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Sulfoconjugation of Dopamine. The Structures of Dopamine-*O*-sulfates, $C_8H_{11}NO_5S$

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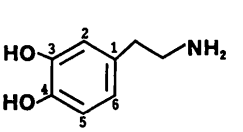
Abstract. 4-(2-Aminoethyl)-2-hydroxyphenyl hydrogen sulfate (dopamine-4-*O*-sulfate): $M_r = 233{\cdot}24$, monoclinic, $P2_1/n$, $a = 9{\cdot}866\ (5)$, $b = 10{\cdot}454\ (4)$, $c = 19{\cdot}799\ (5)$ Å, $\beta = 95{\cdot}78\ (2)°$, $V = 2031{\cdot}4$ Å^3, $Z = 8$, $D_x = 1{\cdot}525$, D_m(flotation in $CHCl_3/C_3H_6Br_2$) = $1{\cdot}52\ (1)$ Mg m^{-3}, Mo $K\alpha$ radiation ($\lambda K\alpha_1 = 0{\cdot}70926$, $\lambda K\alpha_2 = 0{\cdot}71354$ Å), $\mu = 3{\cdot}054$ mm^{-1}, $F(000) = 488$, $T = 298$ K, $R = 0{\cdot}041$, $wR = 0{\cdot}050$ for 2799 observations, $I \geq 3\sigma(I)$. 5-(2-Aminoethyl)-2-hydroxyphenyl hydrogen sulfate (dopamine-3-*O*-sulfate): $M_r = 233{\cdot}24$, monoclinic, $P2_1/c$, $a = 8{\cdot}706\ (5)$, $b = 12{\cdot}749\ (7)$, $c = 9{\cdot}214\ (3)$ Å, $\beta = 102{\cdot}97\ (4)°$, $V = 996{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}555$, D_m(flotation in $CHCl_3/C_3H_6Br_2$) = $1{\cdot}55\ (1)$ Mg m^{-3}, Mo $K\alpha$ radiation, $\mu = 3{\cdot}113$ mm^{-1}, $F(000) = 244$, $T = 273$ K, $R = 0{\cdot}043$, $wR = 0{\cdot}052$ for 1530 observations, $I \geq 3\sigma(I)$. Both dopamine sulfate molecules crystallize as zwitterions. The two crystallographically independent molecules comprising the dopamine-4-*O*-sulfate asymmetric unit are conformational isomers. The disposition of the ethylamine side chains differs in all three molecules; two of these differ considerably from conformations normally observed in crystal structures of dopamine derivatives, *i.e.* τ_1 for one dopamine-4-*O*-sulfate molecule is $-47{\cdot}4°$ and τ_1 for the dopamine-3-*O*-sulfate molecule is $62{\cdot}9°$. There is extensive hydrogen bonding observed in both structures including intramolecular hydrogen bonding between the ionized sulfate group and the phenolic hydroxyl. The intramolecular hydrogen bonds are accompanied by very short phenolic C—OH distances ranging from 1·349–1·364 Å.

Introduction. Sulfoconjugation is an important metabolic pathway determining the fate and pharmacological action of ingested phenolic substances. Among the three catecholamines of pharmacological significance, dopamine (DA) (1) is sulfoconjugated to the highest degree and has the highest affinity toward phenolsulfotransferase (PST). The latter exists in human brain and converts DA to its *O*-sulfates; the ratio of DA-3-*O*- to DA-4-*O*-sulfate is about 4:1 (Renskers, Feor & Roth, 1980). A relatively high percentage of the DA-*O*-sulfates as compared to other catecholamine sulfoconjugates has been isolated from human urine. Because of the presence of DA-*O*-sulfates in brain and other vital peripheral organs (Elchisak & Carlson, 1982), these substrates have attracted considerable attention regarding the possible physiological role of the sulfate esters of catecholamines in general. Jenner & Rose (1973) were the first to demonstrate the *in vitro* conversion of DA to its 3- and 4-*O*-sulfates using preparations from rat liver and brain and, as part of this study, they described a one-step synthesis of the two DA-*O*-sulfates. For the past ten years this procedure has been employed for the preparation of DA-*O*-sulfates which have been used in pharmacological studies. We repeated the Jenner procedure and in addition to the two DA-*O*-sulfates we isolated four additional hitherto unknown products. These have been found to be nuclear sulfonic acid products resulting from alternate modes of sulfonation and will be reported elsewhere (Jain & Kaiser, 1984).



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In view of this finding, we were concerned about the authenticity of DA-*O*-sulfates described in the literature. This concern has recently been expressed by Ocosikowska, Idle, Swinbourne & Sever (1982). For this reason, the crystalline samples of DA-*O*-sulfates isolated in this study were rigorously characterized and compared with authentic samples obtained from Dr J. Stephen Kennedy of the NIMH (m.p., TLC, HPLC, 360 MHz ^{1}H, ^{13}C NMR and mass spectra; color reactions with Gibbs's and Pauly's reagents) prior to their pharmacological evaluations. In this context, we affirmed their structural authenticity by X-ray crystallography. In the process some striking differences in the conformations of the ethylamine side chain were observed.

Experimental. The dopamine-*O*-sulfate molecules were synthesized by the method of Jenner & Rose (1973). Separation of the reaction products was effected by ion-exchange chromatography. Crystals of dopamine-4-*O*-sulfate were grown by slow evaporation from aqueous acetone; the dopamine-3-*O*-sulfate crystals were grown from water. Both crystals were tabular with approximate dimensions 0·40 × 0·40 × 0·40 mm for the 4-*O*-sulfate and 0·20 × 0·20 × 0·15 mm for the 3-*O*-sulfate. Cell constants derived from a least-squares fit to the angular settings of 25 reflections with $30° \le 2\theta(\text{Mo}) \le 35°$ measured on an Enraf–Nonius CAD-4 diffractometer equipped with a graphite monochromator. Systematic absences $0k0$ for k odd, $h0l$ for $h + l$ odd for 4-*O*-sulfate, $0k0$ for k odd, $h0l$ for l odd for 3-*O*-sulfate indicate the space groups $P2_1/n$ and $P2_1/c$, respectively. Intensity data collected with Mo radiation in an ω–θ scan mode as suggested by peak-shape analysis; no systematic fluctuations in three standard reflections measured every 3 h of exposure time for either data set. Data corrected for Lorentz–polarization effects but not for absorption. For 4-*O*-sulfate: 5436 measured intensities, $2\theta < 56°$, $0 \le h \le 13$, $0 \le k \le 13$, $-26 \le l \le 26$, Friedel pairs averaged, agreement factors 0·032 on I, 0·023 on F_o, leaving 5151 independent data. For 3-*O*-sulfate: 2527 measured intensities, $2\theta \le 55°$, $-11 \le h \le 11$, $0 \le k \le 16$, $0 \le l \le 11$, Friedel pairs averaged, agreement factors 0·049 on I, 0·029 on F, leaving 2276 independent data. Both structures determined using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and difference Fourier syntheses. All least-squares refinements were full matrix on F, weights $4F_o^2/\sigma^2(I)$ with $\sigma(I) = [\sigma(I)^2 + (pF_o)^2]^{1/2}$ with $p = 0{\cdot}05$ for 4-*O*-sulfate, $p = 0{\cdot}04$ for 3-*O*-sulfate. Non-hydrogen atoms were refined with anisotropic librational parameters. H-atom positions were located from difference Fourier maps; all H positions and isotropic thermal parameters were refined. For 4-*O*-sulfate $wR = 0{\cdot}050$, $S = 1{\cdot}28$, 2799 observations with $I \ge 3\sigma(I)$, 359 variables, no evidence for extinction, $(\Delta/\sigma)_{\max} = 0{\cdot}09$; a final difference Fourier map contained no peak higher than 0·363 e Å^{-3}, top three peaks within 1 Å of S. For 3-*O*-sulfate $wR = 0{\cdot}052$, $S = 1{\cdot}34$, 1530 observations with $I \ge 3\sigma(I)$, 180 variables, no evidence for extinction, $(\Delta/\sigma)_{\max} = 0{\cdot}11$; a final difference Fourier map contained no peak higher than 0·469 e Å^{-3}, top three peaks within 1 Å of S. Values of the neutral-atom scattering factors and effects of anomalous dispersion from *International Tables for X-ray Crystallography* (1974). H-atom scattering factors from Stewart, Davidson & Simpson (1965). Programs in the CAD-4 *SDP* with local modifications.

Table 1. *Positional parameters, equivalent isotropic thermal parameters and their e.s.d.'s for dopamine-4-O-sulfate*

	x	y	z	B_{eq}*(Å^2)
S′	0·71858 (7)	0·02183 (6)	0·01224 (3)	2·04 (1)
S	0·71503 (6)	0·00565 (7)	0·50382 (3)	2·12 (1)
O(1′)	0·6509 (2)	0·1282 (2)	0·05812 (9)	2·39 (4)
O(1)	0·6851 (2)	0·1155 (2)	0·5583 (1)	2·95 (4)
O(2′)	0·6475 (2)	0·0478 (2)	−0·0531 (1)	3·18 (4)
O(2)	0·6178 (2)	0·0401 (2)	0·4477 (1)	2·96 (4)
O(3′)	0·8622 (2)	0·0497 (2)	0·0174 (1)	3·13 (4)
O(3)	0·8553 (2)	0·0206 (2)	0·4911 (1)	3·34 (4)
O(4′)	0·6913 (2)	−0·1013 (2)	0·0411 (1)	3·13 (4)
O(4)	0·6910 (2)	−0·1152 (2)	0·5356 (1)	2·74 (4)
O(5′)	0·5301 (2)	0·0018 (2)	0·16208 (9)	3·20 (4)
O(5)	0·5589 (2)	0·0125 (2)	0·6646 (1)	3·66 (5)
N′	1·0208 (2)	0·2045 (2)	0·4323 (1)	2·51 (5)
N	1·0136 (2)	0·1991 (2)	0·9324 (1)	2·54 (5)
C(1)	0·7575 (3)	0·1058 (3)	0·6234 (2)	2·89 (6)
C(1′)	0·7058 (3)	0·1392 (3)	0·1264 (1)	2·21 (5)
C(2)	0·8895 (3)	0·1502 (3)	0·6364 (2)	3·93 (7)
C(2′)	0·8156 (3)	0·2194 (3)	0·1439 (1)	2·83 (6)
C(3)	0·9555 (4)	0·1392 (4)	0·7013 (2)	4·09 (7)
C(3′)	0·8642 (3)	0·2339 (3)	0·2117 (2)	3·07 (6)
C(4′)	0·8028 (3)	0·1691 (3)	0·2617 (1)	2·48 (6)
C(4)	0·8911 (3)	0·0861 (3)	0·7533 (2)	3·28 (7)
C(5)	0·7577 (3)	0·0443 (3)	0·7397 (2)	3·37 (7)
C(5′)	0·6937 (3)	0·0894 (3)	0·2432 (1)	2·54 (6)
C(6)	0·6898 (3)	0·0541 (3)	0·6746 (2)	2·86 (6)
C(6′)	0·6418 (3)	0·0752 (3)	0·1758 (1)	2·23 (5)
C(7)	0·9630 (4)	0·0766 (3)	0·8251 (2)	3·81 (7)
C(7′)	0·8455 (3)	0·1906 (3)	0·3364 (1)	3·30 (7)
C(8)	0·9483 (4)	0·2002 (3)	0·8611 (2)	3·71 (7)
C(8′)	0·9953 (3)	0·1884 (3)	0·3570 (1)	2·86 (6)

* $B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}\mathbf{a}_i\cdot\mathbf{a}_j$.

Discussion. Descriptions of both structures follow.

Dopamine-4-O-sulfate. $^-SO_4$–$[C_6H_3(OH)](CH_2)_2$–NH_3^+. The 4-*O*-sulfate crystallizes with two independent molecules per asymmetric unit. Hereafter these molecules will be referred to as (I) and (I′). Positional parameters, along with their standard deviations as estimated from the inverse matrix, are listed in Table 1.* The structures of both (I) and (I′) are displayed together as Fig. 1. Principal bond lengths and angles are presented as Table 2.

* Lists of structure factors, H-atom positions, thermal parameters and tables of torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39736 (59 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Both (I) and (I′) crystallize as zwitterions with the ethylamine side chains protonated and the sulfate group ionized. Within the error of the measurements chemically equivalent bond lengths of the two independent molecules are identical. The equivalent length of bonds S–O(2)[1·438 (2) Å], S–O(3)[1·440 (2) Å] and S–O(4)[1·442 (2) Å] and their primed analogues establishes the ionic nature of this sulfate group. These bond lengths, though longer than would be expected for an S–O double bond and shorter than expected for a single bond, are quite similar to values reported for hexasodium benzenehexasulfonate (Chetkina & Sobolev, 1977). The S–O(1) and S–O(1′) single bonds, by comparison, are considerably longer at 1·623 (2) and 1·622 (2) Å, respectively.

The hydroxyl C–O distances of 1·357 (3) [C(6)–O(5)] and 1·349 (3) Å [C(6′)–O(5′)] are significantly shorter than their sulfonated counterparts of 1·414 (3) [C(1)–O(1)] and 1·410 (3) Å [C(1′)–O(1′)]. In addition, the hydroxyl C–O bond lengths are approximately 0·01–0·03 Å shorter than analogous bonds reported for the protonated phenolic hydroxyls of a number of catecholamines (Carlström, 1973; Carlström & Bergin, 1967; Giesecke, 1976, 1980; Hamor & Jones, 1982; Kolderup, Mostad & Rømming, 1972) but are quite similar in length to the deprotonated phenolic C–O bonds reported for (*R*)-epinephrine (Andersen, 1975*a*), (*R*)-norepinephrine (Andersen, 1975*b*), (–)-phenylephrine (Andersen, 1976) and tyramine hemihydrate (Andersen, 1977). Though longer than would be expected for a C–O$^-$ bond the length of the C(6)–O(5) and C(6)–O(5′) bonds, as compared to other phenolic bonds, suggests that these hydroxyl groups should be considered as partially ionized. This result undoubtedly reflects the strong intramolecular interactions in which the phenolic protons participate (see below).

Bond distances within the phenyl rings show a normal distribution for this molecular fragment with aromatic C–C bonds having an average length of 1·385 (4) and 1·386 (4) Å in (I) and (I′), respectively. Bond distances along the ethylamine side chains are also normal and compare favorably with distances reported for a number of catecholamines in which the amino terminus is protonated.

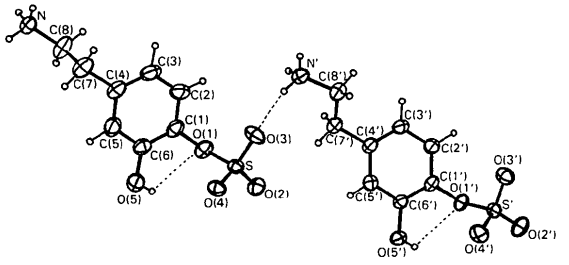

Fig. 1. *ORTEP*II (Johnson, 1976) drawing of the two crystallographically independent dopamine-4-*O*-sulfate molecules showing the numbering scheme employed. Non-hydrogen-atom ellipses are drawn at the 50% probability level; H atoms as small spheres of arbitrary size. Dashed lines indicate hydrogen bonds.

Table 2. *Principal bond distances* (Å) *and bond angles* (°) *for dopamine-4-O-sulfate*

S′–O(1′)	1·622 (2)	S–O(1)	1·623 (2)
S′–O(2′)	1·435 (2)	S–O(2)	1·438 (2)
S′–O(3′)	1·440 (2)	S–O(3)	1·440 (2)
S′–O(4′)	1·444 (2)	S–O(4)	1·442 (2)
O(1′)–C(1′)	1·410 (3)	O(1)–C(1)	1·414 (3)
O(5′)–C(6′)	1·349 (3)	O(5)–C(6)	1·357 (3)
N′–C(8′)	1·497 (4)	N–C(8)	1·491 (4)
C(1′)–C(2′)	1·386 (4)	C(1)–C(2)	1·383 (4)
C(1′)–C(6′)	1·388 (3)	C(1)–C(6)	1·379 (4)
C(2′)–C(3′)	1·387 (4)	C(2)–C(3)	1·386 (4)
C(3′)–C(4′)	1·389 (4)	C(3)–C(4)	1·379 (4)
C(4′)–C(5′)	1·381 (4)	C(4)–C(5)	1·387 (4)
C(4′)–C(7′)	1·513 (4)	C(4)–C(7)	1·527 (4)
C(5′)–C(6′)	1·388 (4)	C(5)–C(6)	1·395 (4)
C(7′)–C(8′)	1·492 (4)	C(7)–C(8)	1·490 (4)
O(1′)–S′–O(2′)	100·6 (1)	C(2)–C(3)–C(4)	121·2 (3)
O(1′)–S′–O(3′)	106·2 (1)	C(2′)–C(3′)–C(4′)	120·3 (3)
O(1′)–S′–O(4′)	106·6 (1)	C(3′)–C(4′)–C(5′)	119·3 (3)
O(2′)–S′–O(3′)	114·5 (1)	C(3′)–C(4′)–C(7′)	121·8 (3)
O(2′)–S′–O(4′)	115·6 (1)	C(5′)–C(4′)–C(7′)	118·8 (3)
O(3′)–S′–O(4′)	111·9 (1)	C(3)–C(4)–C(5)	118·8 (3)
O(1)–S–O(2)	100·6 (1)	C(3′)–C(4′)–C(7′)	121·0 (3)
O(1)–S–O(3)	106·4 (1)	C(5′)–C(4′)–C(7′)	120·2 (3)
O(1)–S–O(4)	106·3 (1)	C(4)–C(5)–C(6)	120·9 (3)
O(2)–S–O(3)	114·6 (1)	C(4′)–C(5′)–C(6′)	121·4 (3)
O(2)–S–O(4)	115·5 (1)	O(5)–C(6)–C(1)	122·8 (3)
O(3)–S–O(4)	112·0 (1)	O(5)–C(6)–C(5)	118·2 (3)
S′–O(1′)–C(1′)	117·0 (2)	C(1)–C(6)–C(5)	119·0 (3)
S–O(1)–C(1)	116·5 (2)	O(5′)–C(6′)–C(1′)	123·6 (2)
O(1)–C(1)–C(2)	121·7 (3)	O(5′)–C(6′)–C(5′)	118·0 (2)
O(1)–C(1)–C(6)	117·4 (3)	C(1′)–C(6′)–C(5′)	118·5 (2)
C(2)–C(1)–C(6)	120·9 (3)	C(4)–C(7)–C(8)	109·3 (3)
O(1′)–C(1′)–C(2′)	120·2 (2)	C(4′)–C(7′)–C(8′)	115·8 (3)
O(1′)–C(1′)–C(6′)	118·6 (2)	N–C(8)–C(7)	113·1 (3)
C(2′)–C(1′)–C(6′)	121·0 (2)	N′–C(8′)–C(7′)	109·4 (3)
C(1)–C(2)–C(3)	119·3 (3)		
C(1′)–C(2′)–C(3′)	119·5 (3)		

Bond angles within the two molecules are also quite normal when compared to other catecholamine structures with the exceptions of the C(4′)–C(7′)–C(8′) angle of 115·8 (3)° and the C(7)–C(8)–N angle of 113·1 (3)°. Both of these angles differ considerably from their counterparts [C(4)–C(7)–C(8) = 109·3 (3), C(7′)–C(8′)–N′ = 109·4 (3)°] and are significantly wider than a normal tetrahedral angle. Widening of the angle about C(7) probably reflects adjustments within the side chain to minimize unfavorable steric interactions which arise from adoption of the unusual side-chain conformation observed in this molecule (see below). Widening of the angle about C(8′) may result from the hydrogen-bonding interactions in which N′ participates.

The two aromatic rings are virtually planar with no atom deviating from the six-atom plane by more than 0·010 (3) Å in (I) or by more than 0·013 (3) Å in (I′). The nine atoms constituting the ring and its primary substituents in (I) are also virtually planar with no atom disposed more than 0·013 (3) Å out of the plane. In (I′), however, the best least-squares plane through the nine atoms is less rigorous, with deviations as large as 0·072 (3) Å at C(7′). All three primary substituents of the phenyl ring in (I′) sit on the same side of the plane

of the six-membered ring with C(7′) lying a full 0·116 (3) Å out of the plane. In (I), the ethylamine side-chain atoms and the phenyl C at the point of attachment [C(4)] are coplanar; in (I′) these same four atoms are not coplanar.

The conformation of the ethylamine side chain in (I), described by the torsion angles τ_1 [C(3)–C(4)–C(7)–C(8) = 83·8°] and τ_2 [C(4)–C(7)–C(8)–N = 178·9°], is fully extended and similar to conformations reported in the crystal structures of nearly all the salts of sympathomimetic amines. Furthermore, the conformation observed for (I) is in agreement with quantum-mechanical calculations on protonated epinephrine (Pullman, Coubelis, Courriere & Gervois, 1972). In contrast, the ethylamine side-chain conformation in (I′) is distinct from conformations observed in structures of related catecholamines. Thus, the torsion angle τ_1 [C(3′)–C(4′)–C(7′)–C(8′) = −47·4°] is nearly 45° away from values of ±90° which are normally observed. This represents the first structural documentation of such a *gauche* conformation about the C(7)–C(8) bond (Carlström, 1973). The torsion angle τ_2 [C(4′)–C(7′)–C(8′)–N′ = 177·2°] is typical of the normal *trans* disposition observed in other structures.

The crystal structure of dopamine-4-*O*-sulfate is stabilized by an extensive hydrogen-bonding network. All possible donors are involved in hydrogen bonds as are all possible acceptors with the exception of O(2′). There is intramolecular hydrogen bonding between the hydroxyl and sulfate groups in each independent molecule as illustrated in Fig. 1. A list of the metrical parameters for all proposed hydrogen bonds is presented in Table 5 and a drawing of the unit-cell contents is included as Fig. 2. The two independent molecules are linked through an intermolecular hydrogen bond involving N′–H(2N′)···O(3). This motif is repeated along a chain such that adjacent asymmetric units are linked by an interaction involving N–H(2N)···O(3′). Atom H(3N) appears to be involved in a bifurcated interaction. There are additional close intramolecular contacts between atoms O(5) and O(4) [3·267 (3) Å] and atoms O(4′) and O(5′) [3·193 (3) Å] which we consider outside a reasonable range to be categorized as hydrogen-bonding interactions through the hydroxyl H atoms.

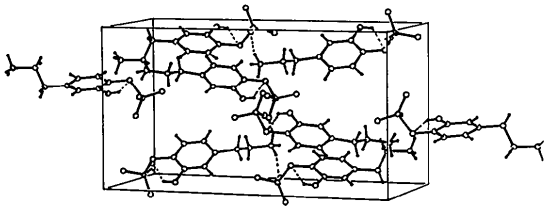

Fig. 2. Projection of the unit-cell contents for dopamine-4-*O*-sulfate. All atoms are drawn as spheres of arbitrary size. Dashed lines indicate proposed hydrogen bonds.

Dopamine-3-O-sulfate. The 3-*O*-sulfate crystallizes as a zwitterion as illustrated in Fig. 3. Atomic parameters are given in Table 3. Principal bond lengths are displayed on the figure while principal bond angles are listed in Table 4. Bond lengths for the 3-*O*-sulfate molecule are all comparable to values observed in the 4-*O*-sulfate structure. The S–O bond lengths are, within an estimated standard deviation, equivalent to values found in the 4-*O*-sulfate structure. Again, the ionic nature of the sulfate group is clearly demonstrated by equivalence of the three S–O bonds, S–O(2) [1·443 (2) Å], S–O(3)[1·438 (2) Å] and S–O(4)

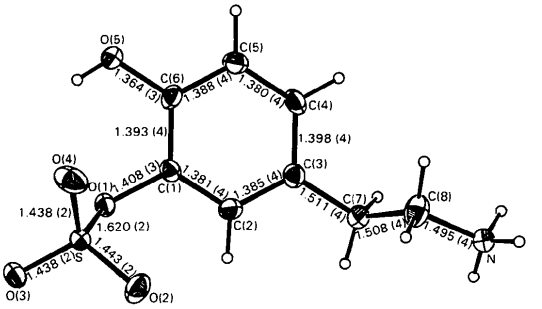

Fig. 3. *ORTEP*II drawing of the dopamine-3-*O*-sulfate molecule. Non-hydrogen atoms are displayed as principal ellipses at the 50% probability level; H atoms as small spheres of arbitrary size. Bond distances in Å; numbers in parentheses are e.s.d.'s.

Table 3. *Positional parameters, equivalent isotropic thermal parameters and their e.s.d.'s for dopamine-3-O-sulfate*

	x	*y*	*z*	B_{eq}*(Å²)
S	0·37727 (8)	0·06459 (6)	0·16430 (8)	1·35 (1)
O(1)	0·2796 (2)	−0·0282 (2)	0·0640 (2)	1·48 (4)
O(2)	0·2684 (3)	0·1133 (2)	0·2409 (2)	2·23 (4)
O(3)	0·4194 (2)	0·1304 (2)	0·0525 (2)	1·94 (4)
O(4)	0·5085 (3)	0·0150 (2)	0·2632 (3)	2·58 (5)
O(5)	0·4300 (2)	−0·2192 (2)	0·1473 (3)	2·09 (4)
N	−0·3402 (3)	−0·1456 (2)	0·4523 (3)	1·69 (5)
C(1)	0·2103 (3)	−0·1029 (2)	0·1423 (3)	1·38 (5)
C(2)	0·0649 (3)	−0·0837 (2)	0·1733 (3)	1·55 (6)
C(3)	−0·0065 (3)	−0·1583 (2)	0·2454 (3)	1·57 (5)
C(4)	0·0727 (3)	−0·2531 (2)	0·2842 (3)	1·85 (6)
C(5)	0·2173 (4)	−0·2732 (2)	0·2520 (4)	1·98 (6)
C(6)	0·2877 (3)	−0·1980 (2)	0·1794 (3)	1·55 (5)
C(7)	−0·1693 (3)	−0·1396 (2)	0·2722 (3)	1·73 (6)
C(8)	−0·1736 (4)	−0·1423 (3)	0·4348 (3)	2·19 (6)

* $B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

Table 4. *Principal bond angles (°) for dopamine-3-O-sulfate*

O(1)–S–O(2)	106·0 (1)	C(2)–C(3)–C(4)	117·8 (2)
O(1)–S–O(3)	101·7 (1)	C(2)–C(3)–C(7)	120·6 (2)
O(1)–S–O(4)	106·3 (1)	C(4)–C(3)–C(7)	121·5 (2)
O(2)–S–O(3)	113·6 (1)	C(3)–C(4)–C(5)	121·8 (3)
O(2)–S–O(4)	113·3 (1)	C(4)–C(5)–C(6)	119·8 (3)
O(3)–S–O(4)	114·6 (1)	O(5)–C(6)–C(1)	122·1 (2)
S–O(1)–C(1)	115·6 (2)	O(5)–C(6)–C(5)	119·3 (3)
O(1)–C(1)–C(2)	120·3 (2)	C(1)–C(6)–C(5)	118·6 (2)
O(1)–C(1)–C(6)	118·4 (2)	C(3)–C(7)–C(8)	113·1 (2)
C(2)–C(1)–C(6)	121·2 (2)	N–C(8)–C(7)	110·4 (2)
C(1)–C(2)–C(3)	120·6 (2)		

[1·438 (2) Å]. The hydroxyl C—O bond length C(6)—O(5)[1·364 (3) Å] is significantly shorter than its sulfonated counterpart C(1)—O(1)[1·408 (3) Å]. This same comparison is true in the 4-*O*-sulfate structure; however, the C(6)—O(5) length in the 3-*O*-sulfate structure is slightly longer than its two 4-*O*-sulfate counterparts. This lengthening may be attributable to the increased hydrogen-bond participation of the proton attached at O(5) in the 3-*O*-sulfate (see below).

The phenyl-ring bond distances show a normal average length of 1·387 (4) Å with intraring angles between 117·8 and 121·8°. The ethylamine side-chain bond distances are similar to those reported for other catecholamines where the amino terminus is protonated. The aromatic ring is planar with no atom deviating by more than 0·008 (3) Å from the best least-squares plane through the six atoms. All three primary substituents sit out of the plane of the ring on the same side with C(7) lying 0·088 (3) Å out of the plane. The ethylamine side chain of the 3-*O*-sulfate is not planar.

As we observed for the C(4′)—C(7′)—C(8′) bond angle in the 4-*O*-sulfate structure, the C(3)—C(7)—C(8) angle of 113·1 (2)° in dopamine 3-*O*-sulfate is considerably wider than a normal tetrahedral angle. Once again a wider angle about C(7) correlates with adoption of an unusual conformation for the ethylamine side chain. Thus, the torsion angle τ_1[C(4)—C(3)—C(7)—C(8)] of 62·9° is distinct from values of ±90° normally observed in crystal structures of sympathomimetic amines and distinct as well from the unique value of −47·4° for τ_1 observed for (I′) in dopamine-4-*O*-sulfate. The τ_2 torsion angle [C(3)—C(7)—C(8)—N] of −168·3° in dopamine-3-*O*-sulfate is typical of the normal *trans* disposition observed in other structures.

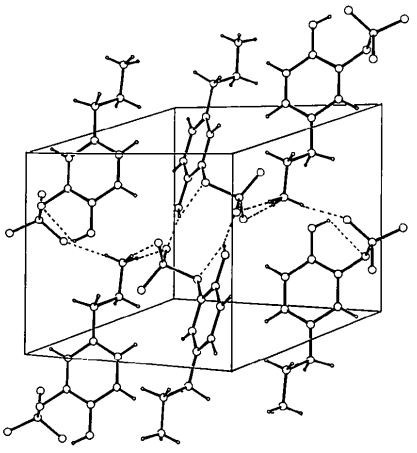

Fig. 4. Projection of the unit-cell contents for dopamine-3-*O*-sulfate. All atoms are drawn as spheres of arbitrary size. Dashed lines indicate proposed hydrogen bonds.

Table 5. *Proposed hydrogen-bonding interactions*

		Distances (Å)	Angle (°)
Dopamine-4-*O*-sulfate			
O(5)–H(O5)···O(1)	O(5)···O(1)	2·769 (3)	112 (3)
	H(O5)···O(1)	2·41 (4)	
O(5′)–H(O5′)···O(1′)	O(5′)···O(1′)	2·811 (3)	111 (3)
	H(O5′)···O(1′)	2·45 (4)	
N–H(1N)···O(4′)	N···O(4′)	3·081 (3)	171 (3)
	H(1N)···O(4′)	2·21 (4)	
N–H(2N)···O(3′)	N···O(3′)	2·830 (3)	176 (5)
	H(2N)···O(3′)	1·99 (5)	
N–H(3N)···O(2)	N···O(2)	2·919 (3)	135 (4)
	H(3N)···O(2)	2·19 (5)	
N–H(3N)···O(4)	N···O(4)	2·916 (3)	127 (4)
	H(3N)···O(4)	2·26 (5)	
N′–H(1N′)···O(4)	N′···O(4)	3·000 (3)	156 (3)
	H(1N′)···O(4)	2·17 (3)	
N′–H(2N′)···O(3)	N′···O(3)	2·845 (3)	167 (4)
	H(2N′)···O(3)	1·99 (4)	
N′–H(3N′)···O(4′)	N′···O(4′)	2·999 (3)	152 (3)
	H(3N′)···O(4′)	2·11 (4)	
Dopamine-3-*O*-sulfate			
O(5)–H(1O5)···O(1)	O(5)···O(1)	2·789 (3)	110 (3)
	H(1O5)···O(1)	2·42 (4)	
O(5)–H(1O5)···O(3)	O(5)···O(3)	2·734 (3)	153 (4)
	H(1O5)···O(3)	2·01 (4)	
N(1)–H(1N1)···O(3)	N(1)···O(3)	2·936 (3)	159 (3)
	H(1N1)···O(3)	2·09 (4)	
N(1)–H(2N1)···O(2)	N(1)···O(2)	2·786 (3)	165 (3)
	H(2N1)···O(2)	1·83 (4)	
N(1)–H(3N1)···O(4)	N(1)···O(4)	2·817 (3)	174 (4)
	H(3N1)···O(4)	2·01 (5)	

Extensive hydrogen bonding stabilizes the dopamine-3-*O*-sulfate crystal structure. Fig. 4 shows a unit-cell diagram which illustrates the proposed interactions. Metrical parameters for the hydrogen bonds are listed in Table 5. All three amino H atoms are donors in intermolecular hydrogen bonds to sulfate O acceptors. As in the 4-*O*-sulfate structure there appears to be an intramolecular hydrogen bond between the hydroxyl and sulfate groups with O(5) acting as a donor to sulfate oxygen O(1). In the 3-*O*-sulfate structure, however, the hydroxyl H also appears to participate in an intermolecular interaction involving O(3) of a symmetry-related molecule. The participation of O(5) as a donor in two hydrogen bonds would lead to less residual electron density localized in the C(6)—O(5) bond and hence a slightly longer bond length than was observed in the 4-*O*-sulfate molecules. Indeed, as was cited above, that is the observation for the 3-*O*-sulfate.

Structural discussion

The crystal and molecular structures of the isomeric DA-3- and DA-4-*O*-sulfates are remarkably similar in several aspects. Both molecules crystallize as zwitterions formally with the sulfate group ionized and the amino group protonated. Both molecules also display intramolecular hydrogen-bond formation between the unsubstituted hydroxyl and the sulfate O attached to the phenyl ring. In addition, in both structures unusual synclinal dispositions for the ethylamine side-chain τ_1 torsion angle are observed.

The three independent DA-*O*-sulfate molecules display three different conformations for the ethylamine

side chain. All three molecules display the normally observed antiperiplanar disposition for the amino group with τ_2 values near 180°. Komiskey, Bossart, Miller & Patel (1978) have demonstrated, using conformationally restricted dopamine analogues, that the *trans* form of DA has greater affinity for its receptor site; thus to the extent that the conformation described by τ_2 of the ethylamine side chain dictates binding affinity there appears to be no restriction to receptor binding imposed by sulfoconjugation of dopamine. Two unusual torsion angles (τ_1) about the exocyclic bond connecting the side chain to the catechol ring in DA-*O*-sulfates are observed. The τ_1 values of 62·9° for the 3-*O*-sulfate structure and −47·4° for one of the 4-*O*-sulfate molecules are both unique when compared to analogous angles reported for other catecholamine and related structures. While τ_1 values near 70° have been reported for 2,4,5-trimethoxyamphetamine (Baker, Chothia, Pauling & Weber, 1973), phenethylamine hydrochloride (Tsoucaris, 1961), tyramine hydrochloride (Tamura, Wakahara, Fujiwara & Tomita, 1974) and 4-ethyl-2,5-dimethoxyamphetamine (Kennard, Giacovazzo, Horn, Mongiorgi & Riva di Sanseverino, 1974) in fully 75% of related structures reported to date τ_1 values are within 10° of 90°. A most unusual value for τ_1 of −3·2° describing an eclipsed conformation has been reported for the (−)-epinephrine hydrogen tartrate structure (Carlström, 1973). The adoption of such a wide range of τ_1 values in crystal structures of catecholamines and related molecules undoubtedly is influenced by the varying hydrogen-bonding interactions in which the ethylamine side chain participates. This same range of conformer populations, however, may be regarded as mirroring the situation in solution and may emphasize the free mobility of this moiety. Conversely, the observation of two synclinal conformations about the exocyclic bonds in DA-*O*-sulfates, though insufficient to establish a preference for such a disposition of the ethylamine side chains of sulfoconjugated DA analogues, suggests that further structural studies of sulfoconjugated molecules might be of value in understanding the activity of such metabolities (Ackerman, Hieble, Sarau & Jain, 1984) if a clearly defined preference for the synclinal conformation is established.

The zwitterionic character of the DA-*O*-sulfates is also of potential importance. The crystal structures clearly establish the formal ionization of the sulfate groups and protonation of the amino termini. A comparison of the phenyl-ring C—O(hydroxyl) bond distances in the DA-*O*-sulfates to distances reported in related structures suggests that the hydroxyl group may be considered to be partially ionized as well. This situation arises as a result of intramolecular hydrogen-bond formation between the hydroxyl group and the sulfated catechol O in both molecules. Thus, the ionization state of the hydroxyl group in DA-*O*-sulfates may differ significantly from that in other DA analogues in a given biological microenvironment.

A final interesting observation on the DA-*O*-sulfate crystal structures is the extensive network of hydrogen bonding observed particularly as regards the sulfate group. The hydrogen-bonding and complex-formation characteristics of the catechol moiety have been the subject of much discussion (Pretongolo, Tomasi, Macchia & Macchia, 1974; Belleau, 1966; Pratesi & Grana, 1965). It is clear that the sulfoconjugation of DA imparts to these molecules the ability to engage in more extensive and varied hydrogen-bonding interactions than is the case for DA or its many simpler analogues found in nature.

We are indebted to Dr J. Stephen Kennedy of the NIMH for supplying authentic samples of 3-*O*- and 4-*O*-sulfates which were helpful in the identification of the mixture components resulting from the sulfonation of DA.

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Picric Acid–Naphthalene 1/1 π Complex, $C_6H_3N_3O_7.C_{10}H_8$. A Disordered Structure

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Abstract. $M_r = 357{\cdot}28$, monoclinic, $P2_1/a$, $a = 16{\cdot}248\ (5)$, $b = 6{\cdot}871\ (2)$, $c = 14{\cdot}306\ (5)$ Å, $\beta = 96{\cdot}62\ (5)°$, $V = 1586{\cdot}47$ Å^3, $Z = 4$, $D_m = 1{\cdot}47\ (1)$, $D_x = 1{\cdot}496$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 1{\cdot}16$ mm^{-1}, $F(000) = 736$, $T = 293$ K, $R = 0{\cdot}066$ for 918 observed reflexions ($I > 3\sigma_I$). Molecules lie in (010) parallel to each other, stacking alternately picric acid and naphthalene with hydrogen bonds linking picric acid molecules across alternative symmetry centres and also along **a**. The two arrangements are present in ratio ≈4:1, and it was not feasible to separate the two sets of atomic coordinates.

Introduction. Unit-cell dimensions have been reported (Herbstein & Kaftory, 1975) as have the crystal structure determinations of a number of homologues (Carstensen-Oeser, Göttlicher & Habermehl, 1968; Herbstein & Kaftory, 1976). Physical properties have been reported by Mindovich (1956) and by Westwood (1978). In none of these reports was there any indication of structural disorder, and this work was undertaken at the instigation of Dr Westwood in order to explain some peculiarities observed.

Experimental. Sample prepared by Dr C. V. Westwood of the Chemistry Department, City of London Polytechnic; recrystallized (*ca* $1{\cdot}5 \times 0{\cdot}2 \times 0{\cdot}2$ mm) from ethanol; m.p. 401 K. D_m by flotation in NaI solution. Lattice parameters from rotation and Weissenberg photographs, refined by least-squares fit to 16 selected reflexions measured on a Stoe Stadi-2 diffractometer; intensities from $h0l \rightarrow h6l$ levels on the diffractometer using ω scans, interlayer scaling and $0k0$ intensities from *c* Weissenberg. 1559 measured reflexions, 918 observed with $I > 3\sigma_I$; index range h 0 to 16, k 0 to 6, l −15 to +17; $2\theta_{max} = 110°$. Seven standard reflexions, no variation. Corrections for Lp and an empirical correction for extinction to eight reflexions during refinement. No absorption correction. Structure solved by trial-and-error as direct methods failed. Patterson map indicated layer structure with $b/4$ separation. Refinement by least squares on F using initially B_{iso} and finally B_{ij}. H atoms included at calculated positions with $B_{iso} = 8{\cdot}0$ Å^2, but not refined. Difference Fourier during refinement showed two alternative sites for the O of the picric acid OH; site occupation refinement converged to 0·80 for O(1) position and 0·20 for O(8) and these values used in further SFLS refinement until final shifts all $<0{\cdot}3\sigma$. Final $R = 0{\cdot}066$, $R_w = 0{\cdot}136$, $\sqrt{w} = 1/F_o$. Max. electron density in final difference Fourier map $\pm 0{\cdot}2$ e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1962). *NRC* programs (Ahmed, Hall, Pippy & Huber, 1970) implemented on our DEC-10 computer.

Discussion. The final atomic coordinates and equivalent isotropic temperature parameters are listed in Table 1.* Bond lengths and interbond angles are in Table 2. The arrangements of the molecules in the unit cell, together with the atom numbering and hydrogen bonds are shown in Fig. 1.

Molecules of both picric acid and naphthalene lie approximately parallel to (010) in layers with $y = \frac{1}{8}, \frac{3}{8}, \frac{5}{8}$ and $\frac{7}{8}$ and π-bonding interactions across the 3·4 Å ($b/2$) spacing; the overlap diagram is shown in Fig. 2 as a normal projection along **b**. C(14) of the naphthalene ring lies almost exactly above the mid-point of the picric acid ring.

* Lists of structure factors, anisotropic thermal parameters and calculated H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39515 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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