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## Experimental and Theoretical Determination of Electronic Properties in L-Dopa

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### Abstract

(2*S*)-3-(3',4'-Dihydroxyphenyl)alanine (L-dopa), C<sub>9</sub>H<sub>11</sub>NO<sub>4</sub>, *M<sub>r</sub>* = 197.19, monoclinic, *P*2<sub>1</sub>, *a* = 13.619 (6), *b* = 5.232 (2), *c* = 6.062 (3) Å, β = 97.56 (4)°, *V* = 428.191 Å<sup>3</sup>, *Z* = 2, *D<sub>x</sub>* = 1.529 g cm<sup>-3</sup>, *D<sub>m</sub>* = 1.515 g cm<sup>-3</sup> (*T* = 293 K), λ(Mo *K*α) = 0.71069 Å, μ = 1.2 cm<sup>-1</sup>, *F*(000) = 208, *T* = 173 K, *R*(*F*) = 0.017 for 4208 reflections with sin θ/λ < 1.078 Å<sup>-1</sup>. The electron distribution has been determined by multipole refinement with the Hansen/Coppens aspherical scattering factor expansion, including multipole terms up to

octopoles for C, N and O and up to dipoles for H. The molecular dipole moment was determined as 12 (2) D, within an e.s.d. of the *ab initio* value reported here of 11 D. The bond critical-point properties of the total electron density were determined, giving negative values for ∇<sup>2</sup>ρ<sub>c</sub> consistent with covalent bonds, and are in fair agreement with the *ab initio* results. An analysis of the hydrogen-bond critical points gave small positive ∇<sup>2</sup>ρ values, consistent with ionic, closed-shell interactions between the participating atoms. A set of theoretical structure factors was generated from the *ab initio* charge distribution and subjected to multipole refinement, to enable a more detailed comparison with experiment.

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## Introduction

L-Dopa, a precursor of dopamine, is used in the treatment of Parkinson's disease (Kiss & Gergely, 1985). While the neurotransmitter dopamine is unable to cross the blood/brain barrier, L-dopa can be administered orally and will be metabolized at the target location. However, less than 1% of the oral intake will reach the brain (Merck Index, 1983), with the majority of the drug being decarboxylated in precerebral areas. Various efforts have been undertaken to improve the therapeutic efficacy (Kiss, 1985), in particular by controlled release formulation. Discovering the electronic properties of L-dopa might enable its interactions with potential agents for controlled release to be better understood.

The crystal structure of L-dopa was first established by Mostad, Ottersen & Romming (1971). The related structure of the physiologically active neurotransmitter dopamine in the form of its hydrochloride has been previously elucidated by Bergin & Carlstrom (1968). In a recent investigation by Klein (1991), the charge-density distribution of dopamine hydrochloride was studied.

In this investigation we attempt to derive in detail the electronic properties of L-dopa molecules in the crystal, and subsequently compare this with *ab initio* Hartree-Fock results for an isolated molecule (but with the experimental in-crystal conformation). Following this approach it is possible to determine the effect of the crystal field on the charge-density distribution in this particular case. This is of interest because in solution  $\rho(r)$  will be different again, and the difference between free molecule and in-crystal  $\rho(r)$  indicates the probable magnitude of intermolecular effects in solution.

Comparing theoretical and experimental electron distributions at an atoms-in-molecules level gives results highly dependent on the applied models. Hence, a common method was used for both the experimental and the theoretical distributions. The latter was generated from an *ab initio* wavefunction using the experimental coordinates, and represented as a set of 4208 structure-factor amplitudes (Howard, 1991) – corresponding to the same reflections used in the final refinement of experimental data. This means that Fourier termination effects are identical for the experimental and theoretical distributions. The aspherical atomic density expansion (Hansen & Coppens 1978) was used to partition the molecular densities into pseudo-atoms.

## Experimental

L-Dopa, obtained from Lancaster synthesis, was recrystallized from water by evaporation. A specimen with the dimensions  $0.13 \times 0.45 \times 0.50 \text{ mm}^3$  was selected and mounted. The X-ray data set was collected at 173 (2) K using an Enraf-Nonius CAD-4 diffractometer, equipped with an Enraf-Nonius FR558 SH nitrogen cold gas stream apparatus. No attempt was made to calibrate the

crystal temperature accurately, since the experiment was independent from a neutron diffraction experiment. Graphite monochromated  $\text{MoK}\alpha$  radiation generated from a sealed tube at 50 kV and 29 mA generator settings was used.

The unit-cell dimensions were determined at room temperature from 25 reflections in the range  $12.2 < \theta < 17.1^\circ$ . The resulting orientation matrix was redetermined several times while the crystal was annealed. Diffracted intensities were recorded by  $\omega/2\theta$  scans with an  $\omega$  scan width of  $0.8 + 0.35 \tan \theta$  using a 4 mm aperture. The maximum scan speed was  $6.7^\circ \text{ min}^{-1}$ . A hemisphere of reciprocal space with  $0.037 < \sin \theta / \lambda < 1.078 \text{ \AA}^{-1}$  was collected in two shells. The inner shell extended to  $50^\circ$  in  $2\theta$ . Using the zigzag mode, indices were varied in the range  $h - 29 \rightarrow 29$ ,  $k - 11 \rightarrow 11$  and  $l - 1 \rightarrow 13$ . The stability of the experimental conditions was monitored by two reference reflections (912,  $\bar{1}11$ ) at intervals of 1 h with respect to exposure time.

Integrated intensities were obtained following the method of Lehmann & Larsen (1974) implemented in the *DREAM* package (Blessing, 1987, 1989). A numerical absorption correction (DeTitta, 1984) was carried out, with resulting transmission factors between 0.95 and 0.986. The merging *R*-factor  $R_{\text{int}} = \Sigma(|Y - Y_{\text{mean}}|) / \Sigma wY$  was 2.12% for 9245 measured reflections, resulting in 4634 unique reflections. 4208 reflections had positive intensities greater than  $2\sigma(I)$ , and these were used in the subsequent refinements. Standard deviations of intensities were estimated from counting statistics corrected by a bivariate analysis of variance (Blessing, 1987).

The electron distribution in the crystal was determined by multipole least-squares refinement using the program *LSMOL* (Koritsanszky, 1987). The core and valence scattering factors were taken from *International Tables for X-ray Crystallography* (Cromer, 1974) for elements C, N and O, while H-atom scattering factors were taken from Stewart, Davidson & Simpson (1965). Radial function exponents  $n$  and  $\alpha$  were left at their default values. Anomalous dispersion was applied initially using the values reported by Cromer (1974), but the effect was negligible and therefore the Bijvoet equivalent data were averaged. The same observation was made by Klein (1991) for some of the least-squares refinements in the charge-density study of dopamine.

The initial refinement included atomic positions and anisotropic displacement parameters for C, N and O. H-atom positions were obtained from spherical refinement, but were subsequently held at fixed distances of  $\text{H}-\text{C}(\text{aromatic}) = 1.08$ ,  $\text{H}-\text{C}(\text{sp}^3) = 1.06$ ,  $\text{H}-\text{N}(\text{sp}^3) = 1.01$  and  $\text{H}-\text{O}(\text{sp}^3) = 1.0 \text{ \AA}$  (Allen *et al.*, 1987). Initially the valence electron density was refined using first monopoles and  $\kappa'$  parameters. A local coordinate system was set up with the  $x$ -vector along a bond and the  $z$ -vector perpendicular to the ring system or

Table 1. Final set of atomic coordinates and displacement parameters

(a) Atomic coordinates and isotropic displacement factors for H atoms. Non-H atoms show equivalent displacement factors (Hamilton, 1959). Estimated standard deviations in parentheses.

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j.$$

	x	y	z	$U_{iso}/U_{eq} (\text{\AA}^2)$
N(1)	-0.41832 (3)	0.18630	-0.73708 (5)	0.010
O(1)	-0.49248 (2)	0.1747 (1)	-1.16904 (5)	0.011
O(2)	-0.34926 (3)	0.2859 (1)	-1.28767 (5)	0.014
O(3)	-0.17759 (3)	-0.4571 (1)	-0.16225 (6)	0.011
O(4)	-0.03209 (3)	-0.1293 (1)	-0.05717 (6)	0.012
C(1)	-0.40121 (2)	0.2247 (1)	-1.13910 (5)	0.008
C(2)	-0.34603 (2)	0.2064 (1)	-0.90180 (5)	0.008
C(3)	-0.27628 (3)	-0.0241 (1)	-0.88425 (5)	0.010
C(4)	-0.21231 (2)	-0.0467 (1)	-0.66253 (5)	0.009
C(5)	-0.22802 (3)	-0.2421 (1)	-0.51378 (5)	0.009
C(6)	-0.16658 (2)	-0.2693 (1)	-0.31226 (5)	0.008
C(7)	-0.08953 (3)	-0.0941 (1)	-0.25686 (5)	0.009
C(8)	-0.07394 (3)	0.1021 (1)	-0.40339 (6)	0.010
C(9)	-0.13491 (3)	0.1255 (1)	-0.60576 (6)	0.010
H(1N1)	-0.38280	0.19737	-0.58017	0.020
H(2N1)	-0.45585	0.01987	-0.75881	0.037
H(3N1)	-0.47107	0.32186	-0.76835	0.025
H(1O3)	-0.23423	-0.55679	-0.22696	0.037
H(1O4)	0.00439	0.02592	-0.01396	0.061
H(2)	-0.30194	0.37332	-0.87437	0.017
H(31)	-0.22776	-0.01035	-1.00692	0.037
H(32)	-0.32211	-0.18725	-0.91728	0.011
H(5)	-0.28664	-0.37984	-0.55499	0.016
H(8)	-0.01240	0.22863	-0.35402	0.027
H(9)	-0.12544	0.27192	-0.72676	0.039

(b) Anisotropic displacement factors ( $\text{\AA}^2$ ) for non-H atoms. The anisotropic displacement factor has the form  $\exp[-2\pi^2 \sum_i \sum_j U_{ij} h_i h_j \mathbf{a}_i^* \cdot \mathbf{a}_j^*]$ . Estimated standard deviations in parentheses.

	$U_{11}$	$U_{22}$	$U_{33}$	$U_{12}$	$U_{13}$	$U_{23}$
N(1)	0.0094 (1)	0.0125 (1)	0.0069 (1)	0.0009 (1)	0.0005 (1)	-0.0001 (1)
O(1)	0.0093 (1)	0.0135 (1)	0.0104 (1)	-0.0008 (1)	-0.0022 (1)	0.0000 (1)
O(2)	0.0145 (1)	0.0201 (2)	0.0066 (1)	-0.0054 (1)	-0.0001 (1)	0.0026 (1)
O(3)	0.0142 (1)	0.0098 (1)	0.0089 (1)	-0.0014 (1)	-0.0004 (1)	0.0021 (1)
O(4)	0.0128 (1)	0.0130 (1)	0.0090 (1)	-0.0014 (1)	-0.0035 (1)	0.0005 (1)
C(1)	0.0096 (1)	0.0085 (1)	0.0064 (1)	-0.0009 (1)	-0.0011 (1)	0.0007 (1)
C(2)	0.0084 (1)	0.0079 (1)	0.0060 (1)	0.0002 (1)	-0.0005 (1)	0.0001 (1)
C(3)	0.0112 (1)	0.0101 (1)	0.0070 (1)	0.0026 (1)	-0.0005 (1)	-0.0005 (1)
C(4)	0.0090 (1)	0.0091 (1)	0.0071 (1)	0.0009 (1)	-0.0003 (1)	0.0008 (1)
C(5)	0.0097 (1)	0.0091 (1)	0.0079 (1)	-0.0007 (1)	-0.0009 (1)	0.0005 (1)
C(6)	0.0093 (1)	0.0083 (1)	0.0071 (1)	-0.0001 (1)	-0.0002 (1)	0.0003 (1)
C(7)	0.0086 (1)	0.0092 (1)	0.0075 (1)	0.0002 (1)	-0.0003 (1)	0.0001 (1)
C(8)	0.0095 (1)	0.0108 (1)	0.0094 (1)	-0.0013 (1)	0.0000 (1)	0.0008 (1)
C(9)	0.0102 (1)	0.0106 (1)	0.0091 (1)	-0.0008 (1)	0.0002 (1)	0.0020 (1)

three-atom plane and  $\kappa''$  parameters and higher spherical harmonic functions  $y_{lmn}$  up to octopole level were introduced. The expansion was limited to dipoles for hydrogen. The function  $w(F_{\text{obs}} - F_{\text{calc}})^2$  was minimized using weights of  $w = 1/\sigma^2(F_{\text{obs}})$ . Using a total of 4208 reflections to refine 400 variables, a final set of agreement factors of  $R = 1.7\%$  and  $wR = 2.4\%$  resulted, with goodness-of-fit  $S = 0.98$ .\* The final set of atomic coordinates and displacement parameters is given in Table 1 and a full set of multipole parameters is given in Table 2.† Fig. 1 shows the molecular

conformation and thermal ellipsoids, together with the chosen numbering scheme.

The rigid-bond test (Hirshfeld, 1976) on the displacement parameters gave an average  $\Delta(A, B) = 0.0002(1) \text{\AA}^2$ . The largest  $\Delta$  was 0.0004, indicating complete accordance with the test. No significant features are apparent on the residual map (Fig. 2). All calculations were performed on a Digital Equipment Corporation VAX 3600 running VMS.

### Computational

An *ab initio* charge distribution was generated from a single determinant restricted-Hartree-Fock (RHF) calculation employing the coordinates obtained from the final multipole refinement. The GAUSSIAN90 (Frisch *et al.*, 1990) program was used on the CONVEX supercomputer

\* Values of  $R$  and  $wR$  were calculated according to  $R = \sum |F_{\text{obs}} - F_{\text{calc}}| / \sum F_{\text{obs}}$ ,  $wR = \sum w(F_{\text{obs}} - F_{\text{calc}})^2 / \sum wF_{\text{obs}}^2$ ,  $S^2 = \sum w(|F_{\text{obs}} - F_{\text{calc}}|)/(n-p)$ .

† Lists of the used local coordinate system and structure factors have been deposited with the IUCr (References SE0154). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.



cluster at the University of London Computer Centre (ULCC). A double- $\zeta$  basis set (Dunning, 1970) of 160 functions was used. An extended basis set calculation would have been feasible, but the limiting factor was the computation of structure factors from the theoretical density in a reasonable time period.

From the wavefunction of the ground singlet state, structure factors (ignoring thermal motion) were calculated using the *FSTRUCT* program (Howard, 1991), with  $P2_1$  space-group symmetry operations. These were used as  $F_{\text{obs}}$  in a full least-squares refinement using *LSMOL*, with unit weights and scale factor fixed at unity. Starting values for the population parameters were taken from the experimental data set, and the refinement converged rapidly from this point. Final agreement factors of  $R = 0.9\%$  and  $wR = 1.4\%$  were calculated. The multipole population parameters are listed together with the experimental data in Table 2.

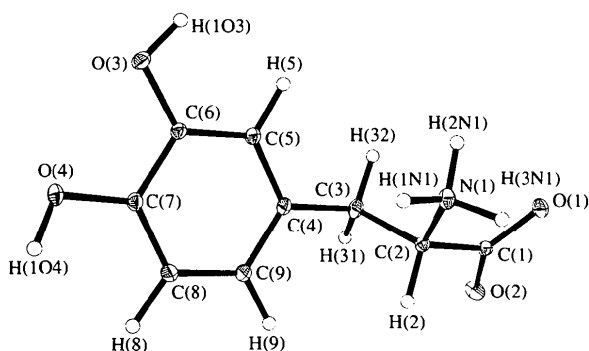


Fig. 1. Molecular conformation and thermal ellipsoids (*SHELXTL-Plus*; Sheldrick, 1990) of L-dopa. Thermal ellipsoids are drawn at 50% probability.

## Discussion

The residual maps for the experimental data show no significant density in the molecular plane, indicating a satisfying description of the electron density by the multipole model used. The residual map for the theoretical structure-factor refinement (Fig. 3) shows negative density at the core positions. This must be attributed to the difference in the Hartree-Fock scattering factor for non-H atoms and the contracted set of Gaussians used in the *ab initio* calculations. This small mismatch is not expected to significantly influence the fit to the valence electron distribution.

Various models for the  $\kappa'$  and  $\kappa''$  parameters were investigated. These values are listed in Table 3. Using the theoretical data,  $\kappa'$  and  $\kappa''$  values for hydrogen were refined and both gave values very close to 1.2. These values were subsequently fixed for refinements of theoretical and experimental structure factors. Refinement of individual  $\kappa$  sets for the carboxyl oxygen and hydroxyl oxygen indicated very diffuse density functions ( $\kappa'' = 0.54$ ) around the carboxyl oxygen in the experimental data set, but contracted ( $\kappa'' = 1.27$ ) in the theoretical data set, a very large difference. For the hydroxyl oxygen, this difference was smaller (0.22). We attribute these differences to the strong hydrogen bonds formed by the carboxyl group, which of course are not present in the theoretical data (adjacent molecular densities overlap, but do not interact). In an experimental charge-density study of formamide (Howard, Huke, Mallinson & Frampton, 1994), an identical effect

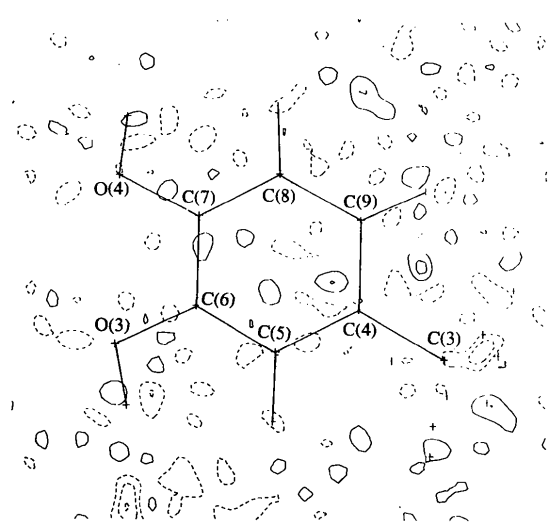


Fig. 2. Experimental residual electron density for L-dopa in the plane of the phenyl ring. Contours are plotted at  $0.05 \text{ e} \cdot \text{Å}^{-3}$  intervals and negative contours are dashed.

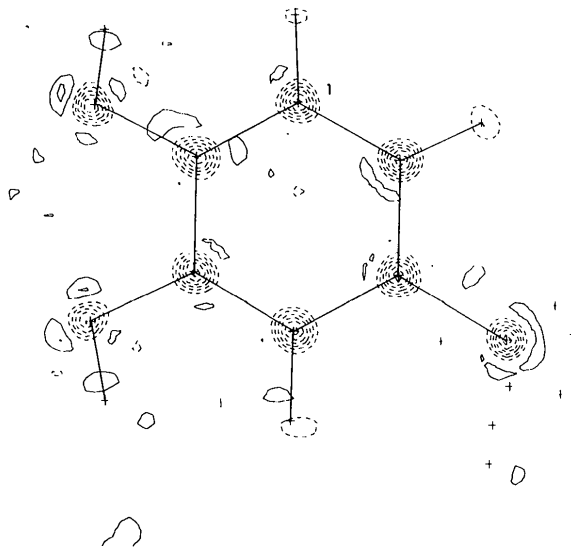


Fig. 3. Residual electron-density map for the theoretical data refinement. Orientation and contour levels as in Fig. 2.

Table 3. Applied  $\kappa'$  and  $\kappa''$  values for experimental and theoretical structure-factor refinement

The values for O(carboxyl) and O(hydroxyl) are obtained from a refinement with individual  $\kappa$  parameters for each group. The atomic electron density is expressed as

$$\rho(r) = F_c \rho_c(r) + \kappa'^3 P_v \rho_v(r) + \sum_{l=0}^{l_{\max}} \sum_{m=-l}^{l_{\max}} \kappa'^3 P_{lm} N r^{nl} e^{-lr} \gamma_{lm}(\Theta, \varphi)$$

Estimated standard deviations of refined parameters are in parentheses.

	Experimental		Theoretical	
	$\kappa'$	$\kappa''$	$\kappa'$	$\kappa''$
N	0.995 (6)	0.92 (4)	0.983 (3)	0.82 (3)
O	0.985 (2)	0.78 (3)	0.970 (1)	1.09 (1)
C	1.008 (4)	0.91 (2)	1.007 (1)	0.80 (1)
H	1.200	1.200	1.200	1.200
O(carb)	0.98	0.54	0.97	1.27
O(hydr)	0.99	0.80	0.97	1.02

has been found for the carbonyl oxygen, which also participates in strong hydrogen bonding.

The experimental electron deformation densities are shown in Figs. 4 and 5. All carbon-carbon bonds show the expected positive densities and maxima are located between nuclei. Carbon-heteroatom bonds, especially C—O bonds, are less pronounced. This is a well known effect in deformation densities where the promolecular reference density consists of non-oriented ground states (Schwarz, Ruedenberg & Mensching, 1989). The hydroxyl lone pairs are all observed and those in the carboxylate group plane are separated. The deformation density maps obtained from the refined theoretical data are very similar to the experimental maps (Fig. 6). Differences are observed around heteroatoms, especially in the lone-pair regions, which are more pronounced in the theoretical data (Fig. 7).

The refinement of both the experimental and theoretical data resulted in similar values for the monopole and dipole populations. Averaged differences are 0.10(6)e for monopoles. The theoretical-experimental monopole population differences for C(2), C(4) and H(32) are more than twice this average. It is not obvious that any of these atoms are involved in strong intermolecular interactions, so the origin of these differences is unclear. When the atomic monopole charges from the experimental refinement are summed into functional groups, carboxylate has a charge of  $-0.80e$  and ammonium of  $+0.43e$ . The values obtained from the theoretical monopole population are  $-0.70$  and  $+0.24e$ , respectively. For the L-alanine model *E* (Destro, Marsh & Bianchi, 1988), these values are  $-0.59$  and  $+0.42e$ . Hence, both theory and experiment predict that these groups contain less localized charge than the formal notion of  $\pm 1$ . The reported value for the ammonium group in dopamine (Klein, 1991) is only  $+0.2e$ . A larger difference is observed for the 3,4-dihydroxyphenyl moiety. For L-dopa the total charge in this moiety is  $+0.36$  (experimental) and  $+0.08e$  (theoretical) compared with  $-0.5e$  in dopamine.

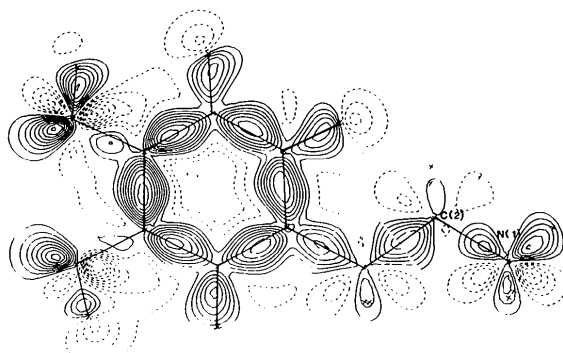


Fig. 4. Experimental static-deformation density for L-dopa, composed from three sections containing the phenyl ring, C(4)—C(3)—C(2), and C(3)—C(2)—N(1). Contour levels are at  $0.1e \text{ \AA}^{-3}$  intervals and negative contours are dashed.

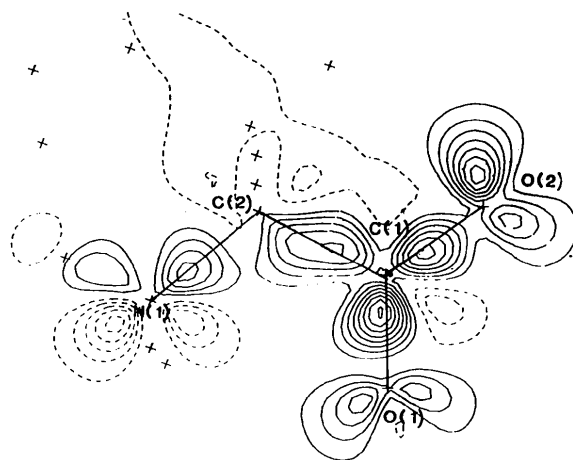


Fig. 5. Experimental static deformation density in the carboxylate function and the C—N bond. Contour levels as in Fig. 4

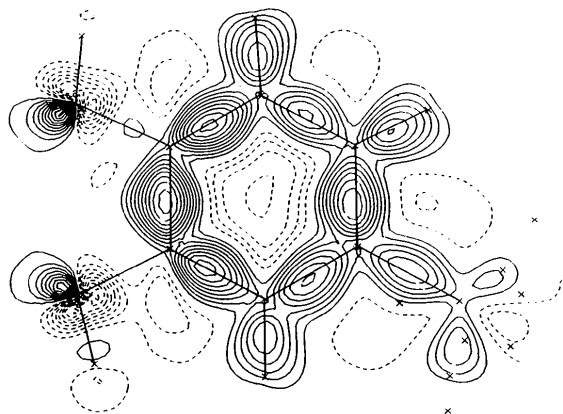


Fig. 6. Deformation density obtained from the theoretical data refinement. Contour levels as in Fig. 4.

Tables 2(a) and (b) show a significant population of H-atom dipoles  $P_{1-1}$ ,  $P_{10}$ , which are perpendicular to the respective bond. It was found that seven of these 22 parameters have a population larger than  $2\sigma$ , suggesting that bond-directed dipoles only (on hydrogen) are insufficient. Souhassou *et al.* (1991, 1992) used this constraint in two recent studies. Alternatively, the dipoles perpendicular to the C—H bonds may be compensating for absent anisotropic displacement parameters of H atoms. However, the refinement of the theoretical structure factors, with atoms at rest, also had eight out of 22 significantly populated non-bonded directed dipoles on hydrogens, which confirms that these functions are necessary.

The molecular dipole moments obtained from this study are presented in Table 4. The vectorial components are reported in a Cartesian reference frame

$$\mathbf{M} = \begin{bmatrix} a & 0 & c \cos \beta \\ 0 & b & 0 \\ 0 & 0 & c \sin \beta \end{bmatrix},$$

from Prince (1982) in such a way that  $x$  is parallel to the  $a$ -axis,  $y$  in the  $ab$ -plane and  $z$  forming a right-handed coordinate system. Further details of the method for computing the dipole moment and the estimated standard deviation are given by Howard, Hursthouse, Lehmann, Mallinson & Frampton (1992). The molecular dipole of the molecule with coordinates given in Table 1 forms an angle of  $10^\circ$  with the  $c$ -axis. Within a molecule, the direction may be described as pointing from the carboxylate towards the ammonium. The angle between the experimental and theoretically obtained dipole

Table 4. Dipole moments in D ( $3.33564 \times 10^{-30}$  Asm) obtained from experimental structure factors, theoretical structure factors and exact wavefunctions

Estimated standard deviations in parentheses.				
	$p_x$ (D)	$p_y$ (D)	$p_z$ (D)	$ p $ (D)
Experimental	0.7 (6)	-0 (5)	12 (2)	12 (5)
Theoretical	-0.7 (8)	-0.3 (9)	7.6 (7)	8 (1)
Exact	-0.1	0.3	11.0	11.0

moments is  $4^\circ$  and the magnitudes are in excellent agreement. Table 4 also reports the dipole moment obtained from the refinement of theoretical structure factors, *i.e.* the *ab initio* charge distribution projected into multipole form. This projection procedure significantly affects the molecular dipole, reducing its magnitude from 11 to 8(1)D, and altering its direction by some  $20^\circ$ . The dipole moment obtained from a  $\kappa$  refinement is also 8D; the angle formed with the latter is  $8^\circ$  and with the experimental  $5^\circ$ , respectively.

A very similar magnitude and orientation for the dipole moment was reported for L-alanine by Destro, Marsh & Bianchi (1988). Thus, the moment is affected very little by the dihydroxyphenyl substituent. The angle between experimental L-dopa and L-alanine dipole moments obtained from a molecular fit of the carboxylate and ammonium groups is  $30^\circ$  (Fig. 8). Further similarities are observed for the hydrogen bonding. In both L-alanine and L-dopa, one of the carboxyl oxygens forms a bifurcated hydrogen bond to different ammonium protons. The other carboxyl O atom forms only one such hydrogen bond. There is an additional strong O(3)—H...O(2) hydrogen bond in L-dopa, which is not possible for L-alanine.

To explore the chemical bonding in more detail, a critical point (CP) analysis (Bader, 1990) of the total charge density was carried out using the program *LSPROP* (Howard & Mallinson, 1995). (3,-1) CP's were located for all bonds. Table 5 summarizes the values obtained from the experimental and theoretical structure factors and compares them with the values obtained from the exact wavefunction. The CP properties for the experimental and *ab initio* charge distributions are in quite good agreement, when the latter are projected into the same multipole model as the experiment. Both multipole data sets have  $\rho_c$  values up to 20% larger than those from the exact wavefunction. Again, this demonstrates that the type of multipole model applied here does have serious shortcomings, and more flexible models need to be considered (Swaminathan, Craven, Spackman & Stewart, 1984). Bonds involving H atoms are in good agreement between experiment and refined theoretical data for C—H bonds, but rather poorer for O—H and N—H, the bonds involved in hydrogen bonding. There is one exception, the CP between N(1) and C(2). The difference in  $\rho$  is  $0.43 \text{ e \AA}^{-3}$  between the two refined data sets. Interestingly, a similar discrepancy was found in the theoretical-experimental comparison

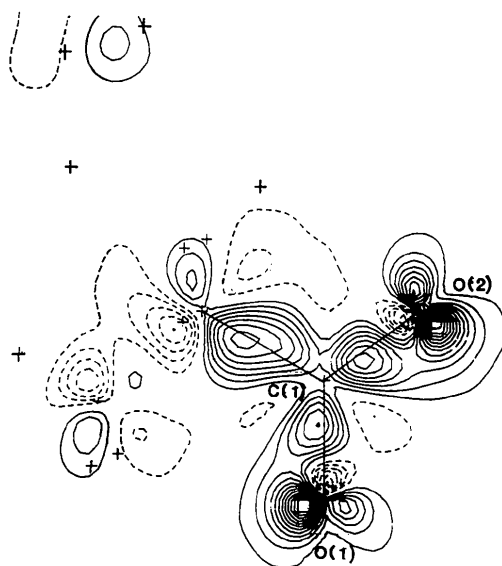


Fig. 7. Deformation density obtained from the theoretical data refinement in the plane of the carboxylate function. Contour levels as in Fig. 4.

for L-alanine, with  $\rho_{\text{exp}} = 1.70$ ,  $\rho_{\text{the}} = 1.24$  and  $\rho_{\text{exact}} = 1.39 \text{ e } \text{\AA}^{-3}$  (Gatti, Bianchi, Destro & Merati, 1992). The location of the CP's is within the same range observed for all other CP's, and the analysis of the Laplacian shows no large differences either. Since other values connected with C(2) are in good agreement between the data sets, it is probable that the parameterization of N(1) is responsible for the observed effect. Specifically, the powers of  $r$  in the Slater-type radial functions  $r^n e^{-\zeta r}$  may be far from optimum for an ammonium environment – this is under investigation.

In the phenyl ring there is good agreement between the Laplacian values of all six bonds. The average values are  $-18(1)$ ,  $-19(2)$  and  $-19.2(4) \text{ e } \text{\AA}^{-5}$  for the experimental & theoretical multipole-refined densities, and the original wavefunction, respectively. The experimental bond ellipticities give an average of 0.33 for the aromatic bonds and 0.13 for the three C—C single bonds. These numbers reflect the partial double-bond character expected in a phenyl ring. By comparison, the C—C single bonds have Laplacian values around  $-9$  to  $-12 \text{ e } \text{\AA}^{-5}$ , while the C—O bonds in the carboxyl group have the largest values of  $-27 \text{ e } \text{\AA}^{-5}$  compared with  $-10 \text{ e } \text{\AA}^{-5}$  for the hydroxyl C—O bond. The large experimental value of  $-18 \text{ e } \text{\AA}^{-5}$  for C(7)—O(4) is anomalous.

Greater differences between experiment and theory may be expected in the intermolecular hydrogen bonds, since the theoretical calculations were for an isolated molecule. Values and symmetry operators for the hydrogen bonds are listed in Table 6. Three of the five

hydrogen bonds involve ammonium protons interacting with the carboxylate group, while a fourth originates from H(1O3). The two hydrogen bonds towards O(1) are perpendicular to the carboxylate plane, and the two hydrogen bonds towards O(2) are in the plane at approximately  $120^\circ$  to the C—O bond. This means the latter are directed straight into the lone-pair regions of an  $\text{Osp}^2$  atom. They are on average  $0.15 \text{ \AA}$  shorter than those approaching from approximately perpendicular directions. The fifth hydrogen bond forms an infinite chain between O(4)—H(1O4) and O(4). This bond bisects the C(7)—O(4)—H(1O4) bond angle, again pointing from slightly above the C—O—H plane towards one of the  $\text{Osp}^3$  lone pairs.

All five intermolecular hydrogen-bond CP's were successfully located and characterized. The density at the CP increases almost linearly with decreasing hydrogen-bond distance, except the shortest hydrogen bond O(2)··H(1O3). This would obviously also occur for two spherical non-interacting O and H atoms, an independent atom model (IAM). The theoretical model presented here might be termed an independent molecule model (IMM), since the O and H atoms are non-spherical, bonded in their respective moieties, but still non-interacting. The differences between experiment and theory are within the estimated error (based on the relative error of the electron density in N—H and O—H bonds), although the refined theoretical hydrogen-bond CP densities are systematically higher.

We can expect that  $\nabla^2 \rho_c$  will be more sensitive to the polarization of charge due to the hydrogen-bonding interaction. As found in previous studies (Stewart, 1991; Klooster, Swaminathan, Nanni & Craven, 1992), these values are positive and increase with decreasing O··H separation. The positive value of  $\nabla^2 \rho_c$  is characteristic of ionic interactions between closed-shell species (Bader, 1990). We note that an IAM model, in which the atoms do not interact at all, also predicts this trend. Whilst the  $\nabla^2 \rho_c$  values predicted from the multipole-projected *ab initio* charge distribution show a linear dependence with the O··H distance, no such trend is obvious for the experimental data, unless much larger errors are anticipated. The errors on these values, computed from the covariance matrix, are certainly underestimates. They take no account of the uncertainty introduced by fixing the H-atom positions and temperature factors. Consequently, these values alone are probably insufficient for a useful analysis of the hydrogen bonding interaction – such an analysis may be achieved by combining data sets for many molecular crystals.

## Conclusions

This investigation has provided detailed information about the electron distribution in L-dopa, which may be compared with analogous studies on the compounds L-alanine and dopamine. The ammonium and carboxylate

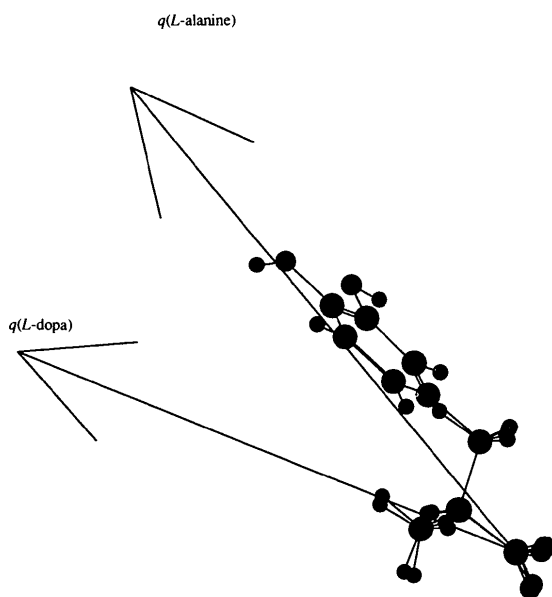


Fig. 8. Superposition of L-dopa and L-alanine molecules. Arrows indicate direction and magnitude ( $1 \text{ \AA} = 1 \text{ D}$ ) of the dipole moments (Chem-X, 1993).



Table 5. Bond critical points for the experimental (top row) and theoretical (middle row) data set, and exact theory (bottom row)

$D$  is the distance between the first atom and the CP. For a definition of the bond ellipticity see Bader (1990, p. 78). Standard deviations in parentheses.

	Hessian	Eigen value		$\rho$ (e Å <sup>-3</sup> )	$\nabla^2\rho$ (e Å <sup>-5</sup> )	Ellipt.	$d$ (Å)
N(1)—C(2)	-12.68	-8.62	12.87	1.62 (3)	-8.4 (4)	0.47	0.591
	-9.91	-4.65	11.57	1.20 (2)	-3.0 (1)	1.13	0.623
				1.37	-4	0.06	
O(1)—C(1)	-28.23	-22.64	12.09	2.84 (2)	-38.8 (4)	0.25	0.614
	-25.46	-20.89	15.17	2.64 (1)	-31.2 (2)	0.22	0.647
				2.40	-18	0.01	
O(2)—C(1)	-28.34	-22.63	18.35	2.70 (2)	-32.6 (6)	0.25	0.649
	-25.79	-21.61	13.23	2.81 (1)	-34.2 (2)	0.19	0.644
				2.43	-19	0.01	
O(3)—C(6)	-18.22	-13.97	15.46	1.95 (2)	-16.7 (2)	0.30	0.586
	-13.99	-11.70	13.76	1.82 (1)	-11.9 (2)	0.20	0.607
				1.84	-11	0.05	
O(4)—C(7)	-17.90	-15.67	10.94	2.01 (2)	-22.6 (3)	0.14	0.614
	-14.97	-10.83	13.92	1.88 (1)	-11.9 (1)	0.38	0.601
				1.80	-10	0.05	
C(1)—C(2)	-12.49	-10.96	11.43	1.71 (1)	-12.02 (2)	0.14	0.508
	-14.04	-10.73	10.43	1.845 (6)	-14.34 (1)	0.31	0.485
				1.56	-11	0.04	
C(2)—C(3)	-13.24	-11.37	11.53	1.79 (1)	-13.07 (1)	0.16	0.510
	-11.63	-11.25	9.72	1.748 (7)	-13.16 (2)	0.03	0.537
				1.54	-11	0.03	
C(3)—C(4)	-13.44	-12.17	11.44	1.84 (1)	-14.17 (1)	0.10	0.493
	-14.18	-11.23	10.26	1.87 (1)	-15.2 (3)	0.26	0.503
				1.60	-13	0.02	
C(4)—C(5)	-18.67	-14.02	10.45	2.26 (1)	-22.24 (5)	0.33	0.530
	-17.44	-13.67	9.17	2.213 (9)	-21.9 (2)	0.28	0.487
				1.95	-19	0.15	
C(4)—C(9)	-19.19	-15.50	10.91	2.34 (1)	-23.78 (3)	0.24	0.493
	-18.97	-13.90	9.00	2.375 (8)	-23.86 (4)	0.37	0.525
				1.98	-19	0.15	
C(5)—C(6)	-18.96	-13.63	9.74	2.22 (2)	-22.85 (6)	0.39	0.467
	-19.12	-13.57	7.88	2.28 (1)	-24.8 (3)	0.41	0.435
				1.97	-19	0.18	
C(6)—C(7)	-21.39	-15.82	9.80	2.42 (2)	-27.41 (4)	0.35	0.521
	-20.94	-17.02	7.62	2.520 (9)	-30.4 (1)	0.23	0.527
				2.00	-20	0.20	
C(7)—C(8)	-20.43	-14.69	7.75	2.403 (8)	-27.36 (6)	0.39	0.543
	-20.41	-13.74	10.39	2.31 (1)	-23.77 (5)	0.49	0.524
				1.99	-19	0.17	
C(8)—C(9)	-17.85	-13.75	8.67	2.135 (8)	-22.93 (2)	0.30	0.507
	-19.02	-15.12	10.38	2.30 (2)	-23.76 (3)	0.26	0.489
				1.96	-19	0.14	
N(1)—H(1N1)	-25.951	-24.499	29.290	1.96 (6)	-21. (1)	0.06	0.753
	-25.304	-24.185	30.568	2.06 (3)	-18.9 (4)	0.05	0.731
				2.15	-35	0.00	
N(1)—H(2N1)	-30.971	-30.391	32.938	2.38 (7)	-28. (2)	0.02	0.740
	-26.454	-25.984	29.541	2.11 (2)	-22.9 (3)	0.02	0.741
				2.16	-36	0.00	
N(1)—H(3N1)	-29.672	-28.997	29.101	2.10 (6)	-30. (1)	0.02	0.773
	-28.805	-28.374	32.686	2.33 (3)	-24.5 (5)	0.02	0.739
				2.15	-36	0.00	
O(3)—H(1O3)	-36.629	-32.475	37.735	2.38 (5)	-31.4 (8)	0.13	0.752
	-29.359	-28.473	39.867	2.15 (2)	-18.0 (3)	0.03	0.748
				2.27	-36	0.03	
O(4)—H(1O4)	-42.740	-39.300	37.901	2.66 (6)	-44 (1)	0.09	0.769
	-28.390	-27.740	39.711	2.03 (2)	-16.4 (4)	0.02	0.759
				2.26	-36	0.03	
C(2)—H(2)	-18.785	-16.674	15.869	1.98 (1)	-19.59 (5)	0.13	0.653
	-18.980	-18.682	18.087	1.88 (3)	-19.6 (2)	0.02	0.690
				1.92	-24	0.07	
C(3)—H(31)	-17.672	-16.930	16.929	1.97 (1)	-17.67 (5)	0.04	0.656
	-18.179	-16.978	16.988	1.98 (3)	-18.17 (7)	0.07	0.636
				1.90	-23	0.02	
C(3)—H(32)	-18.745	-16.958	16.254	1.97 (1)	-19.45 (9)	0.11	0.644
	-17.376	-16.680	18.845	1.69 (3)	-15.2 (3)	0.04	0.712
				1.87	-21	0.03	
C(5)—H(5)	-17.366	-16.619	17.630	1.90 (1)	-16.4 (1)	0.04	0.664
	-18.630	-17.047	18.807	1.85 (2)	-16.9 (1)	0.09	0.682
				1.78	-20	0.01	
C(8)—H(8)	-18.954	-16.778	17.205	1.99 (1)	-18.53 (5)	0.13	0.660
	-18.407	-16.407	15.163	1.93 (2)	-19.65 (5)	0.12	0.620
				1.80	-21	0.01	

Table 5 (cont.)

C(9)—H(9)	Hessian	Eigen value		$\rho$ (e Å <sup>-3</sup> )	$\nabla^2\rho$ (e Å <sup>-5</sup> )	Ellipt.	<i>d</i> (Å)
		-17.682	18.501	2.06 (1)	-18.91 (6)		
	-19.101	-16.785	15.922	2.03 (2)	-19.96 (5)	0.14	0.609
				1.81	-21	0.01	

Table 6. Hydrogen-bond critical points for both the experimental (top row) and theoretical refined (bottom row) data set

Bond	Length (Å)	Hessian	Eigen value	$\rho$ (e Å <sup>-3</sup> )	$\nabla^2\rho$ (e Å <sup>-5</sup> )	Ellipt.	<i>d</i> (Å)
O(1)··H(2N <sup>i</sup> )	1.96	-0.715	-0.641	4.007	0.145	2.65	0.11
		-0.616	-0.521	3.932	0.126	2.80	0.18
O(1)··H(3N <sup>ii</sup> )	1.94	-0.919	-0.886	4.716	0.192	2.91	0.04
		-0.865	-0.667	4.162	0.161	2.63	0.30
O(2)··H(1N <sup>iii</sup> )	1.83	-1.259	-1.255	6.149	0.243	3.64	0.00
		-1.436	-1.312	6.068	0.239	3.32	0.10
O(2)··H(1O3 <sup>iv</sup> )	1.76	-1.338	-1.282	6.518	0.221	3.90	0.04
		-1.519	-1.147	6.946	0.200	4.28	0.32
O(4)··H(1O4 <sup>v</sup> )	1.88	-1.450	-1.046	5.996	0.200	3.50	0.39
		-1.063	-1.009	5.113	0.190	3.03	0.05

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

group charges are reasonably transferable between L-dopa and L-alanine, as is the molecular dipole moment. The CP analysis of the total density yielded values of  $\rho_c$ ,  $\nabla^2\rho_c$  and bond ellipticities which agree well with an *ab initio* charge distribution, when the latter is effectively projected into multipole form. The location of all hydrogen bond CP's from an experiment without the benefit of atomic parameters from a complementary neutron diffraction experiment is encouraging. A more detailed investigation into the hydrogen bonding is continuing, aiming to show how  $\rho$  and  $\nabla^2\rho$  in hydrogen bonds may relate to the hydrogen bond strength.

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