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Salt-Bridge Formation by *Cinchona* Alkaloids: Quininium Salicylate Monohydrate

BY BARBARA J. OLEKSYN

Faculty of Chemistry, Jagiellonian University, Karasia 3, 30-060 *Kraków, Poland*

AND PAWEŁ SERDA

Regional Laboratory of Physicochemical Analysis and Structural Research, Jagiellonian University, Karasia 3, 30-060 *Kraków, Poland*

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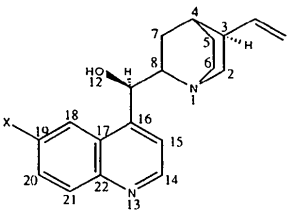
Abstract

$C_{20}H_{25}N_2O_2^+C_7H_5O_3^-.H_2O$, $M_r = 480.56$, orthorhombic, $P2_12_12_1$, $a = 6.957$ (2), $b = 17.108$ (1), $c = 20.477$ (6) Å, $V = 2437$ (1) Å^3, $Z = 4$, $D_m = 1.30$ (1), $D_x = 1.31$ g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 7.194$ cm^{-1}, $F(000) = 1024$, $T = 293$ K, $R = 0.0341$ for 2507 reflections. Hydrogen bonds link the quininium cation, salicylate anion and water molecule to form an eleven-membered ring which can be compared to salt-bridge clusters observed in myoglobin. The effect of protonation on the quinuclidine geometry is discussed.

Introduction

Quinine (I) is an important antimalarial drug which occurs in the bark of the *Cinchona* tree together with other *Cinchona* alkaloids, such as quinidine (II), cinchonidine (III) and cinchonine (IV).



	X	Absolute configuration C8	C9
(I)	—OCH_3	*S*	*R*
(II)	—OCH_3	*R*	*S*
(III)	—H	*S*	*R*
(IV)	—H	*R*	*S*

The similarity of the molecular structures of the free bases, (I)–(IV), in the crystalline state (Pniewska & Suszko-Purzycka, 1989; Kashino & Haisa, 1983; Oleksyn, 1982; Oleksyn, Lebioda & Ciechanowicz-Rutkowska, 1979) suggests that differences, if any, in

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the biological behaviour of *Cinchona* alkaloids may result from: (i) different absolute configurations and/or (ii) different electron density distributions in the quinoline moiety which may be introduced by the —OCH_3 substituent at C19.

In order to test these suggestions we have undertaken X-ray structure analyses of various salts in which *Cinchona* alkaloids are protonated and form cations capable of interactions with anions, most often *via* hydrogen bonds. Such bonds with organic acids are especially interesting when they resemble salt bridges occurring in proteins, and can be treated as models of drug–receptor interactions. These bridges, also called ion bridges or ion pairs, are formed in proteins mainly by negatively charged side chains of aspartate and glutamate with positively charged side chains of lysine, arginine or histidine, and stabilize the secondary and tertiary structure of the macromolecules (Deerfield, Nicholas, Hiskey & Pedersen, 1989). The primary unit of each salt-bridge system is the hydrogen bond between the carboxy group O atom of one amino-acid molecule and the protonated amino group of another, a water molecule often taking part in the system (Baker & Hubbard, 1984, Peters & Peters, 1985, 1986). In this context it seems probable that the glutamate or aspartate of a receptor site might interact with the quinuclidinium protonated nitrogen of *Cinchona* alkaloids *via* salt-bridge formation. The role of the —C9—OH carbinol group in this system should be investigated in conjunction with the absolute configuration at C9 and C8.

This paper is limited to the quininium salts with organic acids, but crystal structure investigations and theoretical studies are in progress for the salicylates and lactates of (II), (III) and (IV), as well as of their epimers.

Experimental

Colourless transparent prismatic crystals of the title compound (Qsal) were supplied by ICN Pharmaceutical K&K Laboratories, New York (USA). Their best developed faces were: {011}, {110}, {010} and {001}, as established previously (Oleksyn, Pędzińska-Paw & Hodorowicz, 1989). A crystal (0.2 × 0.3 × 0.6 mm) was mounted on an Enraf–Nonius CAD-4 automatic diffractometer equipped with graphite-monochromated Cu $K\alpha$ radiation. The lattice parameters published earlier together with D_m measured by flotation (Oleksyn, Pędzińska-Paw & Hodorowicz, 1989) were confirmed, and the former refined by the autoindexing procedure from the settings of 25 reflections in the range $3 < 2\theta < 35°$. The intensity measurement of 2534 independent reflections within the limits $-8 \le h \le 0$, $0 \le k \le 21$, $0 \le l \le 25$, $\sin\theta/\lambda$ in the range 0.038–0.626 $Å^{-1}$, was carried out in the $\omega/2\theta$ scanning mode with the scan width $(0.6 + 0.2\tan\theta)°$. Of the recorded data, 2510 were considered observed [$|F_o| \ge 2\sigma(F_o)$]; the intensities of two standard reflections ($0\bar{4}4$, $1\bar{2}4$), monitored every hour, remained constant to within 1.5%. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods with *SHELX*76 (Sheldrick, 1976). The sites of the quininium cation and salicylate anion were revealed on the first E map, while the water molecule was located on the difference Fourier map after six cycles of isotropic refinement ($R = 0.24$) based on F. The H-atom sites were located in the difference Fourier maps after subsequent anisotropic refinement. In the final cycles three reflections, 040, 002 and 032, which appeared to be affected by extinction, were omitted. The weighting scheme was $0.2716/[\sigma^2(F) + 0.0001F^2]$. The refinement (444 parameters: positional and anisotropic thermal parameters for heavy atoms and positional and isotropic thermal parameters for H atoms, scale factor) was terminated when the shift-to-e.s.d. ratios of most coordinates were less than 0.01 (non-H atoms) and 0.05 (H atoms). The final discrepancy factors were $R = 0.0341$, $wR = 0.0334$, $R_g = 0.0387$, $S = 1.11$ and the final difference Fourier map had no peak higher than 0.2 e $Å^{-3}$. The calculations were carried out on Cyber 72 (CDC) and IBM AT compatible computers.

Discussion

Final coordinates for the non-H atoms and the equivalent isotropic temperature factors are given in Table 1,* while the asymmetric unit with the atom numbering is depicted in Fig. 1. The bond lengths and angles are listed in Table 2.

The asymmetric unit consists of a quininium cation, a salicylate anion and one water molecule linked by hydrogen bonds so that an eleven-membered ring is formed containing N1, H1, O34, C31, O33, H2*W*, O*W*, H12, O12, C9 and C8. The protonated quinuclidine nitrogen atom, N1, is a donor in a hydrogen bond with one of the salicylate carboxyl oxygens, O34, while the other, O33, is an acceptor of H2*W* of the water molecule which closes the ring by its interaction with the proton at O12. A similar ring system occurs in the structure of quininium 2,2-dimethylcyclopropanecarboxylate (QPro) (Graham *et al.*, 1987). In both the structures the

* Lists of structure factors, anisotropic displacement parameters, and positional and isotropic displacement parameters of hydrogen atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55760 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: KA0021]

Table 1. *Atomic coordinates and equivalent thermal parameters* ($\times 10^4$)

$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	U_{eq} (Å^2)
N1	0.3654 (3)	0.5425 (1)	0.4149 (1)	359 (5)
C2	0.1878 (3)	0.5307 (1)	0.3746 (1)	423 (6)
C3	0.2449 (4)	0.4960 (1)	0.3078 (1)	428 (6)
C4	0.4548 (3)	0.4680 (1)	0.3129 (1)	409 (6)
C5	0.5824 (4)	0.5398 (1)	0.3193 (1)	473 (7)
C6	0.5085 (4)	0.5897 (1)	0.3760 (1)	429 (6)
C7	0.4837 (4)	0.4160 (1)	0.3728 (1)	415 (6)
C8	0.4377 (3)	0.4627 (1)	0.4353 (1)	342 (5)
C9	0.6036 (3)	0.4689 (1)	0.4850 (1)	372 (6)
C10	0.1079 (4)	0.4332 (2)	0.2866 (1)	581 (9)
C11	−0.0054 (5)	0.4372 (3)	0.2359 (2)	812 (12)
O12	0.7795 (2)	0.4851 (1)	0.4531 (1)	478 (5)
N13	0.6598 (3)	0.2450 (1)	0.5848 (1)	503 (6)
C14	0.7905 (4)	0.2722 (1)	0.5445 (1)	503 (7)
C15	0.7759 (4)	0.3445 (1)	0.5117 (1)	448 (7)
C16	0.6214 (3)	0.3921 (1)	0.5224 (1)	364 (5)
C17	0.4805 (3)	0.3673 (1)	0.5682 (1)	362 (6)
C18	0.3172 (3)	0.4125 (1)	0.5863 (1)	405 (6)
C19	0.1825 (3)	0.3821 (1)	0.6277 (1)	465 (7)
C20	0.2029 (4)	0.3059 (2)	0.6533 (1)	575 (8)
C21	0.3589 (4)	0.2626 (2)	0.6385 (1)	545 (7)
C22	0.5043 (4)	0.2919 (1)	0.5964 (1)	431 (6)
O23	0.0213 (3)	0.4195 (1)	0.6489 (1)	604 (6)
C24	−0.0119 (5)	0.4963 (2)	0.6255 (2)	656 (10)
C25	0.3381 (3)	0.7091 (1)	0.6136 (1)	414 (6)
C26	0.4719 (4)	0.7538 (1)	0.6480 (1)	499 (7)
C27	0.4244 (5)	0.7854 (2)	0.7083 (1)	584 (9)
C28	0.2446 (5)	0.7737 (2)	0.7341 (1)	575 (9)
C29	0.1082 (4)	0.7318 (2)	0.7004 (1)	525 (8)
C30	0.1552 (4)	0.6998 (1)	0.6403 (1)	442 (7)
C31	0.3895 (4)	0.6709 (1)	0.5503 (1)	519 (8)
O32	0.6519 (3)	0.7664 (1)	0.6248 (1)	777 (8)
O33	0.5514 (3)	0.6866 (2)	0.5261 (1)	921 (10)
O34	0.2734 (2)	0.6249 (1)	0.5242 (1)	550 (5)
OW	0.8966 (4)	0.6228 (1)	0.4893 (2)	860 (9)

Table 2. *Bond lengths* (Å) *and bond angles* (°) *involving non-*H *atoms with e.s.d.'s in parentheses*

N1—C2	1.500 (3)	C17—C18	1.423 (3)
N1—C6	1.511 (3)	C17—C22	1.424 (3)
N1—C8	1.514 (3)	C18—C19	1.367 (3)
C2—C3	1.543 (3)	C19—C20	1.411 (4)
C3—C4	1.541 (3)	C19—O23	1.363 (3)
C3—C10	1.500 (4)	C20—C21	1.348 (4)
C4—C5	1.521 (3)	C21—C22	1.419 (4)
C4—C7	1.529 (3)	O23—C24	1.418 (4)
C5—C6	1.530 (3)	C25—C26	1.395 (3)
C7—C8	1.543 (3)	C25—C30	1.394 (3)
C8—C9	1.542 (3)	C25—C31	1.494 (3)
C9—O12	1.414 (3)	C26—C27	1.389 (4)
C9—C16	1.526 (3)	C26—O32	1.356 (3)
C10—C11	1.307 (5)	C27—C28	1.373 (4)
N13—C14	1.314 (3)	C28—C29	1.376 (4)
N13—C22	1.369 (3)	C29—C30	1.387 (3)
C14—C15	1.410 (3)	C31—O33	1.259 (3)
C15—C16	1.367 (3)	C31—O34	1.248 (3)
C16—C17	1.422 (3)		

C6—N1—C8	114.2 (2)	C16—C17—C22	117.3 (2)
C2—N1—C8	107.7 (2)	C16—C17—C18	124.1 (2)
C2—N1—C6	109.0 (2)	C18—C17—C22	118.7 (2)
N1—C2—C3	109.1 (2)	C17—C18—C19	120.1 (2)
C2—C3—C10	111.6 (2)	C18—C19—O23	125.6 (2)
C2—C3—C4	107.7 (2)	C18—C19—C20	120.9 (2)
C4—C3—C10	113.5 (2)	C20—C19—O23	113.5 (2)
C3—C4—C7	111.1 (2)	C19—C20—C21	120.4 (2)
C3—C4—C5	107.9 (2)	C20—C21—C22	121.1 (2)
C5—C4—C7	108.8 (2)	C17—C22—C21	118.9 (2)
C4—C5—C6	108.7 (2)	N13—C22—C21	117.5 (2)
N1—C6—C5	108.8 (2)	N13—C22—C17	123.6 (2)
C4—C7—C8	109.7 (2)	C19—O23—C24	117.5 (2)
N1—C8—C7	107.9 (2)	C30—C25—C31	120.6 (2)
C7—C8—C9	115.3 (2)	C26—C25—C31	121.2 (2)
N1—C8—C9	111.7 (2)	C26—C25—C30	118.3 (2)
C8—C9—C16	109.5 (2)	C25—C26—O32	121.8 (2)
C8—C9—O12	110.9 (2)	C25—C26—C27	120.2 (2)
O12—C9—C16	109.3 (2)	C27—C26—O32	118.0 (2)
C3—C10—C11	125.2 (3)	C26—C27—C28	120.2 (3)
C14—N13—C22	116.6 (2)	C27—C28—C29	120.7 (2)
N13—C14—C15	124.1 (2)	C28—C29—C30	119.3 (3)
C14—C15—C16	120.2 (2)	C25—C30—C29	121.2 (2)
C9—C16—C15	119.8 (2)	C25—C31—O34	119.5 (2)
C15—C16—C17	118.1 (2)	C25—C31—O33	117.5 (2)
C9—C16—C17	122.2 (2)	O33—C31—O34	123.0 (3)

parameters of the hydrogen bonds are very similar (see Table 3). Table 3 also includes, for comparison, the data for the N—H···O(carboxylic) interaction in the 2:1 salt of quinine with diphenic acid (QDiph) (Kubicki, Borowiak, Gawron, Giel & Gawroński, 1990).

Two similar hydrogen-bonding systems were described by Peters & Peters (1986) as parts of the so-called clusters of the hydrogen-bonded amino-acid residues and water molecules in myoglobin. As shown schematically in Fig. 2, the introduction of the quininium —N1—H in place of the amino group of 62 Lys in system 1 and 145 Lys in system 2 might add three extra links to the existing rings.

This hypothetical complex of the quininium cation with a protein might be treated as a model of a quinine–biological receptor interaction in which the active site of a receptor is blocked by the alkaloid. The blocking molecule not only prevents the acidic residue (Glu or Asp) from interaction with the basic one (Lys), but also changes the hydrophilic site of the protein into a more hydrophobic one. This in turn may disturb the local geometry and the site behaviour towards its closest neighbours.

An additional argument for the mode of action suggested above might be the preference of the *Cinchona* alkaloid epimers, much less active as anti-malarials, to form intramolecular hydrogen bonds. Such a bond was found in 10-bromo-10,11-dihydro-

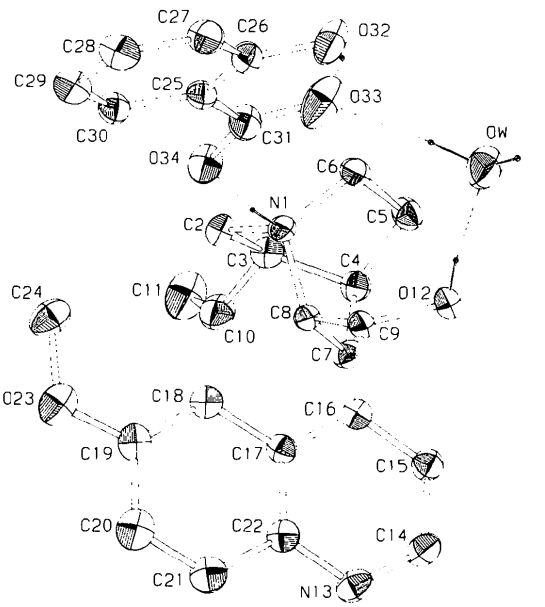

Fig. 1. *ORTEP* projection of the asymmetric unit of quininium salicylate monohydrate with atom numbering. Hydrogen bonds are indicated by dashed lines. Thermal ellipsoids are plotted at 30% probability.

Table 3. *Intermolecular hydrogen-bond parameters* (Å, °) *in three salts of the quininium cation*

Salt	*D*	H	*A*	*D*···*A*	*D*—H	H···*A*	*D*—H···*A*
QSal	N1	H1	O34	2.721 (2)	0.98 (3)	1.75 (3)	173 (2)
	O12	H12	O*W*	2.600 (3)	0.86 (4)	1.74 (3)	174 (4)
	O*W*	H2*W*	O33	2.744 (4)	0.90 (6)	1.86 (5)	167 (5)
	O*W*	H1*W*	O34'	2.717 (3)	0.82 (6)	1.99 (6)	147 (5)
QPro*	N24	H24	O6	2.634	0.835	1.792	174.5
	O22	H22	O33	2.613	0.772	1.848	170.7
	O33	H331	O5	2.675	0.738	2.363	107.5
QDiph*†	N1′	H1′	O41	2.644 (4)	1.00	1.66	168
	N1	H1	O38	2.603 (4)	0.88	1.73	170

Symmetry code: (i) $x + 1, y, z$.

* Standard deviations unavailable, possibly incorrect position of H331 in QPro.

† Two Q cations in asymmetric unit; O12 is not linked to water molecule.

epiquinidine (Chekhlov, Kaluski, Struchkov, Malushinska & Kitaigorodski, 1974) and can be inferred for other epimers from their melting points, which are much lower than for the alkaloids (I)–(IV).

In general the bond lengths and angles of the quininium cation are in good agreement (within 3σ) with the corresponding values in QPro and QDiph. The quinoline moiety is not planar which is consistent with its low aromaticity characterized by the HOMA index defined by Gdaniec, Turowska-Tyrk & Krygowski (1989). As shown in Table 4, the HOMA value for quinoline in QSal is lower than that for the protonated 7-chloroquinoline moiety of chloroquine, and for quinoline in quinine monohydrate toluene solvate (QTol), but is very close to the values for quinoline in QPro and in QDiph.

The methoxy substituent at C19 adopts an orientation similar to quinine (Pniewska & Suszko-Purzycka, 1989), QPro and QDiph, the angle C18—C19—O23 being relatively large because of a possible steric interaction between H18 and the methyl group, while O23 is maintained in the plane of C18, C19 and C20.

The effect of the N1 protonation on the bond lengths and angles in the vicinity of this atom is similar to that described earlier for the quinuclidinium moiety of *Cinchona* alkaloids (Oleksyn, 1987).

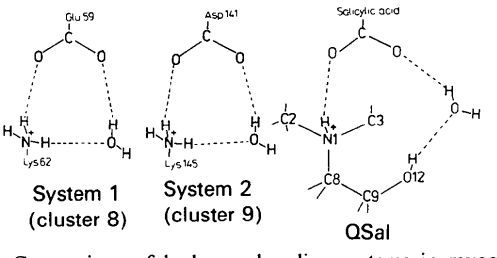

Fig. 2. Comparison of hydrogen-bonding systems in myoglobin and QSal. System 1 belongs to cluster 8 which involves residues Lys 62 and Glu 59. System 2 belongs to cluster 9 which involves residues Lys 145 and Asp 141. The drawings are simplified schemes with dimensions omitted.

Table 4. *Values of the aromaticity index for the quinoline moiety*

$$HOMA = 1 - 257.7/11\ \Sigma_{i=1}^{9}(1.388 - d^{CC})^2 + \Sigma_{i=1}^{2}(1.341 - d^{CN})^2$$

where d^{CC} and d^{CN} are C—C and C—N bond lengths, respectively.

Compound	HOMA	Reference
Benzene	0.996	Gdaniec, Turowska-Tyrk & Krygowski (1989)
7-Chloroquinolinium	0.820	Karle & Karle (1988)
QTol	0.790	Pniewska & Suszko-Purzycka (1989)
QPro	0.765	Graham *et al.* (1987)
QDiph mol. 1	0.737	
mol. 2	0.786	
mean value	0.761	Kubicki, Borowiak, Gawron, Giel & Gawroński (1990)
QSal	0.760	This work

Table 5. *Comparison of angles* (°) *in the vicinity of* N1 *for quinine monohydrate toluene solvate (QTol) and for the quininium cation in salts with salicylic acid (QSal), 2,2-dimethylcyclopropanecarboxylic acid (QPro) and diphenic acid (QDiph)*

				QDiph	
Angle*	QTol	QSal	QPro†	Molecule 1	Molecule 2
α	110.2 (2)	108.6 (2)	108.9	108.8 (4)	108.9 (4)
β	110.3 (2)	109.1 (2)	109.1	108.4 (4)	108.8 (4)
γ	109.9 (2)	107.9 (2)	108.4	108.4 (4)	108.8 (4)
μ	108.2 (3)	109.0 (2)	108.2	107.8 (3)	108.4 (3)
ν	107.8 (2)	107.7 (2)	108.5	108.7 (3)	108.4 (3)
ρ	110.3 (3)	114.2 (2)	113.8	114.2 (3)	113.7 (3)
σ_1	111.9 (3)	109.1 (2)	110.5	109.6 (4)	110.3 (4)
σ_2	111.7 (2)	108.8 (2)	108.8	109.4 (4)	108.8 (4)
σ_3	111.2 (2)	107.9 (2)	108.5	107.3 (3)	108.6 (3)
$\Delta\alpha$	0.73	−0.87	−0.57	−0.67	−0.57
$\Delta\beta$	0.83	−0.36	−0.37	−0.67	−0.68
$\Delta\gamma$	0.43	−1.61	−1.07	−1.09	−0.67
$\Delta\mu$	−1.27	−0.45	−1.27	−1.67	−1.07
$\Delta\nu$	−1.67	−1.64	−0.97	−0.77	−1.07
$\Delta\rho$	0.83	4.78	4.33	4.73	4.83
Σ_1	1.99	−2.84	−2.01	−2.43	−1.92
Σ_2	−2.11	2.69	2.09	2.29	2.09

* α = C4···N1—C2, β = C4···N1—C6, γ = C4···N1—C8, μ = C2—N1—C6, ν = C2—N1—C8, ρ = C6—N1—C8, σ_1 = C3—C2—N1, σ_2 = C5—C6—N1, σ_3 = C7—C8—N1 and C4···N1 is the approximate direction of the free electron pair. Δ(angle) = angle τ, $\tau = 109.47°$, $\Sigma_1 = \Delta\alpha + \Delta\beta + \Delta\gamma$, $\Sigma_2 = \Delta\mu + \Delta\nu + \Delta\rho$.

† Standard deviations unavailable.

Table 5 lists the values of the angles α = C4···N1—C2, β = C4···N1—C6, γ = C4···N1—C8 and μ = C2—N1—C6, ν = C2—N1—C8, ρ = C6—N1—C8. The C4···N1 line, according to electrostatic potential calculations (Oleksyn, Suszko-Purzycka, Dive & Lamotte-Brasseur, 1992) corresponds approximately to the direction of the N1 free electron pair before protonation. Also included are the discrepancies of these angles from the regular tetrahedral value ($\tau = 109.47°$) and of the angles σ_i, of C—C—N type for the quininium cation in the three salts and for the neutral molecule. From these values, which show regularities not previously noticed for the bicyclooctane ring, the following conclusions concerning the protonation effect can be drawn. (i) The angles α, β and γ decrease in comparison to those of unprotonated quinine, where certain repulsion between the free electron pair and the electrons of the N—C bonds leads to higher values of these angles. (ii) The angles μ, ν and ρ increase so that the sum, Σ_2, of their discrepancies

from the τ angle compensates Σ_1, *i.e.* the sum of the discrepancies of α, β and γ from τ. The increase in the angle ρ is much higher than that in μ and ν, most probably for steric reasons. It is worth noting that Σ_1 and Σ_2 change sign on passing from the neutral quinine to its cation. (iii) The angles σ_1, σ_2 and σ_3 decrease as a result of protonation and seem to be correlated with α, β and γ, respectively.

The regularities (i) and (iii) seem to indicate that the electron distribution not only in the bonds N1—C2, N1—C6, N1—C8, but also in C2—C3, C6—C5, C8—C7, is influenced by the lone pair at N1 in the free quinine base and by the proton in the quininium cation, respectively. In the base, the angles α, β, γ are greater and the 'cage' formed by the bonds mentioned above is flatter due to the repulsion between their electrons and those of the lone pair. In the cation a slight shift of the bond electrons toward the proton causes a decrease in the angles and removes the flattening.

The regularity (ii) may be ascribed to the tendency of the N1 atom to retain the sp^3 electron distribution.

The overall shape of the molecule is best described by two torsion angles, C15—C16—C9—O12 and O12—C9—C8—C7, which are −11.8 (3) and 43.7 (3)°, respectively. They are close in value to those which correspond to one of the potential minima calculated earlier (Dupont, Konsur, Lewinski & Oleksyn, 1985) and agree, to within 13°, with the relevant angles observed for quinine and its other salts. The quinuclidine skeleton in QSal and in the other two salts, QPro and QDiph, tends to be more twisted around the N1···C4 line than that in neutral quinine.

The geometry of the salicylic acid molecule is very similar to that described by Gellert & Hsu (1988) in crystalline 2-aminopyridinium salicylate (AmSal). Namely, the —O32—H32 hydroxyl group forms a strong intramolecular bond with one of the carboxyl O atoms, O33. The parameters for this bond, D—H = 1.047 (2), $D\cdots A$ = 2.535 (3), H$\cdots A$ = 1.552 (2) Å and $\angle D$—H$\cdots A$ = 153.5 (2)°, are close to those observed in AmSal. An interesting feature, occurring in both salicylate anions, is a lengthening of this C—O bond of the carboxyl group hydrogen bonded to the hydroxyl [1.270 (4) in AmSal and 1.265 (3) Å in QSal] relative to the other C—O bond [1.256 (4) in AmSal and 1.246 (3) Å in QSal]. The six-membered ring of the salicyl moiety is planar within 0.012 (2) Å and its HOMA index is high (0.980).

The crystal packing is shown in Fig. 3. The ion pairs are linked to each other by intermolecular hydrogen bonds, OW—H1W···O34^{i} [(i) = $x+1$, y, z], thus forming chains along the [100] direction. The chains interact through van der Waals forces. A very similar packing occurs in QPro, in which the parameters of the corresponding hydrogen bonds agree well with those in QSal (*cf.* Table 3).

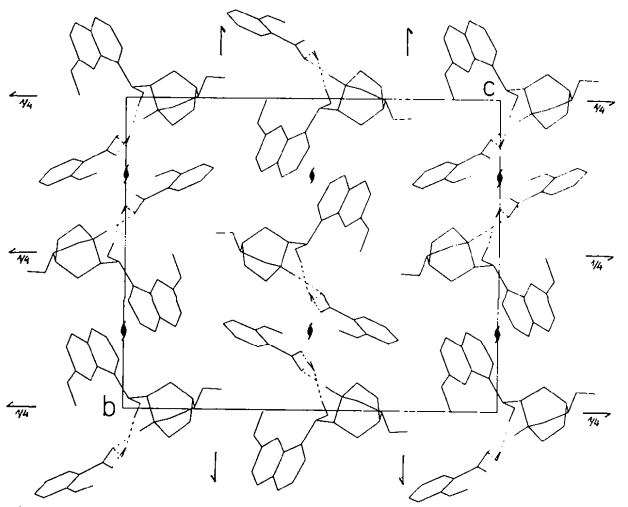

Fig. 3. Projection of quininium salicylate monohydrate unit-cell content along the x axis. Hydrogen bonds are indicated by dashed lines.

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