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Amitriptylinium picrate: conformational disorder

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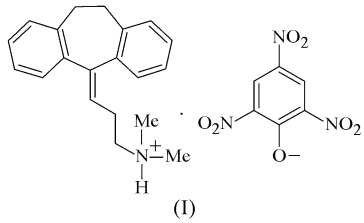
In the structure of the title salt [systematic name: 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-aminium 2,4,6-trinitrophenolate] of a tricyclic antidepressant, $C_{20}H_{24}N^{+}\cdot C_6H_2N_3O_7^{-}$, the dimethylaminopropyl subunit possesses a classical static conformational disorder. The central cycloheptadiene ring adopts a bent conformation that is intermediate between boat and chair forms, leading to a butterfly shape for the hetero-tricyclic moiety. In a complementary fashion, donors from amitriptyline and acceptors from picrate form intermolecular C—H···O hydrogen bonds and N—H···O salt bridges. These hydrogen bonds cluster amitriptyline and picrate ions into a closed $R_4^4(36)$ hetero-tetramer, whereas intermolecular C—H···π interactions between amitriptyline ions cluster them into homo-dimers. Significant π–π stacking interactions are also observed between aromatic rings of amitriptyline and picrate, and these, combined with the C—H···π interactions, associate molecules into linear arrays along the [1$\bar{1}$1] direction.

Comment

Amitriptyline (Elavil) is a well known tricyclic antidepressant with anticholinergic and sedative properties. It is believed to prevent the reuptake of norepinephrine and serotonin at neurotransmitters [Garattini *et al.*, 1998; DrugBank (Wishart *et al.*, 2006) ID APRD00227]. The structure of the title salt, amitriptylinium picrate, (I), is presented here.

The dimethylaminopropyl subunit (DMAP; atoms N1/C1–C5) of (I) exhibits a classical static conformational disorder. There are two conformational states of DMAP, where the state corresponding to the minor disordered component is interconvertible from the major component by approximate rotations of 60, −120 and 120° about the C4—C5, C1—C4 and C1—N1 bonds, respectively. The torsion angles in (I) are provided in Table 1. A text search for conformational disorder in the Cambridge Structural Database (CSD, Version 5.28; Allen, 2002) revealed that such compounds represent hardly 0.001%



(I)

of all reported structures. A great majority of them are populated by conformational disorders of terminal hydrocarbon chains and multiple puckering states of alicyclic rings. The multi-conformational states of a molecule or part thereof, separated by low-energy barriers, are also represented in conformational polymorphs. Even if all of the 0.5% of polymorph cases present in the CSD (van de Streek & Motherwell, 2005) are included, this under-representation is in sharp contrast to the otherwise plentiful conformational states of a molecule that are populated in solution. This anomalous observation could be partially rationalized by the fact that, among several conformers in solution, only those that exhibit similar steric bulk and are relatively disposed in a similar manner occur in the crystal structure, so that there is a minimal violation of crystal translational symmetry.

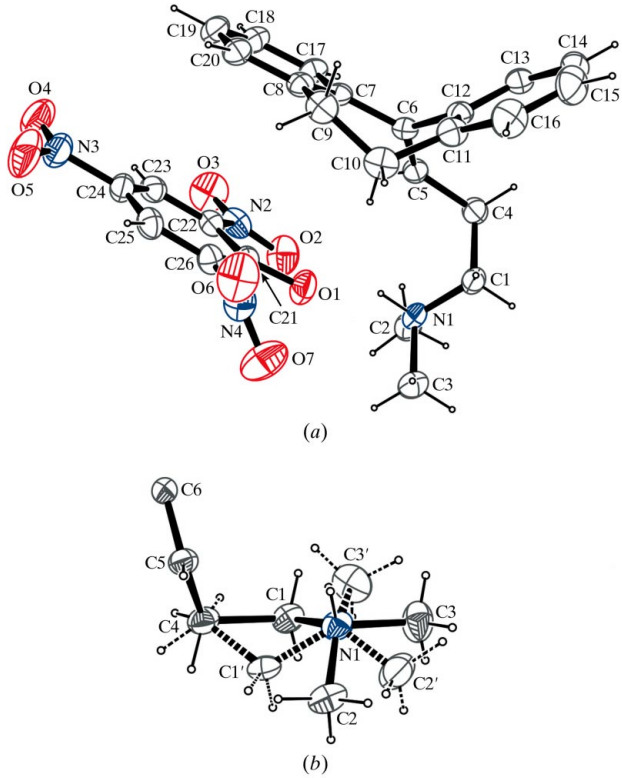


Figure 1
(*a*) A view of (I), showing the atom-numbering scheme. Only the major component is shown. Displacement ellipsoids are drawn at the 30% probability level. (*b*) The major and minor components of the disordered DMAP subunit. Dashed lines indicate the minor fraction.

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The central seven-membered cycloheptadiene ring of (I) (C6–C12) adopts a bent conformation (Table 1), giving rise to an overall butterfly shape of the tricyclic ring (Fig. 1). The fused benzene rings (C11–C16 and C7/C8/C17–C20) on either side subtend an angle of 51.3 (1)°. The bent transition state is an intermediate conformation state of a cycloheptane, between boat and chair, and is characterized in the ideal case by the following contiguous torsion angles as calculated by Bocian *et al.* (1975) and Bocian & Strauss (1977): 75.1, −60.3, −1.8, 1.7, 60.3, −75.1 and 0.0°. Similar conformations of the tricyclic ring were also observed in nortriptyline and amitriptyline hydrochloride (Klein *et al.*, 1991, 1994) and related compounds (Vijay *et al.*, 2005; Portalone *et al.*, 2007).

The crystal packing of (I) is predominantly stabilized by co-operative interactions, as shown in Fig. 2. Amitriptyline (AMP) and picrate (PCT) molecules play a complementary role. Intermolecular salt bridges and hydrogen bonds are formed between the donors of AMP and the acceptors of PCT (Table 2). N1—H1(or H1′)···O1 salt bridges and C19—H19···O5^{ii} [symmetry code: (ii) $1-x, 1-y, 1-z$] hydrogen bonds cluster them into a hetero-tetramer. This assembly is characterized by an $R_4^4(36)$ pattern (Bernstein *et al.*, 1995). Orthogonal to this assemblage, AMP molecules are clustered into homo-dimers, which are mediated by C14—H14···*Cg*1^{iii} interactions [symmetry code: (iii) $-x, 1-y, -z$].

Significant π–π interactions are also observed in the packing of (I). *Cg*3 (the centroid of the PCT C21–C26 ring) makes a stacking interaction with *Cg*1 (the centroid of the AMP C7/C8/C17–C20 ring) of the same asymmetric unit, with a centroid-to-centroid distance of 3.774 (1) Å and a perpendicular distance of 3.475 Å. On its other face, PCT is associated by a parallel stacking interaction, with *Cg*3···*Cg*3^{iv} = 3.406 Å, a slippage of 1.348 Å and a centroid-to-centroid distance of 3.663 (1) Å [symmetry code: (iv) $1-x, -y, 1-z$].

These interactions between AMP and PCT pairs, in combination with C—H···π interactions with another two AMP molecules, form a one-dimensional chain along the [1$\bar{1}$1] direction (Fig. 2). The co-operative association of intermolecular interactions into characteristic patterns has been unambiguously characterized using graph-theory-based notations (Bernstein *et al.*, 1995). Unfortunately, such notations are of limited applicability, as they cannot be used to characterize interactions involving π-acceptors or those which do not come under the category of donor–acceptor types, such as aromatic π–π interactions. It would be of particular interest to formulate a similar scheme which can be specifically applied in those cases.

Apart from co-operative interactions, the major component of DMAP is involved in C4—H4*A*···O3^{i} hydrogen bonding [symmetry code: (i) $-x, -y, 1-z$]. A short contact associated with the methyl atom, C3—H3*B*···O4^{v} [H···A = 2.56 Å and C—H···A = 172°; symmetry code: (v) $1-x, -y, 1-z$], is also observed. However, short contacts like this involving methyl atoms are unlikely to have any structural significance, due to the very low acidity of the C—H bond and the rapid rotation of the methyl group about the N1—C3 bond.

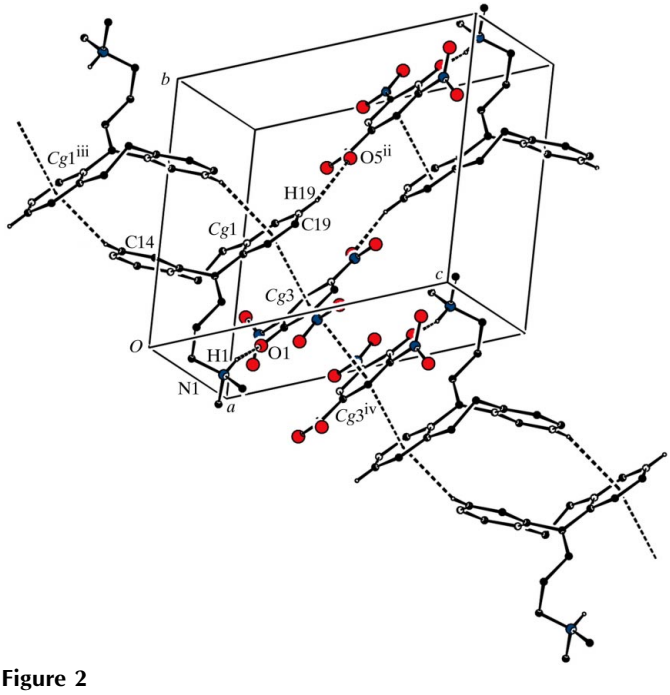

Figure 2
Co-operative interactions observed in (I): intermolecular hydrogen-bonded $R_4^4(36)$ hetero-tetramers of AMP and PCT along [111], and association of AMP and PCT into a one-dimensional array along [1$\bar{1}$1], mediated *via* C—H···π and π–π stacking interactions. *Cg*1 and *Cg*3 are the centroids of rings C7/C8/C17–C20 and C21–C26, respectively. Only the major fraction of the disorder is shown. [Symmetry codes: (ii) $1-x, 1-y, 1-z$; (iii) $-x, 1-y, -z$; (iv) $1-x, -y, 1-z$.]

Experimental

Compound (I) was prepared by the reaction of AMP with picric acid at room temperature. Aqueous solutions of amitriptyline hydrochloride (0.942 g, 0.03 *M*) and picric acid (0.689 g, 0.03 *M*) were mixed and stirred. The mixture yielded a yellow precipitate, which was filtered off, washed thoroughly with water and dried over P_2O_5 in a vacuum desiccator. Single crystals of (I) suitable for X-ray diffraction analysis were grown by slow evaporation of a solution in methanol (m.p. 393 K).

Crystal data

$C_{20}H_{24}N^+\cdot C_6H_2N_3O_7^-$
M_r = 506.51
Triclinic, $P\bar{1}$
a = 10.0649 (11) Å
b = 11.0187 (12) Å
c = 12.0352 (13) Å
α = 73.357 (2)°
β = 79.305 (3)°
γ = 85.411 (4)°
V = 1256.1 (2) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 301 (1) K
0.48 × 0.31 × 0.26 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.969, T_{max} = 0.975
7632 measured reflections
4802 independent reflections
3598 reflections with $I > 2\sigma(I)$
R_{int} = 0.040

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.178
S = 1.06
4802 reflections
365 parameters
15 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}

Table 1
Selected torsion angles (°).

C2—N1—C1—C4	59.4 (3)	C11—C12—C6—C7	66.2 (2)
C3—N1—C1—C4	−179.4 (3)	C12—C6—C7—C8	−44.7 (2)
C2′—N1—C1′—C4	−178.9 (4)	C6—C7—C8—C9	1.6 (3)
C3′—N1—C1′—C4	−50.3 (4)	C7—C8—C9—C10	−18.0 (3)
N1—C1—C4—C5	55.6 (3)	C8—C9—C10—C11	71.5 (2)
N1—C1′—C4—C5	−64.4 (3)	C9—C10—C11—C12	−68.4 (2)
C1—C4—C5—C6	86.3 (3)	C10—C11—C12—C6	−5.4 (3)
C1′—C4—C5—C6	142.7 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O1	0.87	1.87	2.648 (2)	149
N1—H1′···O1	0.87	1.88	2.648 (3)	146
C4—H4*A*···O3^{i}	0.97	2.59	3.343 (3)	135
C19—H19···O5^{ii}	0.93	2.50	3.379 (4)	158
C14—H14···*Cg*1^{iii}	0.93	2.87	3.667 (3)	144

Symmetry codes: (i) $-x, -y, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $-x, -y+1, -z$.

The geometric parameters of both disordered components were restrained to be the same by applying soft SADI restraints (*SHELXL97*; Sheldrick, 1997). In the final stage of refinement, the statistical fractions of the major and minor disordered components were held fixed to the nearest rounded values of 0.6 and 0.4, respectively. All H atoms were placed in geometrically expected positions and refined with riding options, with aromatic/sp^2 C—H = 0.93 Å, methyl C—H = 0.96 Å, methylene C—H = 0.97 Å and N—H = 0.87 Å, and with U_{iso}(H) = 1.2U_{eq}(parent), or 1.5U_{eq}(C) for methyl groups. In the crystal structure, two (AMP)C(methyl)···O(PCT) short contacts are observed, namely C3···O1 of 2.992 (6) Å and C3′···O7^{v} of 2.932 (6) Å [symmetry code: (v) $1-x, -y, -z$]. However, refinement of the H-atom parameters did not converge well. A search for occurrences of short C(methyl)···O contacts of less than 3.0 Å in the CSD revealed 513 hits. Such short contacts may arise due to the presence of weak intermolecular C(methyl)—H···O interactions, as observed previously in many examples (Schneider *et al.*, 2000; Panda *et al.*, 2001; Domagała *et al.*, 2004; Latip *et al.*, 2005). This appears to be relevant in the present case, as atom C3 is adjacent to the electron-withdrawing group N1.

Data collection: *SMART* (Bruker, 1999); cell refinement: *SAINT* (Bruker, 1999); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3097). Services for accessing these data are described at the back of the journal.

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