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Conformational flexibility of carpaine and its hydrobromide derivative

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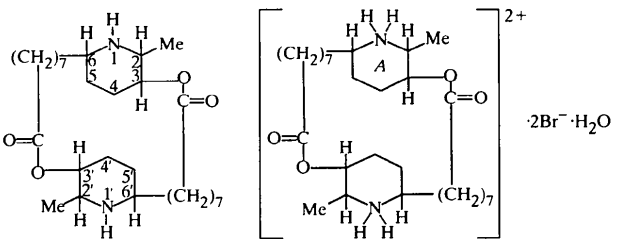
Abstract

The X-ray structures of the two compounds carpaine ($C_{28}H_{50}N_2O_4$) and carpaine dihydrobromide monohydrate ($C_{28}H_{52}N_2O_4^{2+}\cdot 2Br^-\cdot H_2O$) have been determined, together with the absolute configuration of the hydrobromide derivative. The structure of the hydrobromide derivative shows that the molecule is flexible and the changes in the conformations are brought about by the hydrogen bonding of the protonated-N atoms with the two Br atoms and the water molecule.

Comment

Carpaine, an alkaloid isolated from the leaves of *Carica Papaya* L., was assigned the structure of (I) on the basis of work from several laboratories (Rapoport & Baldridge, 1951, 1952; Govindachari & Narasimhan, 1955; Tichy & Sicher, 1962; Friedmann & Spiteller, 1964; Coke & Rice, 1965). The alkaloid has been shown to exhibit *in vitro* antitumour activity against mouse-lymphoid leukaemia and Ehrlich ascites tumour cells (Oliveros-Belardo *et al.*, 1972). A large number of mono- and diamides of carpaine have been prepared and shown to have more antitumour activity than the alkaloid (Fahy *et al.*, 1994). Carpaine is a macrocyclic compound with a 26-membered ring rarely encountered among plant secondary metabolites. In view of current interest in host–guest studies, carpaine would be a suitable candidate in this regard. It would be desirable to gain an idea of the nature and size of the cavity and the conformational flexibility of the molecule and also confirm the absolute configuration derived by degradation studies since both carpaine and its hydrobromide, (II), are available in crystalline form.



The crystal structure of carpaine shows that it contains only one half of the molecule in the asymmetric unit and the two halves are related by a twofold symmetry. In carpaine hydrobromide however, the asymmetric unit contains a single molecule with two Br atoms and a water molecule.

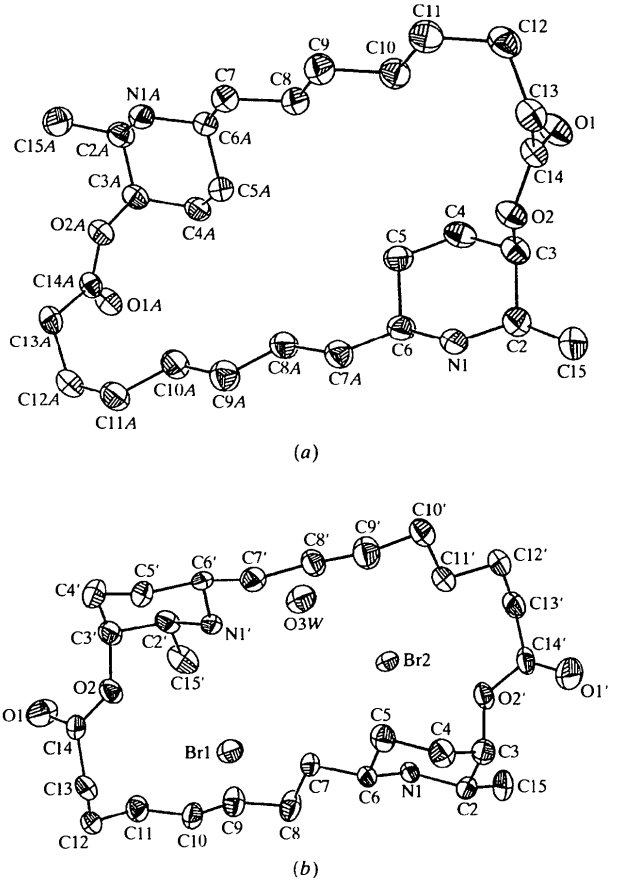


Fig. 1. *ORTEP*II (Johnson, 1976) diagrams of (*a*) carpaine and (*b*) its hydrobromide derivative at the 30% probability level.

The bond lengths and angles are normal in carpaine (Allen *et al.*, 1987). The N—H bonds of the piperidine rings and C=O bonds of the carboxyl groups point outwards, which means that the inclusion of any guest

molecule would be through hydrophobic interactions only. The cavity size as measured between the atoms C7···C7*A* and C13···C13*A* is 6.07 × 11.93 Å^2 in carpaine.

In carpaine dihydrobromide monohydrate the N atoms N1 and N1′ of the piperidine rings are protonated. The effect of this protonation is observed by an increase in bond lengths involving the N atoms (Allen *et al.*, 1987) and is also reflected in bond angles by a decrease in the values of C2—N1—C6 and C2′—N1′—C6′ by 2 to 3° from the expected values. The conformations of the piperidine rings in both structures approximate to a chair (Duax *et al.*, 1976). The C7–C12 alkyl chain in carpaine, atoms C6*A*, N1*A* and C2*A* of the piperidine ring and the C15*A* atom lie on a plane. The absolute configuration of carpaine itself could not be established from our analysis [Flack (1983) parameter −0.2 (5)], but analysis of carpaine dihydrobromide hydrate allowed the absolute structure of the dication to be established [Flack parameter −0.02 (3)]. The absolute configuration is *R* at C6 and C6′ and *S* at C2, C2′, C3 and C3′.

The structure solution of the hydrobromide derivative revealed that the conformations of the two halves of the molecule are not equal. The atoms C4 to C9, C8 to C12, C4′ to C10′ and C9′ to C13′ are respectively planar. The planarity of the alkyl chain of atoms as seen in carpaine is broken at the C8—C9 bond on one side and the C9′—C10′ bond on the other. Also one of the piperidine rings has flipped so that the N—H bond points inwards while in the other it points outwards as in carpaine. The changes in the conformation are brought out by the hydrogen bonding involving the two Br atoms, the N atoms of the piperidine rings and the oxygen of the water molecule. However, the C=O bonds of the two carbonyl groups point outwards in this structure as in carpaine.

In carpaine dihydrobromide monohydrate the conformation starting from the C4—C3 bond in an anticlockwise direction can be described as (*sc*, *ac*, −*ap*, *ac*, −*sc*, −*ap*, −*ap*, −*sc*, −*ap*, *ap*, −*ap*, *ap*, *sc*, *sc*, *ac*, *ap*, −*ac*, *sc*, *sc*, −*ap*, *ap*, −*sc*, *ap*, −*ap*, *ap*, *sc*) and in carpaine it is (−*sc*, −*sc*, −*ap*, −*ac*, *sc*, −*sc*, *ap*, *ap*, *ap*, *ap*) (*sc* = synclinal, *ac* = anticlinal, *ap* = antiperiplanar) (Klyne & Prelog, 1960) for one half of the molecule and the other half is related to it by a twofold symmetry.

There are two Br atoms and one water molecule associated with each carpaine hydrobromide molecule and these atoms along with the N atoms of the two piperidine rings participate in hydrogen bonding. The N atoms of the two piperidine rings are connected by hydrogen bonds as N1—H2N···Br2···H3O1—O3*W*···H4N—N1′. The second Br atom, Br1, is hydrogen bonded to N1′. The intermolecular interaction is also due to the N1—H1N···Br2···H2N—N1($1-x$, $y-\frac{1}{2}$, $1-z$) hydrogen bonds.

The two Br atoms and the water molecule lie inside the cavity. The study shows that carpaine is not a rigid molecule and its conformation may change depending on the nature of the guest molecule.

Experimental

Crystals of carpaine were obtained from acetone by slow evaporation. The carpaine hydrobromide derivative was prepared by dissolving the native carpaine in hot ether and then passing hydrobromide gas into it. The precipate obtained was dissolved in absolute alcohol and crystallized from ethanol by slow evaporation.

Compound (I)

Crystal data

$C_{28}H_{50}N_2O_4$
M_r = 478.70
Orthorhombic
$P2_12_12$
a = 18.864 (8) Å
b = 14.476 (4) Å
c = 5.473 (1) Å
V = 1494.5 (8) Å^3
Z = 2
D_x = 1.064 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 23 reflections
θ = 15–32°
μ = 0.550 mm^{-1}
T = 293 (2) K
Plate
0.30 × 0.20 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
1660 measured reflections
1660 independent reflections
1499 reflections with $I > 2\sigma(I)$
θ_{max} = 70°
$h = 0 \rightarrow 22$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 6$
3 standard reflections every 100 reflections
intensity decay: 0.02%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.136
S = 1.438
1660 reflections
155 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0571P)^2 + 0.1331P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.027 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °) for (I)*

O1—C14	1.193 (3)	N1—C2	1.456 (4)
O2—C14	1.342 (3)	N1—C6	1.466 (3)
O2—C3	1.456 (3)		
C14—O2—C3	117.4 (2)	C2—N1—C6	115.4 (2)
C14—O2—C3—C4	−83.2 (3)	C10—C11—C12—C13	−63.8 (4)
C14—O2—C3—C2	155.5 (2)	C11—C12—C13—C14	86.2 (3)
C6′—C7—C8—C9	174.8 (3)	C3—O2—C14—O1	1.1 (4)
C7—C8—C9—C10	178.4 (3)	C12—C13—C14—O1	45.0 (4)
C8—C9—C10—C11	178.6 (3)	C12—C13—C14—O2	−136.8 (2)

Symmetry code: (i) $2-x$, $1-y$, z.

Compound (II)

Crystal data

$C_{28}H_{52}N_2O_4^{2+}\cdot 2Br^-\cdot H_2O$
$M_r = 658.55$
Monoclinic
$P2_1$
$a = 11.960\ (1)$ Å
$b = 7.403\ (1)$ Å
$c = 18.978\ (1)$ Å
$\beta = 99.67\ (1)°$
$V = 1656.4\ (3)$ Å^3
$Z = 2$
$D_x = 1.320$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54180$ Å
Cell parameters from 25 reflections
$\theta = 13–30°$
$\mu = 3.383$ mm^{-1}
$T = 293\ (2)$ K
Plate
0.40 × 0.30 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.346$, $T_{max} = 0.729$
3872 measured reflections
3274 independent reflections

2672 reflections with $I > 2\sigma(I)$
$R_{int} = 0.010$
$\theta_{max} = 76.53°$
$h = 0 \rightarrow 15$
$k = 0 \rightarrow 9$
$l = -23 \rightarrow 23$
3 standard reflections
every 100 reflections
intensity decay: 0.03%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.091$
$S = 1.101$
3274 reflections
335 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0329P)^2 + 1.2448P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.007$
$\Delta\rho_{max} = 0.35$ e Å^{-3}
$\Delta\rho_{min} = -0.42$ e Å^{-3}

Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.00180 (15)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = −0.02 (3)

Table 2. *Selected geometric parameters (Å, °) for (II)*

O1—C14	1.174 (9)	O2′—C3	1.450 (11)
O2—C14	1.321 (9)	N1—C6	1.525 (7)
O2—C3′	1.452 (9)	N1—C2	1.533 (8)
O1′—C14′	1.174 (9)	N1′—C2′	1.479 (8)
O2′—C14′	1.338 (9)	N1′—C6′	1.507 (6)
C14—O2—C3′	119.2 (7)	C6—N1—C2	111.9 (5)
C14′—O2′—C3	120.3 (7)	C2′—N1′—C6′	113.6 (5)
C14′—O2′—C3—C4	99.3 (7)		
C15—C2—C3—O2′	59.0 (9)		
C6—C7—C8—C9	166.9 (8)		
C7—C8—C9—C10	−72.1 (13)		
C8—C9—C10—C11	177.4 (8)		
C11—C12—C13—C14	63.0 (10)		
C12—C13—C14—O1	51.0 (11)		
C12—C13—C14—O2	−130.3 (7)		
C8′—C9′—C10′—C11′	−65.4 (10)		
C10′—C11′—C12′—C13′	−175.8 (8)		
C11′—C12′—C13′—C14′	−62.7 (11)		
C3—O2′—C14′—O1′	9.3 (11)		
C12′—C13′—C14′—O1′	−72.3 (11)		
C12′—C13′—C14′—O2′	105.9 (8)		

Table 3. *Hydrogen-bonding geometry (Å, °) for (II)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1N···Br2	0.90	2.45	3.316 (6)	163
N1′—H3N···O3*W*	0.90	1.95	2.826 (7)	164
N1′—H4N···Br1	0.90	2.58	3.454 (6)	163
O3*W*—H13O···Br2	0.85	2.54	3.317 (4)	152
N1—H2N···Br2^{i}	0.90	2.53	3.408 (5)	167
O3*W*—H23O···Br1^{ii}	0.85	2.50	3.314 (5)	159

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

For both compounds, data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *SDP* (Frenz, 1978); program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1985); program(s) used to refine structures: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1417). Services for accessing these data are described at the back of the journal.

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