is issue

Constrained Rietveld refinement of $[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide using powder neutron diffraction data

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The room-temperature crystal structure of $[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide has been refined using pulsed neutron diffraction data collected from a powder sample. A Rietveld refinement involving 93 structural parameters converged to give a χ^2 of 1.99 for the fit, with 5366 observations and 111 basic variables. The agreement factors $R_{wp} = 2.47\%$, $R_p = 2.74\%$, $R_1 = 5.70\%$ and $R_E = 1.75\%$ indicate an excellent fit to the data. Slack chemical constraints were used in the refinement to impose prior chemical sense on the final structure. The dopamine cation is extensively hydrogen bonded to bromide ions, and the hydrogenbond geometries are well defined.

Dopamine is a neurotransmitter with both peripheral and central actions, and disorders of dopaminergic function are implicated in a number of neurological and psychiatric disorders, including Parkinson's disease and schizophrenia. As such, dopamine-receptor interactions are of considerable interest in the design and development of new drugs.

Although the primary sequences for both the dopamine D_1 and D₂ receptors are known, the corresponding highresolution structures are not, and so information about the nature of binding sites has been deduced from molecular modelling studies and ligand structure-activity relationships. It has been suggested that key elements in the structure-activity relationship include a cation- π interaction¹ and hydrogen bonding between the receptor and the meta-OH group on the dopamine cation.² The three-dimensional structure of the cation has been determined by an X-ray crystallographic study,³ but X-rays are of limited value in pinpointing hydrogen atom positions. In contrast, neutron diffraction can locate hydrogen atoms with much greater accuracy, and the substitution of deuterium for hydrogen improves the accuracy still further, by virtue of a greatly reduced incoherent scattering contribution, and the large positive scattering length of deuterium.

We report here the crystal structure of $[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide, refined from powder neutron diffraction data.

Experimental

Synthesis⁴

A solution containing 3,4-dimethoxybenzaldehyde (I, 25.9 g) and perdeuteriated nitromethane (10 g) in deuteriated methanol (CH₃OD, 40 ml) was cooled to -10 °C. Potassium hydroxide (9.2 g) in CH₃OD (10 ml) was added in small portions with vigorous stirring, and the solution held at 0 °C for 30 min. The reaction mixture was poured into ice-cold dilute hydrochloric acid (1000 ml) to give 3,4-dimethoxy- β -nitro[β -²H₁]styrene (II, yield: 54.9%, mp: 135 °C). The Soxhlet extraction technique was used to add 5.7 g of compound II to a solution of LiAl[²H]₄ (5 g) in dry ether (300–400 ml). The reaction was complete in ca. 6 h, at which point the mixture was cooled and the excess hydride decomposed by cautious addition of water (20-50 ml). The ether layer was separated and the aqueous layer was extracted with ether (4 \times 50 ml). The combined ether extracts were dried with anhydrous sodium sulfate, and 2-(3,4-dimethoxyphenyl[1,1,2-²H₃]ethylamine hydrochloride (III) precipitated by passing dry HCl gas into the ethereal solution (yield: 37%, mp: 220-224 °C cf. 241 °C for the non-deuteriated hydrochloride salt). Simultaneous cleavage of the methoxy groups and exchange of the aromatic protons for deuterium was achieved by refluxing III (1.0 g) in 48% $\lceil^2 H \rceil Br$ (25 g) under an atmosphere of nitrogen for 2 h. The solvent was removed by evaporation under reduced pressure, and the residue recrystallised from CH₃OD-ether to give colourless needles of $[\beta^{-2}H_1]$ decadeuteriodopamine deuteriobromide (IV, yield: 73.2%, mp: 208 °C cf. 210-214 °C for the non-deuteriated hydrobromide salt).



Data collection

Approximately 1 g of $[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide was lightly packed in an 11 mm diameter cylindrical vanadium can. Neutron diffraction data were collected on HRPD,⁵ the high resolution neutron powder diffractometer at the ISIS spallation neutron source, Rutherford Appleton Laboratory (Table 1). The data set was focused to a Bragg angle of 168.329°, normalised to the incident monitor spectrum and corrected for detector efficiency using a splinesmoothed diffraction pattern collected from a vanadium rod. After reduction, data in the range 42 000–210 000 µs (0.9–4.4 Å) were binned in time channels of $\Delta t/t = 3 \times 10^{-4}$.

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instrumental diffractometer flight path temperature detector sample position data range time channel binning experiment duration	HRPD, neutron time-of-flight powder diffractometer 95.9647 m 293 K ⁶ Li glass, 168.329° 2 θ 1 m 30 000-230 000 μ s time-of-flight (0.6-4.8 Å <i>d</i> -spacing) $\Delta t/t = 1 \times 10^{-4}$ <i>ca.</i> 11 h
sample	
compound	$[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide
formula	$C_8[^2H]_{10}HO_2N\cdot[^2H]Br$
	245.2
recrystallising solvent	CH ₃ OD-ether
refinement	
space group	orthorhombic, $Pbc2_1$
Ż	4
unit cell refinement	whole pattern
unit cell (Å)	a = 10.66714(4), b = 11.47801(5), c = 7.94104(2)
$Dx (g \text{ cm}^{-3})$	1.675
observations	5366
refined parameters	
structural	93
profile	15
cell	3
constraints	
strict (equal ITF ^a)	D9 = D91 = D92 = H9 = H91 = H92, D1 = D2 = D5,
	D7 = D71 = H7 = H71, $D8 = D81$, $D21 = H21$, $D22 = H22$
strict (equal SOF ^b)	D7 = D71, D9 = D91 = D92
strict ($\Sigma SOF = 1$)	D7 + H7, D71 + H71, D9 + H9, D91 + H91, D92 + H92, D21 + H21, D22 + H22
slock (distance/Å)	D21 + H21, D22 + H22 aromatic $C = C = 1.205(5), C = C = 1.50(1), C = N = 1.50(1)$
slack (distance/A)	C = 0 - 1.370(5) $C = 0 - 1.085(5)$ $N = D - 1.03(1)$
	C = 0 = 1.576(5), C = D = 1.005(5), W = D = 1.05(1), O = D = 0.97(1)
slack (angle/°)	aromatic carbons = $120(1)$, all others = $109(1)$
thermal narameters	all atoms isotropic
agreement factors ^c	
unconstrained	$r^2 = 1.85$, $R = 2.36\%$, $R = 2.65\%$, $R_2 = 4.65\%$, $R_2 = 1.75\%$
constrained	$\chi^2 = 1.99, R_{\rm mp} = 2.47\%, R_{\rm p} = 2.74\%, R_{\rm I} = 5.70\%, R_{\rm p} = 1.75\%$

Table 1 Data collection and refinement parameters for $[\beta^{-1}H_1]$ decade uteriodopamine deuteriobromide

^a Isotropic temperature factor; ^b site occupancy factor; ^c defined in ref. 10.

Structure refinement

Refinement of the isomorphous X-ray structure of dopamine hydrochloride³ against the diffraction data was achieved by the Rietveld method,⁶ as implemented in the time-of-flight least-squares program TF12LS.⁷ The peak shape used in the refinement was a convolution of a Voigt function with a wavelength-dependent sum of two decaying exponential functions. Strict and slack constraints were used to modify the refinement process.^{8,9} Strict constraints reduce the number of independent variables in the least-squares fit by forcing certain variables to be related. For example, the isotropic temperature factors of the three deuterium atoms on the benzene ring are



Fig. 1 ORTEP plot of the refined dopamine cation, with isotropic thermal ellipsoids at 20% probability. The refined occupancies for the deuterium atoms on the C7, N and O atoms are given in Table 2.

expected to be very similar, and so can be efficiently represented by a single variable, rather than three independent variables. Slack constraints incorporate prior chemical knowledge in an additional function minimisation. The function minimised in a normal Rietveld refinement is:

$$S_y = \sum_i w_i (y_{oi} - y_{ci})^2$$

where y_{oi} and y_{ci} are the observed and calculated intensities at the point *i* in the diffraction pattern, and $w_i = 1/\sigma^2$, where σ is the standard deviation of the observed intensity at that point. The function minimised for *j* slack constraints is:

$$S_{\rm R} = \sum_j w_j [R_{oj} - R_{cj}(x)]^2$$

where R_{oj} is the supplied ('observed') distance or angle, $R_{cj}(x)$ is the corresponding value calculated from the atomic positions, and w_j is the inverse of the variance of the supplied value. The two functions are then combined using:

$$S_{yR} = S_y + (c_w S_R)$$

where c_w is a weight factor used to vary the influence of the slack constraints on the refinement.

The strict and slack constraints used in the refinement are summarised in Table 1, along with other relevant refinement parameters.

Results

The fractional atomic coordinates, isotropic temperature factors and site occupancies for the refined structure are given

Table 2 Fractional coordinates, isotropic temperature factors and site occupancies for $[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide (esds in parentheses)

atom	x	у	Z	$B_{\rm iso}/{\rm \AA}^2$	SOF
Br	0.0069(6)	0.3251(6)	0.2500ª	3.8(2)	
C1	0.5221(5)	0.2140(5)	0.2128(12)	3.4(2)	
C2	0.6445(5)	0.2056(5)	0.2719(13)	4.0(2)	
C3	0.7177(5)	0.1085(5)	0.2325(13)	2.6(2)	
C4	0.6679(5)	0.0222(5)	0.1297(11)	2.0(1)	
C5	0.5468(5)	0.0321(4)	0.0676(11)	2.2(2)	
C6	0.4725(5)	0.1281(4)	0.1074(11)	2.3(1)	
C7	0.3382(5)	0.1335(5)	0.0496(11)	3.6(2)	
C8	0.2556(6)	0.0532(6)	0.1518(13)	5.4(2)	
N1	0.1204(4)	0.0654(4)	0.1011(12)	3.3(1)	
01	0.8366(6)	0.0898(6)	0.2910(14)	3.4(2)	
O2	0.7357(6)	-0.0706(6)	0.0777(13)	2.8(2)	
D1	0.4676(7)	0.2882(6)	0.2520(14)	5.9(1)	
D2	0.6804(7)	0.2704(6)	0.3596(13)	5.9(1)	
D5	0.5132(6)	-0.0337(6)	-0.0164(13)	5.9(1)	
D7	0.3054(14)	0.2220(9)	0.0536(24)	5.8(5)	0.559(4)
H7	0.3054(14)	0.2220(9)	0.0536(24)	5.8(5)	0.441(4)
D71	0.3449(16)	0.1061(15)	-0.0797(16)	5.8(5)	0.559(4)
H71	0.3449(16)	0.1061(15)	-0.0797(16)	5.8(5)	0.441(4)
D8	0.2641(8)	0.0698(8)	0.2851(14)	7.6(2)	
D81	0.2808(7)	-0.0358(7)	0.1374(14)	7.6(2)	
D9	0.1061(8)	0.0576(8)	-0.0232(15)	5.5(2)	0.918(3)
H9	0.1061(8)	0.0576(8)	-0.0232(15)	5.5(2)	0.082(3)
D91	0.0674(7)	0.0005(8)	0.1596(14)	5.5(2)	0.918(3)
H91	0.0674(7)	0.0005(8)	0.1596(14)	5.5(2)	0.082(3)
D92	0.0893(8)	0.1381(8)	0.1380(15)	5.5(2)	0.918(3)
H92	0.0893(8)	0.1381(8)	0.1380(15)	5.5(2)	0.082(3)
D21	0.8771(9)	0.1608(8)	0.3178(16)	7.5(3)	0.929(7)
H21	0.8771(9)	0.1608(8)	0.3178(16)	7.5(3)	0.071(7)
D22	0.8100(9)	-0.0714(10)	0.1402(14)	6.1(3)	0.878(5)
H22	0.8100(9)	-0.0714(10)	0.1402(14)	6.1(3)	0.122(5)

" Fixed because of polar axis.



Fig. 2 Final observed (points) and calculated (line) profiles for $[\beta^{-1}H_1]$ decadeuteriodopamine deuteriobromide at room temperature. The difference $[(y_{obs} - y_{calc})/\sigma(y_{obs})]$ plot is also shown. The tick marks show the calculated reflection positions for the refined unit cell.

in Table 2, and Fig. 1 shows an ORTEP¹¹ plot of the molecule. The final observed, calculated and difference $[(y_{obs} - y_{calc})/\sigma(y_{obs})]$ profiles are shown in Fig. 2.

Discussion

For heavy atoms, the difference between atomic positions observed with neutrons and X-rays is largely insignificant, and thus there is good agreement between the lengths and angles listed in Table 3 for bonds that involve only C, N and O atoms. However, as expected, the mean C-D bond length observed with neutrons (1.075 Å) is a significant improvement on the X-ray mean of 0.94 Å, and the precision is approximately five times better. The O2-D22...O1 intramolecular hydrogen bond [distance = 2.222(14) Å, angle = $113(1)^{\circ}$] forms a five-membered ring with C3 and C4 which is essentially coplanar with the aromatic ring (Table 4 and Fig. 1). The trans configuration of the side chain [torsion angle $C6-C7-C8-N1 = 176.1(6)^{\circ}$ is a commonly observed feature in the crystal structures of phenylethylamine compounds. The biological significance of this and other structural features has been examined elsewhere.¹² The refined site occupancies for the C7 deuterium atoms (56%, Table 2) are close to the value of 50% expected from the synthetic pathway. Table 2 also shows that no more than ca. 10% of the deuterium atoms attached to N and O atoms were exchanged for hydrogen. The site occupancies of all other deuterium atoms refined to a value so close to unity that they were fixed at this value for the final cycles of refinement.

The deuterium atoms attached to the N and O atoms make five short contacts (2.3-2.5 Å) to symmetry-related bromide ions (Fig. 3 and Table 5). Small spherical anions, which are relatively free from steric constraints, will readily occupy sites

Table 5 Covalent bond lengths (A) and angles () for the neutron remement (esds in parentneses), with X-ray value	ues ^o for compariso
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	neutron	X-ray		neutron	X-ray
Cl-C2	1.391(9)	1.386(4)	C1-D1	1.077(10)	1.08(5)
C2-C3	1.396(8)	1.384(4)	C2-D2	1.089(12)	0.85(5)
C3-C4	1.389(10)	1.396(3)	C5-D5	1.069(11)	0.88(6)
C4-C5	1.387(8)	1.381(4)	C7-D7	1.074(12)	0.86(6)
C5-C6	1.394(7)	1.385(4)	C7—D71	1.077(15)	1.04(5)
Cl-C6	1.397(10)	1.392(4)	C8-D8	1.079(15)	0.87(7)
C6-C7	1.506(8)	1.511(4)	C8-D81	1.063(11)	1.03(6)
С7—С8	1.511(10)	1.497(5)	N1-D9	1.003(15)	0.93(6)
C8-N1	1.504(8)	1.479(4)	N1-D91	1.045(11)	0.93(6)
C3-01	1.367(9)	1.366(3)	N1-D92	0.944(11)	0.89(5)
C4-02	1.352(9)	1.364(3)	01-D21	0.947(12)	0.84(5)
			02—D22	0.935(13)	0.90(7)
C1-C2-C3	120.3(7)	119.8(3)	C1-C2-D2	119.9(7)	120(3)
C2-C3-C4	119.1(6)	119.5(2)	C3-C2-D2	119.5(7)	121(3)
C2-C3-01	124.6(7)	123.5(2)	C4-C5-D5	118.4(6)	125(3)
C4-C3-01	116.3(6)	116.9(2)	C6-C5-D5	120.6(7)	115(3)
C3-C4-C5	120.5(5)	120.3(2)	C6-C1-D1	121.8(7)	121(3)
C3-C4-02	122.4(6)	121.6(2)	C2-C1-D1	117.6(8)	118(3)
C5-C4-02	117.0(7)	118.0(3)	C3-01-D21	111.4(9)	117(3)
C4-C5-C6	120.9(6)	120.4(3)	C4-02-D22	107.5(10)	108(4)
C5-C6-Cl	118.6(5)	119.1(2)	C6-C7-D7	109.8(10)	116(3)
C5-C6-C7	120.3(6)	120.4(3)	C6-C7-D71	102.4(11)	106(2)
C1-C6-C7	120.9(5)	120.5(2)	C8-C7-D7	111.8(10)	102(4)
C6-C1-C2	120.6(6)	120.8(3)	C8-C7-D71	111.9(11)	107(3)
C6-C7-C8	111.4(6)	111.0(3)	D7-C7-D71	109.1(15)	114(5)
C7-C8-Nl	111.0(7)	111.4(3)	C7-C8-D8	111.7(8)	107(3)
			C7-C8-D81	112.4(8)	116(3)
			D8-C8-D81	104.7(11)	96(4)
			D8-C8-N1	109.1(8)	108(3)
			D81-C8-N1	107.6(7)	116(3)
			C8-N1-D9	113.6(8)	115(3)
			C8-N1-D91	109.5(8)	101(3)
			C8-N1-D92	109.6(8)	116(3)
			C9-N1-D91	107.0(9)	122(5)
			D9-N1-D92	109.3(11)	89(5)
			D91-N1-D92	107.6(10)	114(5)

of favourable electrostatic interaction in a crystal lattice. In this case, the $O-D\cdots Br^-$ and $N-D\cdots Br^-$ interactions are favoured by the reduced electron density around the deuterium atoms, which occurs as a consequence of being bonded to the more electronegative O and N atoms. The formal positive charge on the cation also favours $N-D\cdots Br^-$ inter-

Table 4 Displacement of atoms (Å) from the least-squares plane through atoms C1 to C6 $\,$

atom		atom	
C1	0.015(8)	D1	0.056(10)
C2	-0.010(9)	D2	0.062(9)
C3	0.005(9)	D5	-0.052(9)
C4	0.007(8)	O 1	0.047(10)
C5	-0.001(8)	O2	-0.063(9)
C6	-0.004(8)	D21	-0.322(12)
C7	0.089(8)	D22	0.069(11)



Fig. 3 Alternative view of the dopamine cation, showing the interactions with five symmetry-related bromide ions. The covalent bonds are thicker than those in Fig. 1 in order to distinguish the cation from the non-covalent bromide ion contacts, which are indicated by the hollow bonds numbered 1 to 5.

Table 5	Distances (D···Br ⁻) and angles $(N - D \cdots Br)$	and $O - D \cdot \cdot Br$) for the numbered	contacts shown in Fig. 3

bond	deuterium atom	symmetry-related bromide ion	distance /Å	angle /degrees
1	D91	$-x, y-\frac{1}{2}, z$	2.279(11)	163.4(8)
2	D21	1 + x, y, z	2.401(15)	153(1)
3	D22	$1-x, y-\frac{1}{2}, z$	2.447(12)	151(1)
4	D92	x, y, z	2.484(11)	177(1)
5	D9	$x, \frac{1}{2} - y, z - \frac{1}{2}$	2.485(11)	136.9(7)

 $N1 - D9 \cdots O1 = 2.327(14) \text{ Å}$

(O1 in molecule at
$$1 - x, -y, z - 1/2$$
)

 $C7 - D7 \cdot \cdot \cdot O2 = 2.429(13) \text{ Å}$

(O2 in molecule at
$$1 - x$$
, $y + 1/2$, z)

 $C8 - D8 \cdots O2 = 2.324(15) \text{ Å}$

(O2 in molecule at 1 - x, -y, z + 1/2)

The two $C-D\cdots O$ distances are shorter than the mean distance of 2.45 Å reported in a neutron diffraction analysis of $C-H \cdots O$ weak hydrogen bonds in crystalline amino acids.¹³

Since the introduction of the Rietveld method, an ever increasing number of crystal structures have been refined using powder diffraction data. Relatively few of these have been organic molecules of a size comparable to dopamine, because the number of independent parameters to be refined is usually too high relative to the number of independent $|F|^2$ observations present in a typical powder diffraction pattern. However, we have shown here that, provided intrinsic sample line width is not the first limiting factor, data collected at the resolution afforded by HRPD gives an observation to parameter ratio good enough to allow refinement of a structure of this complexity i.e. ca. 100 structural parameters. Synthesis of an almost fully deuteriated sample of dopamine was essential for the HRPD experiment, as the diffraction pattern obtained from a hydrogenous sample is dominated by incoherent scattering. The deuteriated sample size (ca. 1 g), though, was ca. one-fifth of that usually desirable in an HRPD experiment and so, at short times-of-flight, the signal to noise ratio is quite small. Thus, whilst an unconstrained refinement of the starting model converged rapidly to an acceptable solution, a

close examination of the refined model showed small differences between certain bond lengths that one would expect to be almost identical e.g. aromatic C-D bonds. The use of slack chemical constraints in every cycle of refinement effectively increased the observation to parameter ratio and biased the chosen solution towards one that matched chemical expectation. It is important to realise that the weighting factor (c_w) used ensured that the bias was slight; the R_{wp} for the fit only increased from 2.36 to 2.47%. Indeed, the relatively high χ^2 of 4.9 for the constraints shows that the fit to the diffraction pattern is still the dominant factor.

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Paper 6/03500K; Received 20th May, 1996