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Astemizole tetrachlorocuprate(II)

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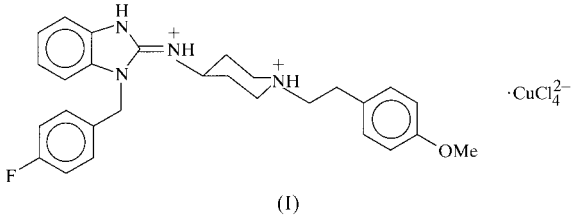
The structure of {3-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-ylidene}{1-[2-(4-methoxyphenyl)ethyl]-4-piperidin-1-io}ammonium tetrachlorocuprate(II), $(C_{28}H_{33}FN_4O)[CuCl_4]$, contains diprotonated cations of astemizole hydrogen bonded to three Cl atoms in two different $CuCl_4^{2-}$ anions, with Cl···N distances in the range 3.166 (4)–3.203 (4) Å. The geometry around copper is flattened tetrahedral with significantly different Cu—Cl distances which lie in the range 2.1968 (14)–2.2861 (12) Å. The phenylethyl C atoms of the (4-methoxyphenyl)ethyl group are disordered indicating the presence of two conformers in the crystals.

Comment

Astemizole is the active ingredient of 'hismanal', a potent antihistaminic drug which has been classified as a long-lasting drug with 24 h effectiveness and has very little or no drowsiness effects (Casy, 1991). A lack of sedation effects may be attributed to the presence of the 1-[2-(4-methoxyphenyl)-ethyl]-4-piperidinyl moiety in astemizole which may hinder the penetration of the central nervous system by this drug (Richards *et al.*, 1984). Continuing our studies on the influence of anions of transition metals, *e.g.* $CuCl_4^{2-}$, on the conformation of antihistamines effective on H_1 receptors (Parvez & Sabir, 1997*a*,*b*,*c*, 1998; Parvez, 1998), we have prepared a diprotonated cationic salt of astemizole. In this paper, we report the crystal structure of astemizole tetrachlorocuprate(II), (I). The crystal structure of astemizole in its free form has already been reported (Peeters *et al.*, 1995).



(I)

Fig. 1 shows an *ORTEP*II (Johnson, 1976) drawing of (I). The structure is composed of diprotonated astemizole cations and $CuCl_4^{2-}$ anions. The molecular dimensions in the astemizole dication are normal and agree well with the corresponding dimensions reported in the literature (Allen *et al.*, 1987). The phenylethyl C atoms are disordered over C20–C27 and C20′–C27′, with site-occupancy factors 0.490 (6) and 0.510 (6), respectively, indicating the presence of two conformers in the crystals. The separation between pairs of C atoms of the phenylethyl ring is in the range 0.12 Å for C25 and 1.27 Å for C21. The important bond distances are Csp^2—F 1.366 (5), mean Csp^3—Csp^3 1.515 (10), Csp^3—Csp^2 1.510 (10), and C—$C_{aromatic}$ 1.383 (12) Å; C22–C27 and C22′–C27′ aromatic ring distances were constrained at 1.39 (1) Å. It is interesting to note that C1—N3 [1.316 (5) Å] is clearly a double bond and that in the benzimidazole ring, the mean distances N—Csp^2 and N—$C_{aromatic}$ of 1.355 (4) and 1.397 (3) Å, respectively, are significantly different from each other. Moreover, the mean Nsp^3—C distance is 1.500 (9) Å, while the N—Csp^3 and C—Nsp^2 distances are 1.481 (5) and 1.452 (5) Å, respectively.

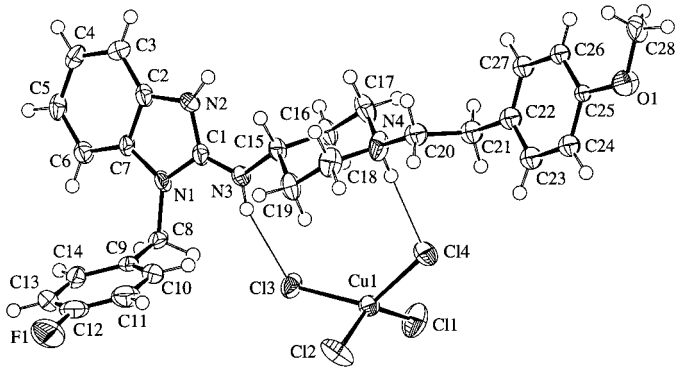


Figure 1
*ORTEP*II (Johnson, 1976) drawing of (I) with 50% probability ellipsoids; the disordered C20′–C27′ atoms are not shown.

The benzimidazole and fluorophenyl rings are essentially planar with maximum deviations of atoms from the least-squares planes being 0.033 (3) and 0.005 (3) Å, respectively. The dihedral angle between these planes is 67.77 (11)°; the corresponding angle in the two molecules of astemizole is around 79° (Peeters *et al.*, 1995). The six-membered piperidinyl ring in (I) has a classical chair conformation with puckering parameters (Cremer & Pople, 1975) Q = 0.573 (5) Å, θ = 1.9 (5)° and φ = 67 (17)°. The mean plane of the methoxy group, which is not disordered, is inclined at 11.7 (7) and 21.5 (6)° to the phenyl rings C22–C27 and C22′–C27′, respectively, for the two conformers present in the crystal. The dihedral angle between the mean planes of these phenyl rings is 29.2 (3)°.

The $CuCl_4^{2-}$ anion exhibits a flattened tetrahedral geometry with Cu—Cl distances between 2.1968 (14) and 2.2861 (12) Å, the shortest distance being for the Cl atom not involved in any hydrogen bond. There are two types of Cl—Cu—Cl angles in the anion, *i.e.* four angles in the range 97.86 (5)–99.93 (5)° and the remaining two are 130.27 (5) and 137.91 (6)°. Similar geometry for $CuCl_4^{2-}$ has been reported in the tetrachlorocuprate salts of clemizole (Parvez & Sabir, 1997*a*), chloropyramine (Parvez & Sabir, 1997*b*), triprolidine (Parvez & Sabir, 1997*c*), dicytosine (Ogawa *et al.*, 1979) and fenethazine (Obata *et al.*, 1985).

The astemizole dication is hydrogen bonded to two Cl atoms of the same anion *via* its ammonium H atoms [N···Cl 3.203 (4) and 3.166 (4) Å]. It is also hydrogen bonded to a Cl atom of a symmetry-related anion involving the H atom attached to N2 of its benzimidazole ring [N···Cl 3.190 (4) Å]. The details of hydrogen-bonding geometry in (I) have been provided in Table 2.

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···Cl2^{i}	0.88	2.32	3.190 (4)	170
N3—H3N···Cl3	0.88	2.37	3.203 (4)	157
N4—H4N···Cl4	0.93	2.24	3.166 (4)	171

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

Experimental

The title compound was synthesized by adding $CuCl_2\cdot 2H_2O$ (1.0 mmol) to astemizole (2.0 mmol; Sigma Inc.) in HCl (15 ml, 6.0 *M*) and boiling for 10 min. The solution was allowed to stand at room temperature whereupon it yielded yellow prismatic crystals after a few days.

Crystal data

$(C_{28}H_{33}FN_4O)[CuCl_4]$
M_r = 665.92
Monoclinic, $P2_1/n$
a = 9.1099 (7) Å
b = 15.9279 (15) Å
c = 20.5073 (19) Å
β = 100.445 (2)°
V = 2926.2 (4) Å^3
Z = 4
D_x = 1.512 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3724 reflections
θ = 1.6–26.4°
μ = 1.15 mm^{-1}
T = 193 (2) K
Prism, yellow
0.17 × 0.13 × 0.05 mm

Data collection

Bruker *P4*/*RA* SMART 1000 CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*: Sheldrick, 1996)
T_{min} = 0.83, T_{max} = 0.95
14320 measured reflections
5981 independent reflections
2704 reflections with $I > 2\sigma(I)$
R_{int} = 0.097
θ_{max} = 26.4°
$h = -4 \rightarrow 11$
$k = -18 \rightarrow 19$
$l = -25 \rightarrow 23$
50 standard reflections
frequency: beginning and end of data collection
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.101
S = 0.81
5981 reflections
346 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0236P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

Cu1—Cl1	2.1968 (14)	N2—C1	1.359 (5)
Cu1—Cl2	2.2382 (13)	N2—C2	1.394 (5)
Cu1—Cl4	2.2545 (13)	N3—C1	1.316 (5)
Cu1—Cl3	2.2861 (12)	N3—C15	1.452 (5)
F1—C12	1.366 (5)	N4—C18	1.490 (5)
N1—C1	1.352 (5)	N4—C17	1.496 (6)
N1—C7	1.400 (5)	N4—C20	1.501 (6)
N1—C8	1.481 (5)	N4—C20′	1.512 (6)
Cl1—Cu1—Cl2	137.91 (6)	C7—N1—C8	125.1 (3)
Cl1—Cu1—Cl4	99.93 (5)	C1—N2—C2	109.1 (4)
Cl2—Cu1—Cl4	99.04 (5)	C1—N3—C15	126.3 (4)
Cl1—Cu1—Cl3	97.86 (5)	C18—N4—C17	109.7 (4)
Cl2—Cu1—Cl3	97.89 (5)	C18—N4—C20	103.0 (4)
Cl4—Cu1—Cl3	130.27 (5)	C17—N4—C20	124.9 (5)
C1—N1—C7	109.7 (3)	C18—N4—C20′	119.9 (5)
C1—N1—C8	125.1 (4)	C17—N4—C20′	101.0 (4)

The phenylethyl C atoms of the (4-methoxyphenyl)ethyl group are disordered (see *Comment*). The N4—C20/C20′, C20/C20′—C21/C21′ and C—C$_{aromatic}$ distances in the (4-methoxyphenyl)ethyl group were fixed at 1.48 (1), 1.50 (1) and 1.39 (1) Å, respectively, using the command *DFIX* and the disordered atoms were refined with isotropic displacement parameters. The H atoms were included in the refinement at idealized positions with C—H = 0.95, 0.98 and 0.99 and N—H = 0.88 and 0.93 Å and the isotropic displacement parameters of the H atoms were tied to the atoms to which they were bonded.

Data collection: *SMART* (Siemens, 1994); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SAPI*91 (Fan, 1991); program(s) used to refine structure: *SHELXTL* (Sheldrick, 1997); molecular graphics: *TEXSAN* (Molecular Structure Corporation, 1994); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1280). Services for accessing these data are described at the back of the journal.

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