.849(1), 2.528(1) and 2.924(1) Å, respectively, whereas two squaric units of the neighboring molecules form cyclamer R_2^2 (10)[24] through two O(4)–H(4)···O(1) hydrogen bonds of 2.528(2) Å (Fig. 5, Table 2).

The optimized structure at a ratio 1 : 1 : 1, SAR : H_2SQ : H_2O, determined by the B3LYP/6-311G(d,p) approach of the hydrated complex of SAR with H_2SQ, **2a**, is shown in Fig. 4b. The optimized

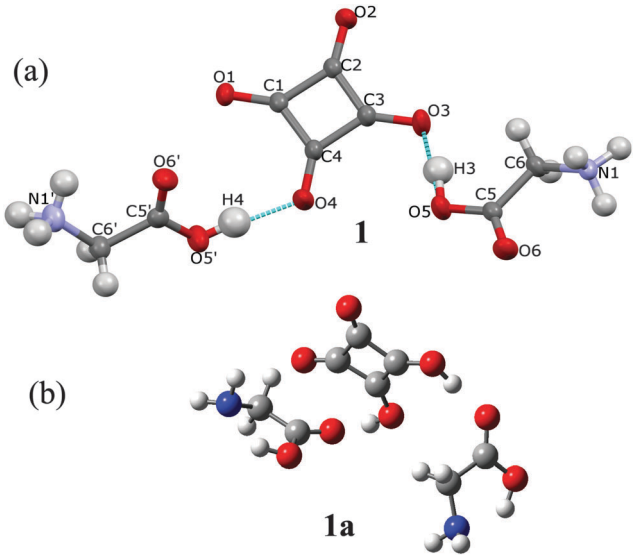


Fig. 2 (a) Two glycinium cations and a squarate dianion in the crystal structure (**1**) and the atomic labeling scheme. Thermal parameters are shown at the 50% probability level and H-bonds are indicated by the dotted lines; (b) the optimized structure of **1a**, determined by the B3LYP/6-311G(d,p) approach, showing two uncharged glycine molecules and squaric acid.

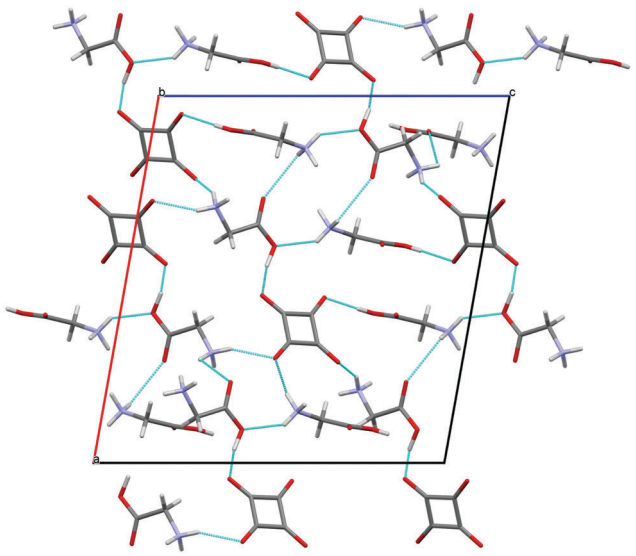


Fig. 3 Structure of crystal **1** viewed down the [010] direction. The hydrogen bonds are indicated by the blue dotted lines.

structure of **2a** differs from the crystal of **2**, by the lack of interactions between the neighboring molecules. H_2SQ interacts with SAR by the O(3)–H(3)···O(5) hydrogen bond of 2.537 Å. The zwitterionic character of sarcosine is confirmed by the C(5)–O(5) and C(5)–O(6) bond lengths of 1.247 and 1.251 Å, respectively (Table 1). The water molecule is engaged in the O(W)–H(1W)···O(6) hydrogen bonds of 2.815 Å with the carboxylate group of the SAR unit. Additionally, the N(1)–H(2N) group forms an intramolecular hydrogen bond with the O(2) atom of 2.722 Å (Table 2).

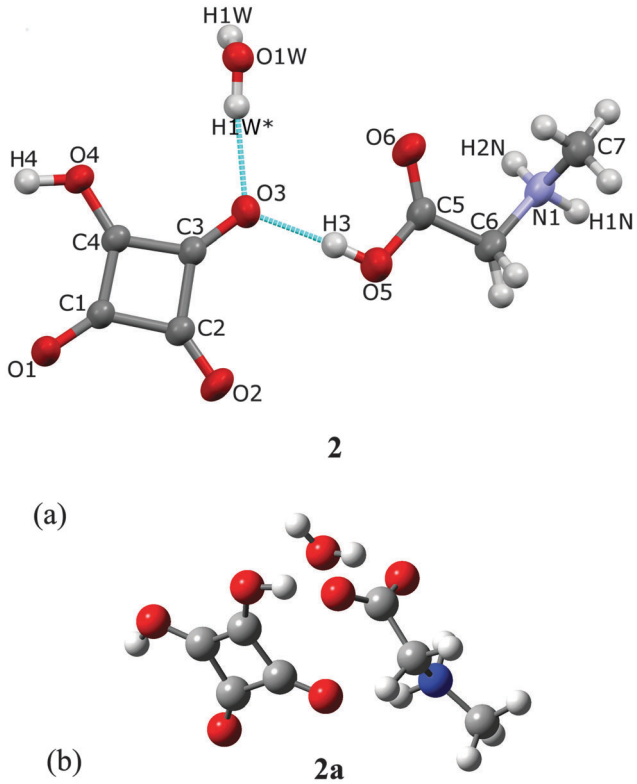


Fig. 4 (a) The hydrogen squarate anion, sarcosinium cation and water molecule in the crystal structure **2** and the atomic labeling scheme. All atoms are at general positions, except O(1W) located on the 2-fold axis, hence only H(1W) of the water molecule is symmetry-independent. H1W* is at equivalent position ($-x$, y, $1.5 - z$). Thermal parameters are shown at the 50% probability level and H-bonds are indicated by the dotted lines; (b) the optimized structure of **2a**, determined by the B3LYP/6-311G(d,p) approach, showing sarcosine, squaric acid and water molecules.

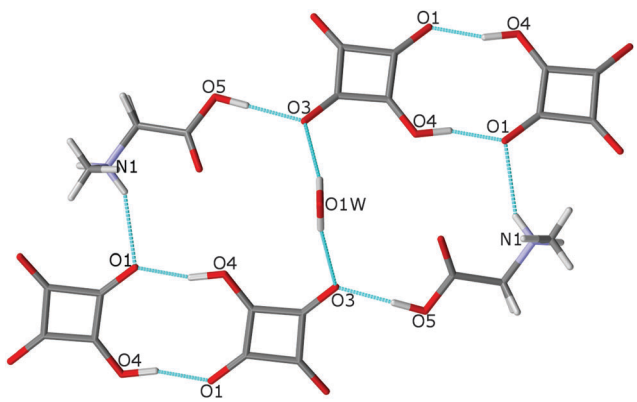


Fig. 5 Two hydrogen-bonded cyclamers R_5^3 (16) and R_2^2 (10) in the structure of **2**. The O–H···O and N–H···O bonds are indicated by dotted lines.

2.3. Linear dimer of the 2 : 2 complex of dimethylglycine with squaric acid (3 and 3a)

The DMG molecule has an amphoteric character and can exist in an anionic or a cationic form, as well as in two uncharged tautomeric forms, one of which is with neutral amino and

carboxylic groups, which is more stable in the gas phase and the dipolar zwitterionic form, which is more stable in aqueous solution.[11,25] According to a survey of the Cambridge Structural Database there are only two reports of crystal structures of the hydrogen-bonded complexes of DMG with acids,[7] where DMG exists in the cationic form.

The investigated complex of DMG with H_2SQ, **3**, consists of two independent 1 : 1 complexes linked together into a linear dimer by the O(4′)–H(4′)···O(1) hydrogen bond of 2.624(2) Å (Fig. 6a, Table 2). In one of these complexes DMG is bonded to H_2SQ through the O(3)–H(3)···O(5) and O(4)–H(4)···O(6) hydrogen bonds of 2.444(2) and 2.527(2) Å, respectively, with both of its oxygen atoms of the carboxylate group engaged. In the second 1 : 1 complex, the proton transfer occurs from H_2SQ to DMG, and the DMG cation is joined to the hydrogen squarate anion through the O(5′)–H(3′)···O(3) hydrogen bond of 2.514(2) Å. The O(6′) atom is not involved in any hydrogen bonds. The optimized structure of dimer **3a** (Fig. 6b) differs slightly from the crystal structure of **3**. In **3a** both DMG units exist in the zwitterionic forms and interact with two H_2SQ molecules by the O–H···O hydrogen bonds longer than in the crystal of **3** (Table 2). The complex **3** has the extended conformation, whereas the optimized complex **3a** is bent. The angles between the plane of the squarate ring in **3** and **3a** are 21.37° and 63.18°, respectively.

In the crystal of **3** the dimers are linked to form two cyclamers described by the graph set $R_6^6(30)$,[24] where the N–H atoms engaged in the N(1)–H(1)···O(1′) and N(1′)–H(1′)···O(2) hydrogen bonds of 2.870(2) and 2.803(2) Å, respectively (Fig. 7, Table 2), play the main role.

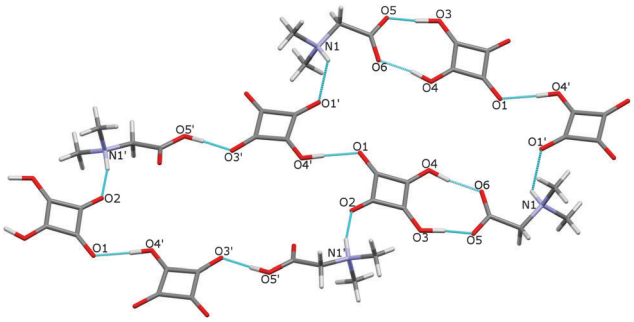


Fig. 7 Two hydrogen-bonded cyclamers R_6^6 (30) in the structure of **3**. The O–H···O and N–H···O bonds are indicated by dotted lines.

2.4. Cyclic dimer of betainium hydrogen squarate (4, 4a)

The name betaine (BET) is used, when the bonding proton is not transferred, and betainium $(BETH)^+$ when the proton is transferred from the acid to betaine.[8c]

BET and H_2SQ form a crystalline complex **4** at the 2 : 2 ratio (Fig. 8a). In crystal **4** one proton from each squaric acid molecule is transferred to two BET molecules, generating hydrogen squarate anions, HSQ^- and protonated betaine cations, $BETH^+$. The HSQ^- anions and the $BETH^+$ cations are linked through the asymmetric O(5)–H(4)···O(4) and O(5′)–H(4′)···O(4′) hydrogen bonds of 2.559(4) and 2.546(4) Å, respectively. Two 1 : 1 complexes are joined into a cyclic dimer by two non-equivalent O(3)–H(3)···O(2′) and O(3′)–H(3′)···O(2) hydrogen bonds of 2.503(4) and 2.501(4), respectively Å (Table 2). The formation of the α-dimer is one of the most common ways of aggregation of HSQ^- anions, which are linked by two short

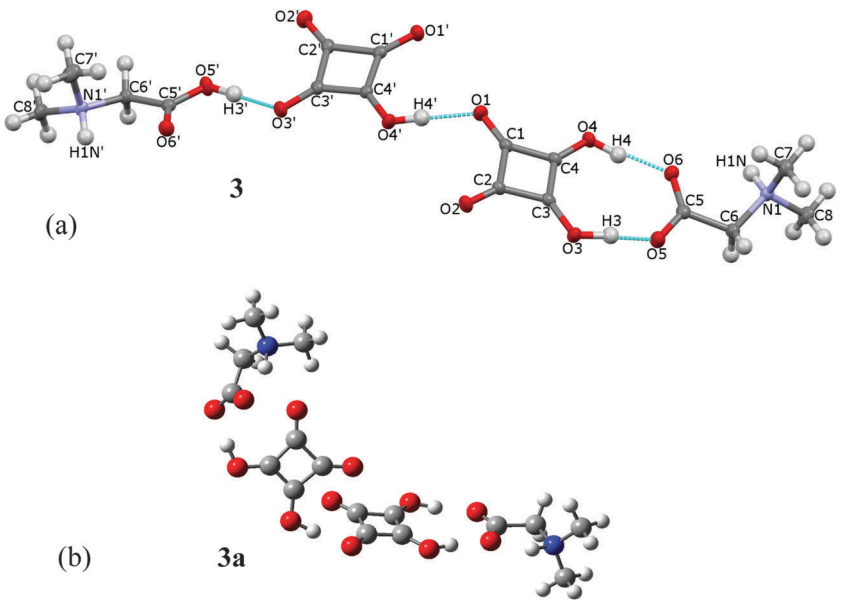


Fig. 6 (a) The crystal structure of the dimer of dimethylglycine-squaric acid and dimethylglycinium-hydrogen squarate, **3**, and its atomic-labeling scheme. All atoms are at general positions and the asymmetric part of the cell contains hydrogen squarate anion, squaric acid, *N*-dimethylglycinium cation and *N*-dimethylglycine as zwitterion. Thermal parameters are shown at the 50% probability level and H-bonds are indicated by the dotted lines; (b) the optimized structure of **3a**, determined by the B3LYP/6-311G(d,p) approach, showing two squaric acids and two dimethylglycinium zwitterions linked into a linear dimer.

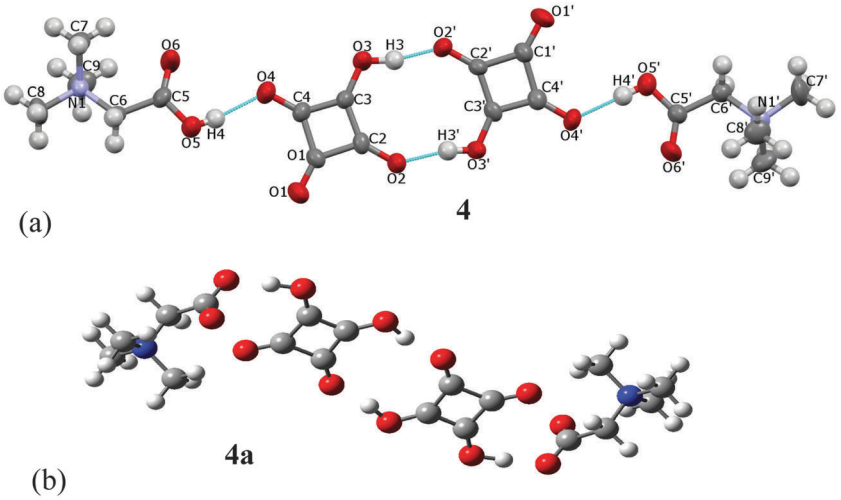


Fig. 8 (a) The crystal structure of the H-bonded cyclic dimer of betainium hydrogen squarate, **4**, and its labeling scheme. All atoms are at general positions and the asymmetric part of the unit cell contains two squarate anions and two betainium cations. Thermal parameters are shown at the 50% probability level and H-bonds are indicated by the dotted lines; (b) the optimized structure of **4a**, determined by the B3LYP/6-311G(d,p) approach, showing two squaric acids and two betaines linked into a centrosymmetrical dimer.

O–H···O hydrogen bonds of 2.47–2.54 Å.[17a,b,d] All structures containing α-dimers of HSQ^- ions have the interesting property of being completely anhydrous, in spite of the fact that most of them crystallized from water.[17c,d,e,g,j,26] The crystal packing of dimers **4** in the unit cell along the [010] axis is shown in Fig. 9.

The optimized structure of the dimer, **4a**, determined by the B3LYP/6-311G(d,p) approach is much more symmetric than that of crystal **4** (Fig. 8b). No protons are transferred from squaric acid to betaine and complexes form a centrosymmetric dimer. The calculated dipole moment is 0.003 D. In the optimized complex **4a**, the O(4)–H(4)···O(5) hydrogen bonds of 2.473 Å, which linked H_2SQ and BET molecules, are shorter than those in complex **4**, whereas the O(3)–H(3)···O(2) bonds of 2.591 Å, which joined 1 : 1 complexes into a centrosymmetric dimer are longer than in **4** (Table 2). The presence of H_2SQ molecules in dimer **4a** is confirmed by the C(2)–C(3)–C(4) and C(3)–C(4)–C(1) bond angles of 92.74° and 91.39°, respectively, whereas in **4** the C(2)–C(3)–C(4) bond angles in both HSQ^- are *ca.* 93°, while those of C(3)–C(4)–C(1) are 89.0(3)° and 89.1(3)°. A similar centrosymmetric dimer has been found in the crystal and optimized structures of the complex of quinuclidine betaine with squaric acid.[26]

In summary the differences between the crystal forms and optimized structures arise from the lack of N–H···O interactions in all isolated glycine–squaric acid complexes.

2.5. Correlation between the number of N^+H donors and the number of the methyl groups in glycine derivatives with the ionization of squaric acid

The increasing presence of N^+H-donors in the glycine derivatives (in the sequence BET → DMG → SAR → GLY) leads to systematic changes in the H-bonding patterns, the molecular arrangement, hydration and, most importantly, in the dissociation of protons transfering from squaric acid to glycine derivatives (Fig. 10). We found that the presence of three N^+H donors (in **1**) results

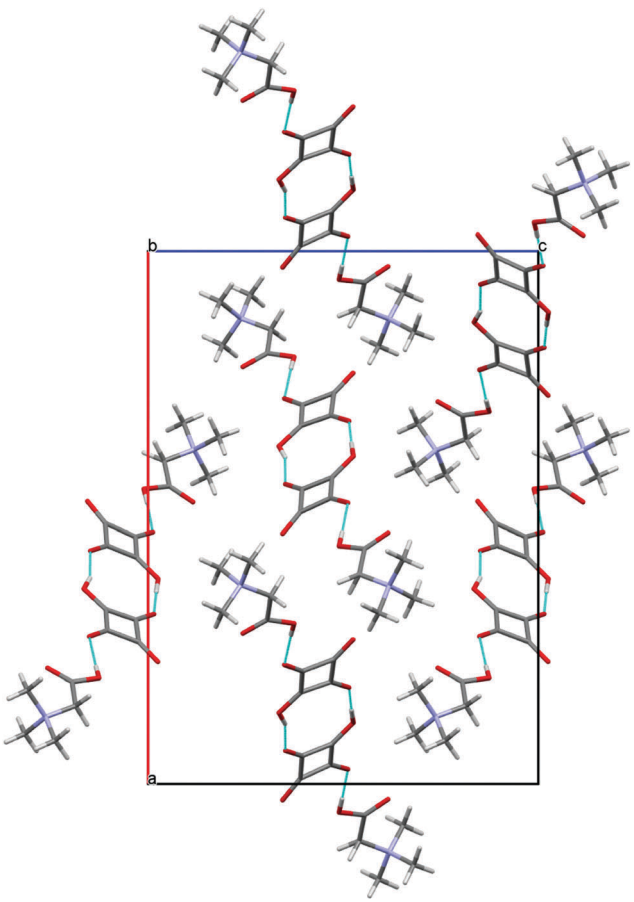


Fig. 9 Structure of crystal **4** projected down [010]. The hydrogen bonds are indicated by blue dotted lines.

in the full dissociation of squaric acid. The dissociation reduces through two N^+H donors, when even a neutral squaric acid

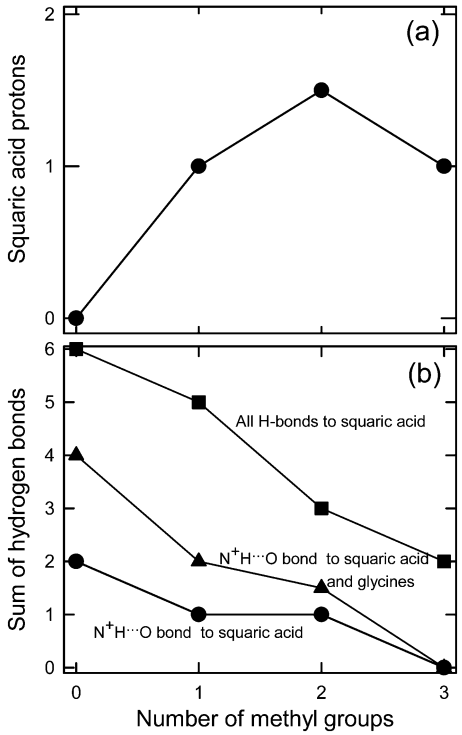


Fig. 10 (a) The numbers of protons in a squaric acid moiety as a function of the number of methyl groups in the glycine derivatives, two protons in H_2SQ, one in HSQ^- and zero in SQ^{2-}; (b) the numbers of H bonds (N–H···O, O–H···O) to squaric acid and glycine derivatives as a function of the number of methyl groups in the glycine derivatives; ● – N^+–H···O bonds to squaric acid moiety, ▲ – N^+–H···O bonds to squaric acid moiety and glycine derivatives; ■ – all H-bonds to squaric acid moiety.

molecule was obtained. When N^+H donors are absent (in **4**), half-dissociated squaric acid anions (HSQ^-) are observed and they aggregate into doubly O–H···O bonded dimers. This process cannot be reproduced by calculations involving one isolated structural unit only, as it does not include N^+H···O bonds to the squaric acid oxygen atoms. Fig. 10 shows the correlation between the frequency of N^+H···O hydrogen bonds as a function of the number of methyl groups in glycine derivatives (no methyl in GLY, one methyl in SAR, two methyls in DMG and three methyl groups in BET). The squarate dianion, SQ^{2-}, has eight H-acceptor sites in $2GLY^+{\cdot}SQ^{2-}$, six of them are used in N^+H···O bonds and the remaining two in O–H···O bonds (8 H-donors to 8-acceptors). The average of the numbers of protons in the symmetry independent H_2SQ molecule and the HSQ^- anion equal to 1.5 is plotted for DMG structure **3**. It can be concluded that each N–H···O hydrogen bond somewhat reduces the double-bond character of the squaric acid carbonyls and in this way contributes to the dissociation of H_2SQ molecules. This systematically happens for one and two methyl substituting ammonium protons and this relation is valid for GLY, SAR and DMG, however, this relation is reversed for BET, when no ammonium protons are available.

2.6. ^1H and ^{13}C NMR spectra

Both proton and carbon-13 NMR spectra of complexes of glycine and its methyl derivatives with squaric acid are very simple, however the effect of the number of methyl groups attached to the quaternary nitrogen atom on the proton and carbon-13 chemical shifts is significant. With increasing number of methyl groups in glycines the resonance signals of the CH_2 and CH_3 protons and methylene and methyl carbon-13 atoms are linearly shifted to a lower magnetic field, whereas the resonance signal of the COOH carbon atom undergoes an upfield shift (Fig. S1, ESI†). The proton and carbon-13 chemical shifts are given in the Experimental section. The single ^{13}C resonance signal of the hydrogen squarate carbon atoms appear in the lower magnetic field and it is observed between 198.64 and 198.86 ppm. The C═O and C–OH groups can form similarly strong H-bonds to the surrounding water molecules and carboxylate groups, leading to the π-conjugation of their C–C and C–O bonds.[17a]

2.7. Infrared spectra

Amino acids exhibit a great deal of hydrogen bonding as evidenced by the presence of many broad bands in their infrared spectra especially in the region 3000–2000 cm^{-1}.[8b,c,27] The solid-state FTIR spectra of complexes **1**, **2**, **3** and **4** are shown in Fig. 11a, c, e, g, while the frequencies computed by the B3LYP/6-311G(d,p) approach for optimized structures **1a**, **2a**, **3a** and **4a** are shown as vertical lines in Fig. 11b, d, f, h, respectively. The proposed assignments of bands were made using the Gauss View molecular visualization program.[28]

In the FTIR spectrum of **1** (Fig. 11a) the νNH band appears at 3160 cm^{-1}, while the νOH vibration is assigned to the broad band in the 3000–2000 cm^{-1} region. The calculated asym. and sym. stretching, in-plane bending and out-of-plane bending NH vibrations for GLY units in **1a** are observed at 3614 and 3603, 3538 and 3507, 1663 and 1643, 984 and 935 cm^{-1}, respectively. The bands at 3367 and 3344 cm^{-1} are attributed to the νO(6)–H···N vibrations, while those at 3212 and 3188 cm^{-1} to the νO(3,4)–H···O(5) modes (Fig. 11b).

In the FTIR spectrum of **2** (Fig. 11c) the bands at 3350, 2830 and 2470 cm^{-1} are assigned to the νO–H mode in water, νN–H···O and νO–H···O vibrations, respectively. The calculated νO–H in water, νN–H···O and νO–H···O vibrations for **2a** appear at 3640, 3235 and 2715 cm^{-1}, respectively (Fig. 11d).

The experimental infrared spectrum of **3** (Fig. 11e) shows broad bands at 2720 and 2480 cm^{-1} attributed to νN–H and νO–H modes, respectively. However, in the calculated spectrum of **3a** (Fig. 11f) there are several intensive bands at 3365 and 3243 cm^{-1} assigned to the νO(3)–H···O(5) and νO(4)–H···O(6) modes, at 3133 cm^{-1} to the νO(4′)–H···O(1) mode, at 2878 cm^{-1} to the νO(3′)–H···O(5′) vibration and at 2471 cm^{-1} to the νN–H mode of atoms engaged in the strong intramolecular hydrogen bonds (Table 2).

The FTIR spectrum of **4** (Fig. 11g) is characterized by a broad absorption centered at 2450 cm^{-1}, which is attributed to the νO–H···O vibration. A similar absorption is observed in the spectra of betaine complexes with mineral and organic acids,[8b,c,9] and its shifts to lower or higher wavenumbers depend on the hydrogen bond strength. The calculated frequencies for **4a** at 3160 and 2260 cm^{-1} are assigned to the stretching

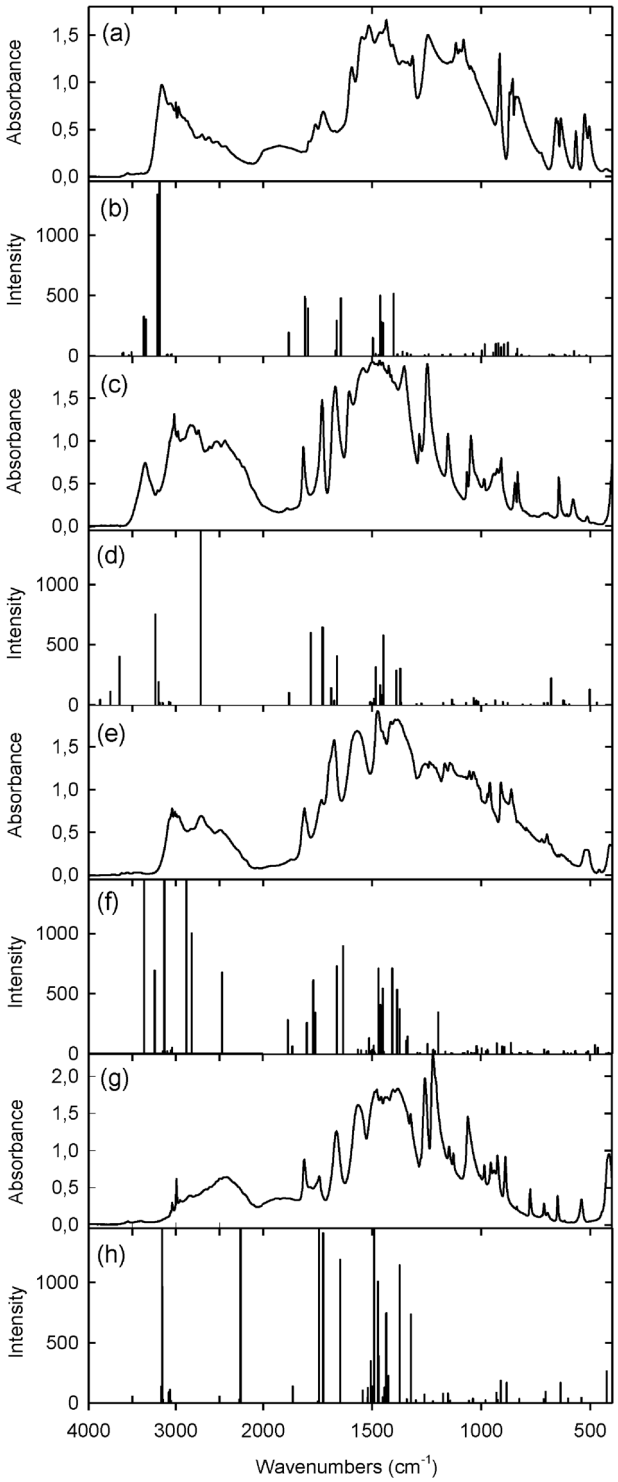


Fig. 11 Experimental solid-state spectra and calculated frequencies by the B3LYP/6-311G(d,p) approach (a) and (b) for **1** and **1a**; (c) and (d) for **2** and **2a**; (e) and (f) for **3** and **3a**; (g) and (h) for **4** and **4a**, respectively.

vibrations of the O–H groups engaged in the longer O(3)–H···O(2) and shorter O(4)–H···O(5) hydrogen bonds, respectively (Fig. 11h, Table 2).

The broadening of the IR absorption in the spectra of the complexes investigated is also observed in the region below 1500 cm^{-1}. A similar broad band in this region was observed in the infrared spectrum of H_2SQ[29] and in the spectra of squaric acid complexes with various bases.[17j,30] This broad absorption overlaps the deformation vibrations of the methyl and methylene groups, hydroxyl groups, and ring and skeletal modes. However, the bands in the 1800–1500 cm^{-1} region are attributed to the νC═O, νC═C and νCOO vibrations. Two bands at 1759 and 1723 cm^{-1} are assigned to νC═O of glycinium moieties in the spectrum of **1**. Similarly, the νC═O band at 1740 cm^{-1} was observed in the spectrum of glycinium monophenylphosphate.[5a] In the spectrum of **2** the νC═O band at 1729 cm^{-1} of the sarcosinium cation is observed and it appears in a similar frequency as in the spectrum of sarcosinium iodide.[6d] In the spectrum of the complex of **3**, both ν_{as}COO and νC═O bands at 1674 and 1731 cm^{-1} are observed and they are assigned to dimethylglycine and the dimethylglycinium cation, respectively. The band at 1740 cm^{-1} in the spectrum of **4** confirms the presence of the betainium cation in complex with squaric acid. In the spectrum of the proton-transfer complex of BET with 2,6-dichloro-4-nitrophenol the νC═O band appears at 1720 cm^{-1}, while in the spectrum of the molecular complex formed between BET and pentachlorophenol the ν_{as}COO band appears at 1664 cm^{-1}.[9b]

The frequencies of the squaric acid moiety are much better recognized in the calculated IR spectra than in the experimental ones, where the νC═O vibrations appear as a single band in the 1815–1790 cm^{-1} region. The calculated frequencies from the 1885–1865 cm^{-1} range are assigned to the ν_sC═O, while those in the 1790–1745 cm^{-1} region are attributed to the ν_{as}C═O modes in the H_2SQ moiety. The spectral features of the squarate units are similar to those observed earlier.[17f,j,18e,27a,31] The experimental and calculated spectra are slightly different, because the experimental spectrum is recorded for the complex in the solid state, while the computations are made for the vibrations of the isolated molecule in the gas phase, and the calculations are based on harmonic frequencies, while the experimental ones are based on the anharmonic frequencies.

The experimental FTIR spectra confirm the crystal structure of the complex investigated, whereas the calculated frequencies correspond well with the structures of the isolated molecules.

The IR data confirm the key information about the proton positions determined in the crystalline complexes by X-ray diffraction.

3. Conclusions

In the crystals of complexes of squaric acid, H_2SQ, with glycine, GLY, **1**, sarcosine, SAR, **2**, dimethylglycine, DMG, **3** and betaine, BET, **4**, the proton from H_2SQ is transferred to amino acid molecules. The exception is the 2 : 2 complex of **3** in which one molecule of DMG is protonated, while the other remains in the zwitterionic form. In the optimized structures of one unit of complexes investigated (**1a**, **2a**, **3a**, **4a**) by the B3LYP/6-311G(d,p) approach, the amino acid moieties are in their zwitterionic forms with the exception of **1a**, in which GLY exists

in an uncharged (neutral) form. The HSQ^- and amino acid molecules are linked by the O–H···O hydrogen bonds with the O···O distances from 2.444 to 2.624 Å. Depending on methylation of glycine in its co-crystals with squaric acid, its dianion, monoanion, neutral and mixed forms are stabilized. Methylation of glycine gradually reverses the dissociation of squaric acid in crystals. The resonance signals of the proton and carbon-13 of the methylene and methyl groups are shifted to a lower magnetic field with increasing number of methyl groups attached to the amino group, while the resonance signal of the carboxylic group is linearly shifted to a higher magnetic field.

4. Experimental section

4.1. General procedure

Amino acids, GLY, SAR and DMG were purchased from Aldrich Chemical Co, whereas BET from Sigma. FTIR spectra were measured in Nujol and Fluorolube suspensions between KBr plates using a Bruker IFS 66v/S instrument, with a resolution of 2 cm^{-1}. Each spectrum was accumulated for 64 scans. The NMR spectra were recorded using a Varian VNMRS-400 spectrometer operating at 402.6435 and 101.2440 MHz for ^1H and ^{13}C, respectively. 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.

4.2. Preparations

4.2.1. Synthesis of diglycinium squarate (1). 0.85 g of GLY and 0.64 g of H_2SQ were dissolved in 2 mL of water. The solvent was evaporated and the residue was recrystallized from a mixture of methanol–water (2 : 1), m.p. 180 °C. Elemental analysis calculated for $C_8H_{10}N_2O_8$: %C, 36.65; %H, 3.84; %N, 10.68; found: %C, 36.33; %H, 3.75; %N, 10.43. ^1H NMR (D_2O, ppm) δ 3.89 (CH_2); ^{13}C NMR (D_2O, ppm) δ 43.07 (CH_2), 173.03 (COO), 198.85 (C═O, H_2SQ).

4.2.2. Synthesis of sarcosinium hydrogen squarate hemihydrate (2). To 0.60 g of SAR in 2 mL of a methanol–water mixture (2 : 1), 0.76 g of H_2SQ in 1 mL water was added. The solvents were evaporated and the residue was recrystallized from a mixture of methanol–water (2 : 1), m.p. 163–164 °C. Elemental analysis calculated for $C_{14}H_{20}N_2O_{13}$: %C, 39.63; %H, 4.75; %N, 6.60; found: %C, 39.47; %H, 4.74; %N, 6.45. ^1H NMR (D_2O, ppm) δ 2.80 (CH_3), 3.93 (CH_2); ^{13}C NMR (D_2O, ppm) δ 35,67 (CH_3), 51.96 (CH_2), 172.28 (COO), 198.86 (C═O, H_2SQ).

4.2.3. Synthesis of the 2 : 2 complex of dimethylglycine with squaric acid (3). 0.40 g of DMG and 0.44 g of H_2SQ were dissolved in 1 mL of water. The crystals were filtered off and recrystallized from a mixture of methanol–water (3 : 1), m.p. 182–183 °C. Elemental analysis calculated for $C_8H_{11}NO_6$: %C, 44.24; %H, 5.10; %N, 6.45; found: %C, 44.15; %H, 5.03; %N, 6.10. ^1H NMR (D_2O, ppm) δ 2.99 (CH_3), 4.06 (CH_2); ^{13}C NMR (D_2O, ppm) δ 46.70 (CH_3), 60.58 (CH_2), 171.41 (COO), 198.64 (C═O, H_2SQ).

4.2.4. Synthesis of betainium hydrogen squarate (4). 0.67 g of BET and 0.46 g of H_2SQ were dissolved in 2 mL of water. The crystals were filtered off and recrystallized from methanol, m.p. 191 °C. Elemental analysis calculated for $C_9H_{13}NO_6$: %C, 46.76; %H, 5.67; %N, 6.06; found: %C, 46.64; %H, 5.61; %N,

Table 3 Crystal data and structure refinement for complexes of squaric acid with glycine (**1**), sarcosine (**2**), dimethylglycine (**3**) and betaine (**4**)

	1	2	3	4
Empirical formula	$C_8H_{12}N_2O_8$	$C_{14}H_{18}N_2O_{12}\cdot H_2O$	$C_{16}H_{22}N_2O_{12}$	$C_9H_{13}NO_6$
Formula weight	264.20	424.32	434.36	213.20
Temperature (K)	296(2)	296(2)	296(2)	296(2)
Wavelength (Å)	1.71073	1.54184	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	*C*2/*c*	*C*2/*c*	$P2_1/c$	$Pca2_1$
Unit cell dimensions				
a (Å)	16.8392(3)	16.6068(2)	17.5110(5)	22.2718(14)
b (Å)	8.3163(2)	7.21436(8)	6.5385(2)	6.0451(3)
c (Å)	15.8267(3)	15.44410(17)	17.3475(4)	16.2765(8)
β (°)	100.063(2)	97.0249(11)	108.249(3)	90.00
Volume ($Å^3$)	2182.27(8)	1836.43(4)	1886.32(9)	2191.4(2)
Z	8	4	4	8
Calculated density (g cm^{-3})	1.608	1.535	1.529	1.402
Absorption coefficient (mm^{-1})	0.146	1.213	0.133	0.119
F(000)	1104	888	912	976
Crystal size (mm)	0.18 × 0.22 × 0.36	0.16 × 0.26 × 0.33	0.22 × 0.28 × 0.38	0.19 × 0.23 × 0.38
θ range for data collection (°)	3.13–27.59	5.37–75.31	2.47–29.13	2.22–29.14
Max/min indices *h*, *k*, *l*	−20/21, −10/10, −19/19	−20/20, −8/7, −18/19	−23/22, −7/8, −23/22	−29/20, −5/8, −22/18
Reflections collected/unique	10 909/2371	6657/1862	11 666/4520	8662/4068
R_{int}	0.0156	0.0098	0.0206	0.0353
Completeness (%)	93.5	98.0	89.3	88.7
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2371/0/199	1862/0/147	4520/0/341	4068/1/297
Goodness-of-fit on F^2	0.697	0.807	0.968	0.766
Final R_1/wR_2 indices [$I > 2\sigma_I$]	0.0382/0.1098	0.0331/ 0.1013	0.0386/0.0970	0.0400/0.0891
R_1/wR_2 indices (all data)	0.0420/0.1159	0.0337/0.1020	0.0610/0.1042	0.0942/0.1069
Largest diff. peak and hole (e $Å^{-3}$)	0.296 and −0.278	0.234 and −0.141	0.297 and −0.328	0.156 and −0.185

6.02. ^{1}H NMR (D_2O, ppm) δ 3.32 (CH_3), 4.21 (CH_2); ^{13}C NMR (D_2O, ppm) δ 56.73 (CH_3), 66.88 (CH_2), 170.30 (COO), 198.73 (C═O, H_2SQ).

4.3. Single crystal X-ray diffraction

X-ray diffraction data of complexes were collected on a KUMA KM-4 CCD diffractometer.[32] 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 3 and the final atomic coordinates in Table S3 of ESI.† CCDC 966748–966751.

4.4. Computation details

The DFT calculations were performed using the GAUSSIAN 03 program package.[34] The calculations employed the B3LYP exchange–correlation functional, which combines the hybrid exchange functional of Becke[35] with the gradient-correlation functional of Lee *et al.*[36] and the split-valence polarized 6-311G(d,p) basis set.[37] The X-ray geometry was used as a starting point for the calculations. The calculated IR frequencies are positive and confirmed that the optimized structures were in the states of minimum energy.

Acknowledgements

The computations were performed at the Poznań Supercomputing and Networking Center.

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