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Structures of artificial sweeteners – cyclamic acid and sodium cyclamate with other cyclamates

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In the course of a study on artificial sweeteners, new crystal structures of cyclamic acid, sodium cyclamate, potassium cyclamate, ammonium cyclamate, rubidium cyclamate and tetra-*n*-propylammonium cyclamate have been determined. Cyclamic acid exists in its zwitterionic form in the crystalline state. The zwitterions are connected through hydrogen bonds of the N—H···O type to form two-dimensional sheets. The sodium, potassium, ammonium and rubidium cyclamates are isostructural, with the cyclamate moieties linked through hydrogen bonds into linear chains. Taking into account the connectivity through cations, two-dimensional layers with a hydrophobic surface are constructed. In tetra(*n*-propyl)ammonium cyclamate the large, non-coordinating cation apparently prevents the formation of chains and thereby facilitates the centrosymmetric head-to-head discrete dimeric arrangement of the cyclamate moieties.

1. Introduction

Artificial sweeteners are chemical compounds classified as first generation (saccharin, cyclamate and aspartame) and new generation (acesulfame-K, sucralose, alitame, neotame and other sweet proteins). The sweet taste of cyclamates was discovered serendipitously by Sveda in 1937 (Audrieth & Sveda, 1944) and they were introduced commercially in the 1950s. Today, cyclamic acid in the form of its sodium or calcium salt is one of the most widely used artificial sweeteners in food and pharmaceuticals. It is in use in more than 50 countries, especially in combination with other sweeteners, to eliminate aftertaste (for example, the synergistic effect of saccharin–cyclamate; Verheyen, 1999; European Commission, 2000, and references therein). However, the petition on cyclamic acid, calcium and sodium cyclamate is being held in abeyance with the FDA in the USA (CFSAN – Office of Food Additive Safety, 2006).

Sweet-taste chemoreception originates in the interaction of a sweet molecule with a putative taste-bud receptor. Exhaustive studies have been performed in an attempt to rationalize the sweet taste of particular compounds and to correlate the structure/taste relationship. It is generally accepted that the molecule of sweetener must possess specific geometrical features. The classical theories (Shallenberger *et al.*, 1969; Kier, 1972) presume the existence of a glucophore with three specific sites: a hydrogen-bond donor and acceptor ($AH-B$) and a hydrophobic part X. The sweet response is elicited through the interaction of such a glucophore with the complementary tripartite $AH-B-X$ site in the taste-bud receptor. The tripartite glucophore concept (despite the neglect of the three-dimensional shape) has its merits as a

Table 1
Crystal and experimental for cyclamic acid (I), sodium cyclamate (II), potassium cyclamate (III), ammonium cyclamate (IV), rubidium cyclamate (V) and tetra-*n*-propylammonium cyclamate (VI).

	(I)	(II)	(III)
Crystal data			
Chemical formula	$C_6H_{13}NO_3S$	$Na^+C_6H_{12}NSO_3^-$	$K^+C_6H_{12}NSO_3^-$
M_r	179.23	201.22	217.33
Cell setting, space group	Monoclinic, *P*2/*c*	Monoclinic, *C*2/*c*	Monoclinic, *C*2/*c*
Temperature (K)	150 (1)	150 (1)	150 (1)
a, *b*, *c* (Å)	8.1711 (10), 10.9972 (12), 9.4601 (11)	31.083 (6), 6.2718 (14), 8.5682 (17)	33.656 (8), 6.274 (3), 8.572 (4)
β (°)	91.575 (5)	94.481 (10)	93.350 (10)
V (Å^3)	849.72 (17)	1665.3 (6)	1807.0 (13)
Z	4	8	8
D_x (Mg m^{-3})	1.401	1.605	1.598
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.34	0.40	0.79
Crystal form, colour	Plate, colourless	Plate, colourless	Prism, colourless
Crystal size (mm)	0.24 × 0.24 × 0.07	0.20 × 0.18 × 0.08	0.13 × 0.13 × 0.12
Data collection			
Diffractometer	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD
Data collection method	ω scans at κ = 55°	ω scans at κ = 55°	ω scans at κ = 55°
Absorption correction	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)
T_{min}	0.928	0.928	0.905
T_{max}	0.980	0.961	0.911
No. of measured, independent and observed reflections	10 483, 2195, 1955	10 594, 1923, 1480	75 861, 1953, 1565
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.033	0.049	0.043
θ_{max} (°)	28.7	27.7	27.4
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.034, 0.090, 1.12	0.053, 0.130, 1.06	0.037, 0.090, 1.07
No. of reflections	2195	1923	1953
No. of parameters	108	113	113
H-atom treatment	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0224P)^2 + 0.7859P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0356P)^2 + 6.6274P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0303P)^2 + 3.2501P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	< 0.0001	< 0.0001	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.47, −0.41	0.70, −0.56	0.36, −0.44

	(IV)	(V)	(VI)
Crystal data			
Chemical formula	$NH_4^+C_6H_{12}NSO_3^-$	$Rb^+C_6H_{12}NSO_3^-$	$C_{12}H_{28}N^+C_6H_{12}NSO_3^-$
M_r	196.27	263.70	364.58
Cell setting, space group	Monoclinic, *C*2/*c*	Monoclinic, *C*2/*c*	Monoclinic, $P2_1/n$
Temperature (K)	150 (1)	293 (1)	150 (1)
a, *b*, *c* (Å)	33.6671 (19), 6.4571 (12), 8.7572 (15)	34.039 (5), 6.451 (2), 8.811 (2)	10.9510 (11), 13.5112 (12), 14.6202 (15)
β (°)	92.961 (2)	92.670 (10)	99.425 (5)
V (Å^3)	1901.1 (5)	1932.7 (8)	2134.0 (4)
Z	8	8	4
D_x (Mg m^{-3})	1.371	1.813	1.135
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.32	5.31	0.17
Crystal form, colour	Plate, colourless	Plate, colourless	Prism, colourless
Crystal size (mm)	0.29 × 0.24 × 0.10	0.12 × 0.11 × 0.09	0.16 × 0.14 × 0.12
Data collection			
Diffractometer	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD
Data collection method	ω scans at κ = 55°	ω scans	ω scans at κ = 55°
Absorption correction	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)	Multi-scan (based on symmetry-related measurements)
T_{min}	0.905	0.536	0.961
T_{max}	0.975	0.625	0.984
No. of measured, independent and observed reflections	24 925, 1936, 1650	10 240, 2549, 2327	25 465, 5074, 3955
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.045	0.039	0.044

Table 1 (continued)

	(IV)	(V)	(VI)
θ_{max} (°)	26.4	29.1	27.9
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.091, 1.20	0.024, 0.060, 1.10	0.041, 0.131, 1.06
No. of reflections	1936	2549	5074
No. of parameters	126	113	225
H-atom treatment	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0148P)^2 + 3.707P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0179P)^2 + 2.7361P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0713P)^2 + 0.5733P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001	0.005	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.19, −0.35	0.28, −0.48	0.24, −0.36

Computer programs used: *COLLECT* (Hooft, 1998), *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997), *SHELXS*97 (Sheldrick, 1997), *ORTEP*II (Johnson, 1976), *PLUTON* (Spek, 2003), *PLATON* (Spek, 2003; Farrugia, 2000), *ORTEP*3 (Farrugia, 1999), *MERCURY* (Macrae *et al.*, 2006), *SHELXL*97 (Sheldrick, 1997), *PARST* (Nardelli, 1983, 1995), *WinGX* (Farrugia, 1999).

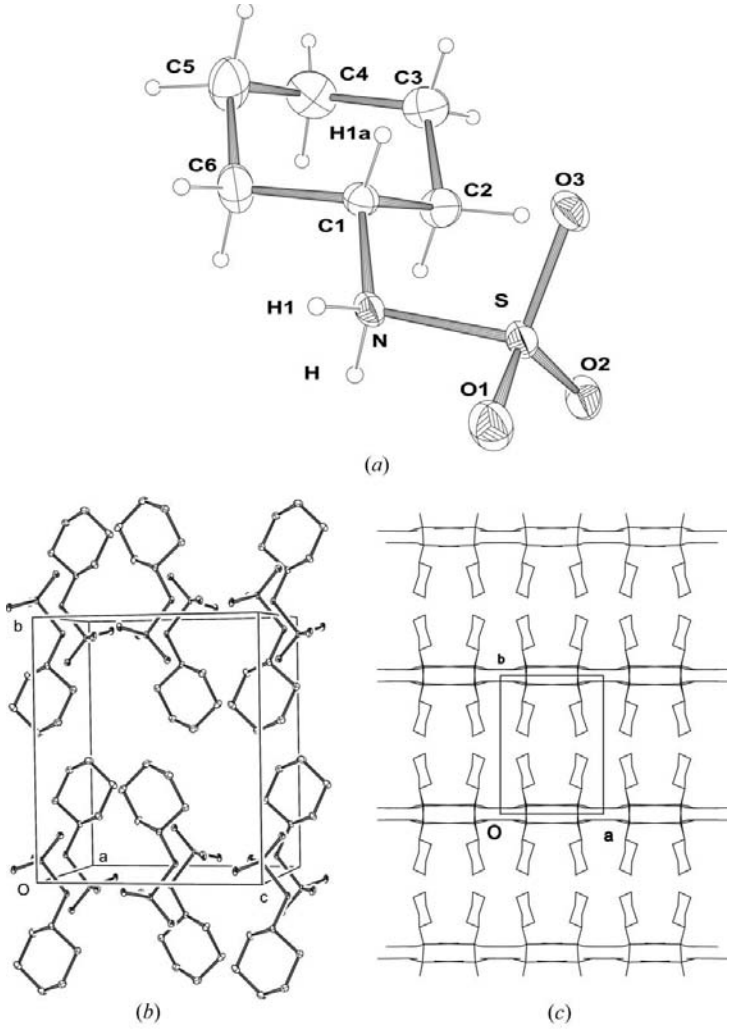


Figure 1
*ORTEP*3 drawing (Farrugia, 1997) of cyclamic acid (*a*) (displacement ellipsoids are drawn at the 50% probability level) and the crystal packing (*b*) and (*c*). H atoms are omitted for clarity.

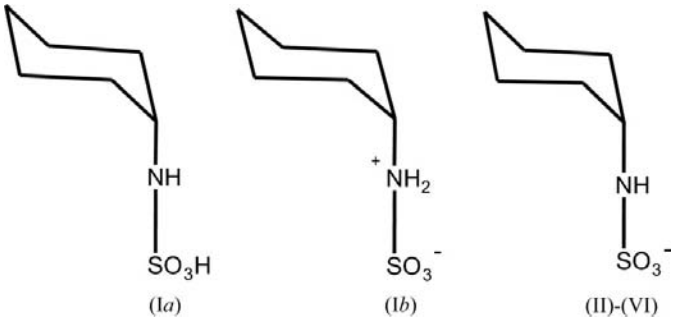
simple criterion in the rationalization of the structure–sweetness relationship for diverse types of compounds. Later, improved and more sophisticated models were proposed by many authors (see, for example, Tinti & Nofre, 1991; Zalewski & Jasiczak, 1994; Ellis, 1995; Walters, 1995; Barker *et al.*, 2002, and references therein). Recent investigations also consider the fact that the sweet-taste perception is mediated by a cascade of various biochemical complexes and several structure–taste studies have been performed on cyclamates and other artificial sweeteners (exemplified by Pautet *et al.*, 1982; Spillane *et al.*, 1989; Suami *et al.*, 1998; Max *et al.*, 2001; Montmayeur *et al.*, 2001; Bassoli *et al.*, 2002; Li *et al.*, 2002; Spillane & Hanniffy, 2003; Morini *et al.*, 2005; Jiang *et al.*, 2005; Nakajima *et al.*, 2006). Some research was also devoted to their solution chemistry (Parke & Birch, 1999; Parke *et al.*, 1999; Birch, 2002; Birch *et al.*, 2004; Klofutar *et al.*, 1999; Klofutar *et al.*, 2006*a*,*b*; Klofutar & Rudan-Tasič, 2006; Rudan-Tasič *et al.*, 2006).

While there are abundant data on the crystal structures of other artificial sweeteners [saccharin (Okaya, 1969; Wardell *et al.*, 2005), aspartame (Hatada *et al.*, 1985), acesulfame-K (Paulus, 1975), sucralose (Kanters *et al.*, 1988), alitame (Feinstein *et al.*, 1991; Goodman *et al.*, 1997), neotame (Wink *et al.*, 1999)], the literature lacks X-ray structural data on cyclamates (Benson & Spillane, 1980; Lee, 1987; Immel, 1995; Yazicilar *et al.*, 2002). To the best of our knowledge there is only one report on the structural investigation of a monoclinic → orthorhombic transition of cyclamic acid at room temperature (Bruck & Stemple, 1967). Therefore, the objective of this paper is to obtain structural data for cyclamic acid and several cyclamates in a crystalline form in order to assist in the further study of the sweetness–structure relationship.

Table 2
Selected geometric data (Å, °) for cyclamic acid (I), sodium cyclamate (II), potassium cyclamate (III), ammonium cyclamate (IV), rubidium cyclamate (V) and tetrapropylammonium cyclamate (VI).

Compound	(I)	(II)	(III)	(IV)	(V)	(VI)
S—O1	1.4290 (12)	1.457 (2)	1.4588 (16)	1.4610 (15)	1.4558 (14)	1.4560 (12)
S—O2	1.4441 (11)	1.470 (2)	1.4592 (18)	1.4504 (16)	1.4526 (16)	1.4497 (12)
S—O3	1.4407 (11)	1.448 (2)	1.4544 (18)	1.4472 (15)	1.4523 (15)	1.4645 (11)
S—N	1.8003 (14)	1.643 (2)	1.641 (2)	1.6559 (18)	1.6401 (16)	1.6720 (14)
N—C1	1.511 (2)	1.478 (4)	1.480 (3)	1.481 (3)	1.474 (2)	1.472 (2)
C1—C2	1.521 (2)	1.532 (4)	1.530 (3)	1.526 (3)	1.515 (3)	1.522 (2)
C2—C3	1.527 (3)	1.528 (4)	1.536 (3)	1.530 (3)	1.541 (3)	1.530 (2)
C3—C4	1.523 (3)	1.533 (5)	1.525 (4)	1.522 (4)	1.515 (4)	1.523 (3)
C5—C6	1.536 (3)	1.528 (4)	1.526 (4)	1.534 (3)	1.540 (4)	1.531 (3)
C1—C6	1.524 (2)	1.531 (4)	1.527 (3)	1.525 (3)	1.520 (3)	1.522 (2)
C2—C1—N—S	63.07 (15)	70.7 (3)	81.3 (2)	82.0 (2)	85.8 (2)	67.01 (16)
O1—S—N—C1	155.71 (11)	168.4 (2)	−174.77 (17)	179.30 (16)	−174.57 (14)	151.49 (12)
O2—S—N—C1	−83.55 (11)	−74.2 (2)	−54.1 (2)	−60.26 (18)	−53.93 (17)	−88.91 (13)
O3—S—N—C1	34.70 (12)	46.9 (2)	67.0 (2)	61.09 (18)	67.25 (16)	31.70 (14)
C1—C2—C3—C4	−57.3 (2)	−55.0 (4)	−56.7 (3)	−56.0 (3)	−55.7 (3)	−55.89 (19)
C2—C3—C4—C5	56.6 (2)	54.6 (4)	55.5 (3)	55.3 (3)	54.6 (4)	53.9 (2)
C3—C4—C5—C6	−56.5 (2)	−54.9 (4)	−54.6 (3)	−55.1 (3)	−54.6 (4)	−53.8 (2)
C4—C5—C6—C1	57.4 (2)	56.4 (4)	54.8 (3)	55.5 (3)	54.7 (4)	56.3 (2)
C5—C6—C1—C2	−59.6 (2)	−56.6 (3)	−55.2 (3)	−55.7 (3)	−54.7 (3)	−58.19 (19)
C6—C1—C2—C3	59.41 (19)	55.4 (3)	56.1 (3)	56.2 (3)	55.7 (3)	57.76 (18)
H—N—C1—H1*a*	−176.6	−175.1	−169.8	−164.4	−162.8	71 (2)
H—N—S—O1	−82.0 (14)	−64 (2)	−43 (2)	−52.0 (18)	−44.2 (18)	28.5 (17)
H—N—S—O2	38.7 (14)	53 (2)	78 (2)	68.5 (18)	76.4 (18)	148.1 (17)
H—N—S—O3	157.0 (14)	174 (2)	−161 (2)	−170.2 (18)	−162.4 (18)	−91.3 (17)
H1—NS—O1	32.9 (15)					
H1—N—S—O2	153.7 (15)					
H1—N—S—O3	−88.1 (15)					

The labelling for the sulfamyl H atoms of cyclamic acid (I) has been changed slightly – H and H1 are attached to N.



2. Experimental

2.1. Sample preparation and crystallization

Crystals of cyclamic acid were prepared by dissolving a sample of commercially available cyclamic acid (Sigma–Aldrich) in distilled water under gentle heating. Slow evaporation of water at ambient temperature produced transparent prismatic crystals of cyclamic acid (I) within 2 weeks. Crystals of sodium cyclamate (II), potassium cyclamate (III), ammonium cyclamate (IV) and tetra-*n*-propylammonium cyclamate (VI) were obtained by slow evaporation of water from the aqueous solutions containing equimolar amounts of cyclamic acid and the corresponding hydroxide. Rubidium cyclamate (V) crystals were obtained by dissolving cyclamic acid and Rb_2CO_3 in distilled water in a 2:1 molar ratio. On standing at ambient temperature colourless crystals appeared within a week. Crystals of several other cyclamates have also been prepared, but their limited quality did not allow a full X-ray structure determination (Leban *et al.*, 2005).

2.2. Data collection and structure determination

All crystallographic measurements were performed on a Nonius Kappa CCD diffractometer (Mo $K\alpha$ radiation, 55 kV, 30 mA) equipped with an Oxford Cryosystems Series 700 open-flow cryostat (Cosier & Glazer, 1986). The diffraction data [with the exception of that for the rubidium salt, 293 (1) K] were collected at 150 (1) K. The standard strategy was used for data collection, cell refinement and data reduction (Hooft, 1998; Otwinowski & Minor, 1997). *SIR*92 (Altomare *et al.*, 1993) and *SHELXS*97 (Sheldrick, 1997) implemented in Version 1.64 of the *WinGX* program package (Farrugia, 1999) were used for structure solution by direct methods. *SHELXL*97 (Sheldrick, 1997) was used for structure refinement and the calculation of difference Fourier maps. The structures were refined by full-matrix least-squares against F^2 using all data. H atoms have been located from the difference-Fourier maps and those of the sulfamate groups were refined isotropically without restraints. Those of the cyclohexane moieties and the tetra-*n*-propylammonium cation in (VI) were placed at calculated positions and treated as riding with U_{iso} values set to 1.2 or 1.5 U_{eq} of the parent atom. For visual interpretation and structural drawings the following programs were used: *ORTEP*3 for Windows (Farrugia, 1997), *PLATON* (Spek, 2003) and *MERCURY* (Macrae *et al.*, 2006). Selected experimental and crystal data for cyclamic acid and reported cyclamates are given in Table 1. Inspection of the crystal data in Table 1[1] shows the isostructurality of sodium, potassium, ammonium and rubidium cyclamates. The separate structures of cyclamic acid (I), sodium cyclamate (II) and tetra-*n*-propylammonium cyclamate (VI) together with molecular packing are depicted in Figs. 1, 2 and 3, respectively. In order to facilitate comparison, all atomic labelling was kept the same, the sulfamyl N atoms are marked as N, and the hydrogen attached to it is marked as H. The additional H atom

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM5046). Services for accessing these data are described at the back of the journal.

attached to N in cyclamic acid (I) is labelled as H1. The O3 atom of each sulfo group is always positioned above the plane of the cyclohexane moiety, on the same side as H1*A*, H3*A* or H5*A*. Some selected geometric data generated by *PARST* (Nardelli, 1983, 1995) are collected in Table 2.

3. Results and discussion

3.1. Crystal structure of cyclamic acid (I)

A prominent feature of cyclamic acid is that it can exist as a neutral molecule [see (I*a*)] or in the zwitterionic form [see (I*b*)]. Analysis of the crystals of (I) has proved the existence of the zwitterionic structure (Fig. 1). The formulation was readily established by the straightforward identification of two H-atom sites adjacent to the N atom and it is further supported by a number of metrical features. The protonation of nitrogen affects the N—S bond length [1.8003 (14) Å], which is significantly longer than the N—S distances observed in related compounds (Allen *et al.*, 1995) and the cyclamates reported here. The S—O distances are 1.4290 (12), 1.4441 (11) and 1.4407 (11) Å for S—O1, S—O2 and S—O3, respectively. The orientation of the sulfamyl group results in a torsion angle for S—N—C1—C2 of 63.07 (15)°. Selected geometric parameters are listed in Table 2 and those of hydrogen bonding in Table 3. The two sulfamyl H atoms are involved in the formation of three hydrogen bonds of the N—H···O type. The N—H2···O3 (symmetry code: $-x, -y, -z$) hydrogen bond connects the molecules into centrosymmetric dimers, which are further linked into chains along the *x* axis through an N—H1—O2 (symmetry code: $1-x, -y, -z$) interaction. In addition, these chains are connected into two-dimensional layers through N—H2···O3 (symmetry code: $x, -y, z-\frac{1}{2}$). Thus, the polar sulfamyl cores lie on a layer almost parallel to the *ac* plane, whereas the cyclohexane tails protrude from each side of the layer bringing the hydrophobic parts of adjacent layers together (Figs. 1 and 4).

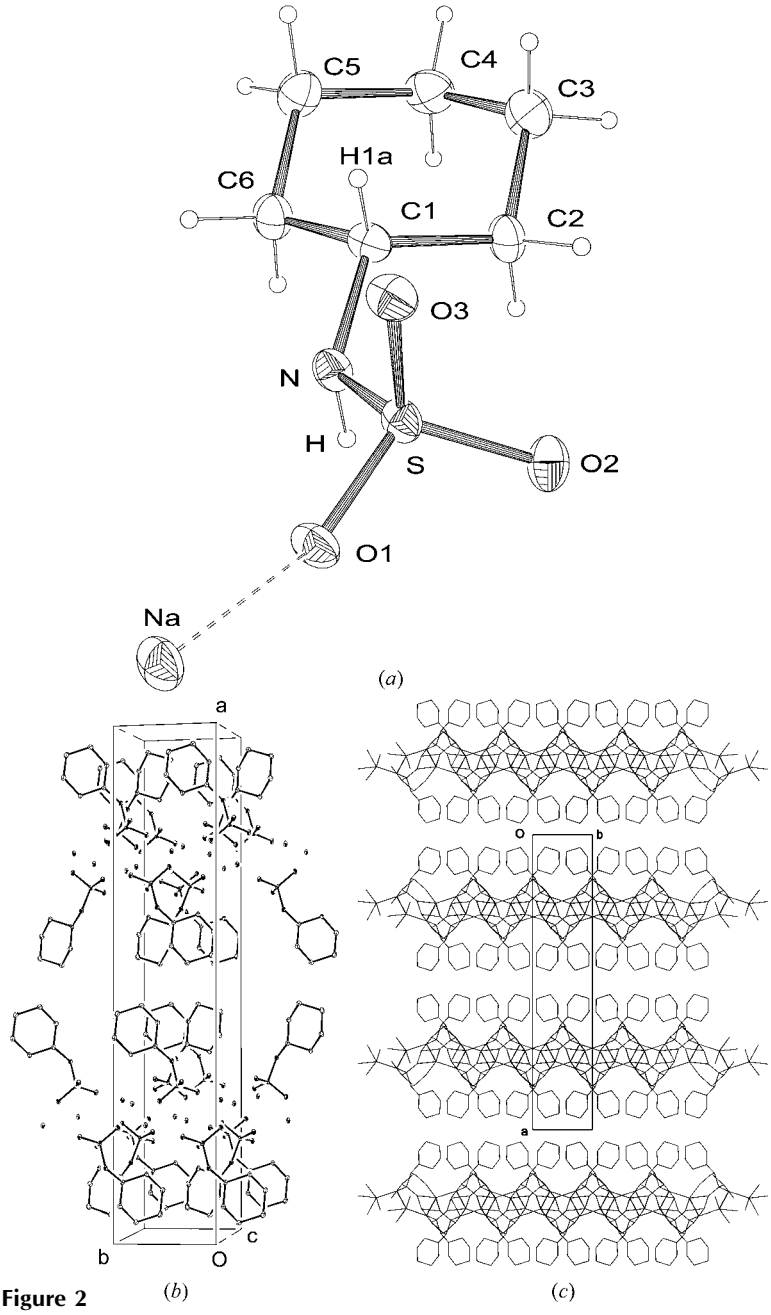


Figure 2
*ORTEP*3 drawing (Farrugia, 1997) of sodium cyclamate (*a*) (displacement ellipsoids are drawn at the 50% probability level) and the crystal packing (*b*) and (*c*), where H atoms are omitted for clarity.

3.2. Crystal structures of Na^+, K^+, NH_4^+ and Rb^+ cyclamates (II, III, IV, V)

Sodium, potassium, ammonium and rubidium cyclamates are isostructural. A view of the asymmetric unit of sodium cyclamate (I) is depicted in Fig. 2. For clear comparison of the structures, the same atomic labelling scheme was used. A striking difference between the structure of the cyclamate anion and the cyclamic acid zwitterion is the S—N bond length. The S—N distances of 1.643 (2), 1.641 (2), 1.6559 (18) and 1.6401 (16) Å for (II), (III), (IV) and (V), respectively, are considerably shorter than that observed in cyclamic acid, 1.8003 (14) Å. A similar observation was made for the structures of sulfamic acid (Sass, 1960) and its ammonium salt (Cain & Kanda, 1972). Apparently, the free electron pair on the sulfamyl nitrogen in the cyclamate anion is involved in attractive interactions with the empty *d* orbital of the S atom, resulting in shortening of the S—N bond. The values of the S—N—C1—C2 torsion angles [70.7 (3), 81.3 (2), 82.0 (2), 85.8 (2)°] are higher than the corresponding torsion angle in cyclamic acid [63.07 (15)°], but the values differ significantly even within the group of four isostructural compounds. Thus, no conclusion regarding the orientation of the sulfamyl group can be drawn.

Table 3
Details of hydrogen bonding for cyclamic acid (I), sodium cyclamate (II) and tetra-*n*-propylammonium cyclamate (VI).

(I)		(II)		(VI)	
N···O2^{i}	2.875 (2)	N···O3^{iv}	3.061 (3)	N···O1^{v}	2.983 (2)
N—H1	0.91 (2)	N—H	0.95 (4)	N—H	0.73 (2)
H1···O2^{i}	1.98 (2)	H···O3^{iv}	2.16 (4)	H···O1^{v}	2.25 (2)
N—H1···O2^{i}	168 (2)	N—H···O3^{iv}	159 (3)	N—H···O1^{v}	173 (2)
N···O3^{ii}	3.029 (2)				
N—H2	0.83 (2)				
H2···O3^{ii}	2.26 (2)				
N—H2···O3^{ii}	156 (2)				
N···O3^{iii}	3.030 (2)				
N—H2	0.83 (2)				
H2···O3^{iii}	2.46 (2)				
N—H2···O3^{iii}	127 (2)				

Symmetry codes: (i) $-x+1, -y, -z$; (ii) $x, -y, +z-\frac{1}{2}$; (iii) $-x, -y, -z$; (iv) $x, -y, +z+\frac{1}{2}$; (v) $1-x, 1-y, 1-z$.

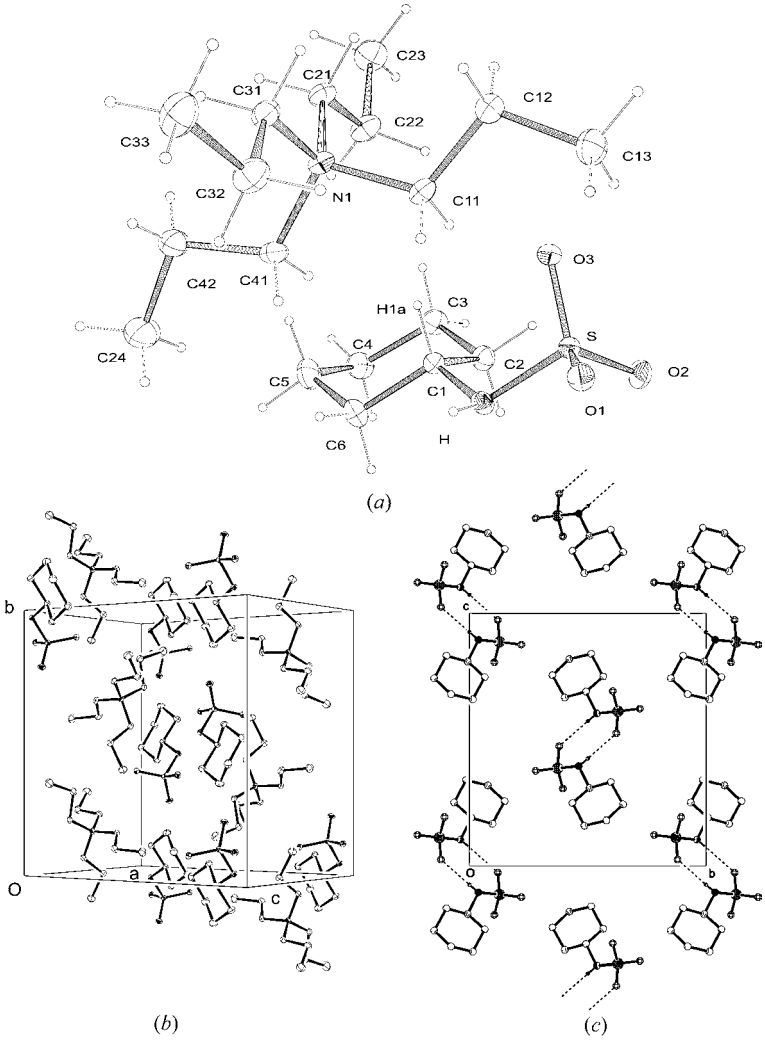


Figure 3
*ORTEP*3 drawing (Farrugia, 1997) of tetra-*n*-propylammonium cyclamate (*a*) (displacement ellipsoids are drawn at the 50% probability level) and the crystal packing (*b*) and (*c*). H atoms are omitted for clarity. Only anions are shown in (*c*).

The single H atom on the sulfamyl N is involved in the formation of an intermolecular N—H···O3 (symmetry code: $x, -y, \frac{1}{2}+z$) hydrogen bond that connects the cyclamate moieties into linear chains propagating along the *b* axis.

The monovalent cations (Na^+, K^+ and Rb^+) are located between these chains and are coordinated predominantly by the O atoms of sulfo groups in such a way that two-dimensional layers are formed perpendicular to the *a* axis. The sodium cation in (II) is coordinated by six O atoms of five different sulfo groups. Five $Na^+\cdots O$ distances span a range between 2.302 (3) and 2.480 (3) Å, whereas an additional oxygen is located at a longer distance [2.859 (3) Å]. The potassium cation in (III) is nine-coordinated with eight $K^+\cdots O$ distances spanning the range 2.727 (2)–3.234 (2) Å and additionally the sulfamyl nitrogen is coordinated as a possible donor of a free electron pair to K^+ at 2.911 (2) Å. The rubidium cation in (V) was found to be ten-coordinated by nine O atoms in the range 2.916 (2)–3.332 (2) Å with the additional sulfamyl nitrogen at 3.052 (2) Å (Harding, 2002). The ammonium cation (NH_4^+) in (IV) serves as a H-atom donor for hydrogen bonds to the neighbouring sulfo O atoms, but the formation of hydrogen bonds does not influence the basic structural arrangement. There is no covalent interaction between the layers, which are separated from each other by the hydrophobic cyclohexane parts – protruding from both sides. It is interesting to note that the sodium, potassium, rubidium and ammonium cylamates are isostructural: because of the smaller size of the Na^+ cation, the sodium salt does not normally fit into such a series, as exemplified by alkali hydrogen acetylenedicarboxylates [Na^+ (Leban, 1974*a*); K^+ (Leban *et al.*, 1973); Rb^+ (Blain *et al.*, 1973); NH_4^+ (Leban, 1974*b*)] and alkali naphthalenetetracarboxylates (Fitzgerald *et al.*, 1993).

3.3. Crystal structure of tetra-*n*-propylammonium cyclamate (VI)

The geometry of the cyclamate anion (Fig. 3) is similar to that observed for the other cyclamates reported here, however, the packing of the cyclamate moieties is influenced by the size and nature of the cation. Besides the greater size, the tetra-*n*-propylammonium cation lacks the coordination abilities and the possibilities for the formation of hydrogen bonds. Thus, no extended arrangements

are expected. The cyclamate units, related by the crystallographic inversion center, are connected to centrosymmetric dimers through N—H···O interactions (Fig. 4), forming eight-membered $R_2^2(8)$ rings (Bernstein *et al.*, 1995), which are already observed as a linking motif in (I). There are no other connections. The cyclamate moieties are arranged in columns of dimers, propagating along **b**, separated by columns of cationic moieties (Fig. 3). Comparison of the structures of cyclamate moieties in the reported cyclamates shows one significant difference. While the S—O3 and N—H groups in the sulfamate moieties are oriented *trans* to one another in sodium cyclamate (II) and in its isostructural compounds (III), (IV) and (V), the torsion angle N—H—S—O3 has a value of −91.3 (17)° in (VI). The orientation of the sulfamyl H atom is probably affected by the formation of centrosymmetric dimers, since the dimeric arrangement was also observed for cyclamic acid which contains two H atoms, one of which is in a suitable orientation to form such dimers. Cyclamic acid as well as sodium and related cyclamates taste sweet, while the tetra-*n*-propylammonium salt tastes bitter. It seems that the position of the H atom on the sulfamyl nitrogen and consequently the hydrogen-bonding pattern is not the major 'sweetness factor', but the size and nature of the cation also possibly influences the sweetness. The remarkable structural feature common to all the sweet cyclamate species, but lacking in the bitter tetra-*n*-propylammonium salt, is the formation of two-dimensional sheets with a hydrophobic surface. Additionally, in (VI) the hydrogen of the sulfamate moiety is attached on the other (of two) possible position at the N atom.

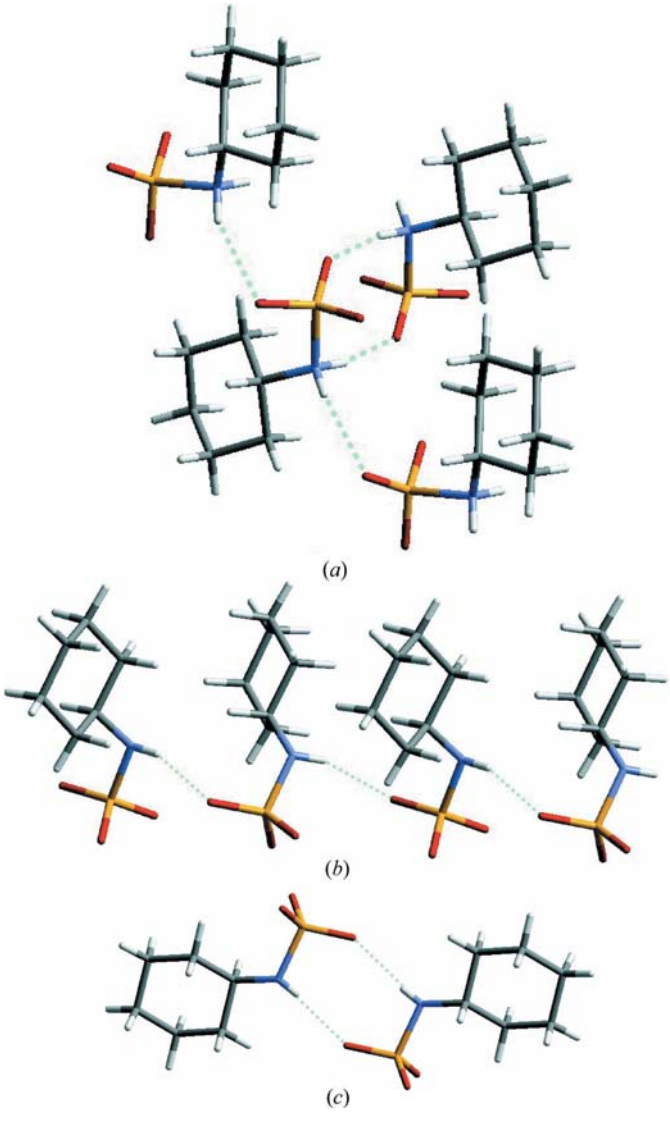


Figure 4
Graphic representation of the hydrogen bonding (*MERCURY*; Macrae *et al.*, 2006) in (*a*) cyclamic acid (I), (*b*) sodium cyclamate (II) and (*c*) tetra-*n*-propylammonium cyclamate (VI).

4. Concluding comments

The structural analyses of cyclamic acid and its five salts show similar geometry for the cyclamate moieties, but with different packing arrangements in the crystal.

Generally, two types of packing were observed:

(i) the formation of a layered two-dimensional structure with a hydrophobic surface and

(ii) the discrete arrangement of cyclamate dimers without further interactions that would form extended arrangements. The latter was observed for tetra-*n*-propylammonium cyclamate, which alone among the reported compounds tastes bitter, while all others have a sweet taste. Nevertheless, additional data are needed to confirm the speculation that the packing in the solid state can also have an influence on the sweet-taste perception.

These observations, together with previous investigations, show that the relationship between sweetness and structure is not an obvious one. This in turn means that the search for simple principles in the design of sweeteners will require further studies and considerably more sophisticated models than those currently available. However, we believe that the structural analyses of cyclamic acid and cyclamates will assist further research on the topic.

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