

hydrogen bonding increases the polarity in the parts which are directly participating in the hydrogen bond. The present study shows that this conclusion also holds for the proton-accepting O atom lone-pair regions in II *trans A*.

It should be borne in mind that the O atoms in II *trans A* are not only H acceptors, but also H donors (WV, Fig. 1). According to Olovsson's conclusion this should increase the O atom lone-pair density at the extension of the H—O bond. Whether or not this is correct for II *trans A* can be studied for sections through the C—O—H plane (Fig. 5*a-c*). We see that for both O atoms the experimental  $D_M(Z, r)$  sections indeed show a slight inclination of the O atom lone-pair lobe towards the extension of the H—O bond. The theoretical (static, because of the large computing time needed to smear the density) map for the isolated IIS molecule, on the other hand, shows (Fig. 5*c*) a slight inclination of the lobe in the opposite direction, thus towards the (positively charged) H atom, as might be expected.

Further experimental and theoretical work on the influence of hydrogen bonding on density distributions is evidently required. Experimentally the positions of H and O should be determined accurately by neutron diffraction. On the theoretical side calculations with more extended basis sets and making reasonable allowance for the crystal field are necessary.

*Acta Cryst.* (1979). B35, 1809–1812

## Electron Density Distributions on C—C Single, Double and Triple Bonds. Pitfalls and Prospects of the Analysis of Accurate X-ray Diffraction Data

BY J. L. DE BOER AND AAFJE VOS

*Laboratorium voor Chemische Fysica, Rijksuniversiteit Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands*

(Received 9 February 1979; accepted 19 March 1979)

### Abstract

Results obtained so far at Groningen for electron densities of compounds having single, double and triple C—C bonds are compared with each other and with densities from *ab initio* theoretical calculations. Suggestions for the improvement of further electron density studies and for the determination of physical properties from diffraction data are made.

### Experimental and theoretical data

Now that accurate density distributions have been obtained for different compounds with C—C single,

We thank Drs Th. Thole and Dr H. van Piggelen for their help with the quantum-theoretical calculations, and Dr J. L. de Boer for reading the manuscript. Part of the work has been supported by the Foundation for Fundamental Research of Matter with X-rays and Electron Rays (FOMRE) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). The computations were carried out at the computer center of the University of Groningen.

### References

- BOER, J. L. DE & VOS, A. (1979). *Acta Cryst.* B35, 1809–1812.  
 CRUICKSHANK, D. W. J. (1949). *Acta Cryst.* 2, 65–82.  
 DULINEN, P. TH. VAN & THOLE, B. T. (1977). *BIGMOL*. Laboratory of Chemical Physics, Univ. of Groningen.  
 HELMHOLDT, R. B. & VOS, A. (1977). *Acta Cryst.* A33, 456–465.  
 OLOVSSON, I. (1978). *Crystal Forces and Hydrogen Bonding. Effect on Charge Density*. Laboratoire de Cristallographie, CNRS, Grenoble.  
 ROOTHAAN, C. C. J. (1951). *Rev. Mod. Phys.* 23, 69–89.  
 RUYSINK, A. F. J. & VOS, A. (1974*a*). *Acta Cryst.* A30, 497–502.  
 RUYSINK, A. F. J. & VOS, A. (1974*b*). *Acta Cryst.* A30, 503–506.  
 WAL, H. R. VAN DER & VOS, A. (1979). *Acta Cryst.* B35, 1793–1804.  
 YAMABE, S. & MOROKUMA, K. (1975). *J. Am. Chem. Soc.* 97, 4458–4465.

double and triple bonds, an evaluation of the results should be attempted. Accurate X-ray diffraction intensities have been measured for ethylene (van Nes & Vos, 1979), acetylene (van Nes & van Bolhuis, 1979) and for the compounds II.  $\frac{1}{2}$ H<sub>2</sub>O (van der Wal, 1979; van der Wal & Vos, 1979*a,b*) and III (Helmholdt & Vos, 1977).

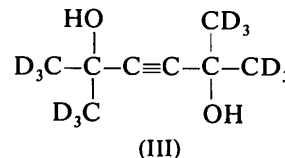
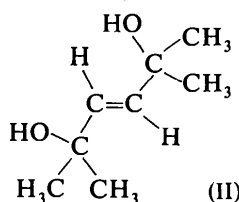


Table 1. *Experimental and theoretical values for the bonding maxima ( $e \text{ \AA}^{-3}$ ) at C-C single, double and triple bonds (see text)*

Compound	Experiment				Theory								
	II	III	C <sub>2</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>2</sub>	IIS	IIIS	C <sub>2</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>2</sub>	C <sub>2</sub> H <sub>2</sub>	C <sub>2</sub> H <sub>2</sub>
<i>T</i> (K)	86	90	85	141									
$\sin \theta(\text{exp})/\lambda$ ( $\text{\AA}^{-1}$ )	1.09	1.00	1.07	0.80									
$\sin \theta(\text{res})/\lambda$ ( $\text{\AA}^{-1}$ )	0.65	0.65	1.07	0.80									
$\langle U_{ii} \rangle$ ( $\text{\AA}^2$ )	0.011	0.016	0.036	0.051	0.011	0.014	0	0.011	0.036	0.030	0	0.013	0.051
Type of map	HO'	HO	<i>M</i> : <i>Z</i> / <i>P</i>	<i>M</i> : <i>Z</i> / <i>P</i>									
Basis set					semi	small	ext.	ext.	ext.	small	ext.	ext.	ext.
C( <i>sp</i> <sup>3</sup> )-C( <i>sp</i> <sup>3</sup> )	0.43	0.34											
C( <i>sp</i> <sup>2</sup> )-C( <i>sp</i> <sup>3</sup> )	0.49				0.49								
C( <i>sp</i> )-C( <i>sp</i> <sup>3</sup> )		0.37			0.35								
C=C	0.59		0.42/0.54		0.60		0.77	0.65	0.48	0.42			
C≡C		0.58		0.60/0.77		0.62					0.80	0.70	0.56

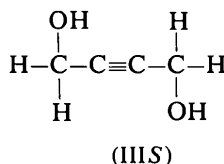
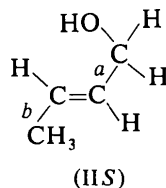
Experimental and theoretical data are listed in Table 1. Maximum  $\sin \theta/\lambda$  values of the experiment are given as  $\sin \theta(\text{exp})/\lambda$ . The resolution of the maps is determined by the maximum  $\sin \theta/\lambda$  values of the reflections on which they are based, given by  $\sin \theta(\text{res})/\lambda$ . As a measure of the thermal smearing the  $\langle U_{ii} \rangle$  values are listed.

The experimental deformation densities for II and III, given in the table, are calculated from

$$D(\mathbf{r}) = K^{-1} \rho_o(\mathbf{r}) - \rho_c(\text{atoms}; \mathbf{r}).$$

For III the scale factor and the overall thermal motion correspond to the full-angle range, while the further parameters (anisotropic thermal motion, positions) are from a HO refinement ( $\sin \theta/\lambda > 0.70 \text{ \AA}^{-1}$ ). This is indicated as HO' in the table. For III all parameters are from the HO refinement ( $\sin \theta/\lambda > 0.65 \text{ \AA}^{-1}$ ). The experimental deformation densities for C<sub>2</sub>H<sub>2</sub> and C<sub>2</sub>H<sub>4</sub> are from multipole maps (*M* maps; van Nes & van Bolhuis, 1979). *Z* and *P* stand for the radial functions used. For *Z* it is the usual single exponential ( $\zeta$ ) function with adjustable  $\zeta$ ; *P* denotes radial functions derived from SCF(<sup>3</sup>*P*) wave functions for C, and the use of polarized H atoms (Stewart, Bentley & Goodman, 1975).

The *ab initio* quantum theoretical calculations for II and III have been made for smaller model molecules, IIS and IIIS respectively.



An extended (10,6,2/5,2) GTO basis set was applied for C<sub>2</sub>H<sub>2</sub> and C<sub>2</sub>H<sub>4</sub>, a semi-extended (9,5,1/5,2) set for IIS and a small (6,3/3) set for IIIS and C<sub>2</sub>H<sub>4</sub>.

In the table only the values of the deformation-density maxima at the C-C bonds are given. The experimental values close to the atomic positions tend to be unreliable, mainly due to errors in the scale factor and overall thermal motion. In this respect it is noticeable that for II,  $\frac{1}{2}\text{H}_2\text{O}$  also at the atomic positions the  $D(\text{HO}'; \mathbf{r})$  values show remarkably good agreement with theory, if a correction of  $-0.25 e \text{ \AA}^{-3}$  for finite resolution (deduced from a theoretical study on C<sub>2</sub>H<sub>2</sub>) is applied. Theoretical values for the C atoms of bond (a) in IIS with corrected experimental values in parentheses are  $-0.44$  ( $-0.41$ ) and  $-0.53$  ( $-0.52$ )  $e \text{ \AA}^{-3}$  (van der Wal & Vos, 1979b).

Consideration of the table and the above information gives rise to the following points:

(1) The theoretical values for the C=C bond maxima in IIS and in C<sub>2</sub>H<sub>4</sub>,  $\langle U_{ii} \rangle = 0.011 \text{ \AA}^2$ , differ by  $0.05 e \text{ \AA}^{-3}$ . A difference also occurs for the bonds (a) and (b) in IIS, where for (a) the bonding maximum is  $0.49 e \text{ \AA}^{-3}$  and for (b)  $0.41 e \text{ \AA}^{-3}$ . This shows that for one bond type, bond maxima are not transferable from one bond to another.

(2) The theoretical static and dynamic data for C<sub>2</sub>H<sub>2</sub> and C<sub>2</sub>H<sub>4</sub> show that the thermal smearing corresponding to  $\langle U_{ii} \rangle \simeq 0.012 \text{ \AA}^2$  decreases the C-C bonding maxima by  $0.10 e \text{ \AA}^{-3}$  for C<sub>2</sub>H<sub>2</sub> and  $0.12 e \text{ \AA}^{-3}$  for C<sub>2</sub>H<sub>4</sub>, while a much larger decrease is obtained for a smearing based on the larger experimental thermal parameters. The influence of smearing on bonding maxima can thus not be neglected, especially for cases where the thermal motion is considerable.

(3) Comparison of experiment and theory reveals that the experimental values for II show good agreement with the theoretical values for IIS (the part of the molecule containing the O atom is taken for the comparison). For the bonding maxima of III there is also good agreement with theory, but both experimental and theoretical values are lower than for II because: (a) in III the thermal smearing is larger than

in II; (b) for III both theoretical and experimental maxima are too low because of systematic errors. For the *theory* this is due to the small basis set, as may be seen by comparing the dynamic values for  $C_2H_4$  with  $\langle U_{ii} \rangle = 0.036$  and the extended basis with those for  $\langle U_{ii} \rangle = 0.030 \text{ \AA}^2$  and the small basis. The *experimental* values tend to be lower than those for II, since for III very high-order reflections have a smaller intensity than for II, thus reducing the high-order character of the refinement. Consequently especially in III bonding effects are partly compensated by errors in the structural parameters. From this comes the warning that agreement between theory and experiment does not necessarily imply that both experiment and theory are correct.

(4) The experimental  $C_2H_2$  and  $C_2H_4$  data show that the maxima in the  $M$  maps depend strongly on the type of radial function used. For II this effect is much smaller, because of the larger reflection range available; in this case the  $M$  map gives a maximum of  $0.59 \text{ e \AA}^{-3}$  for  $C=C$  for  $P$ , and a maximum of  $0.57 \text{ e \AA}^{-3}$  for  $Z$  (van der Wal & Vos, 1979b).

(5) With due account of the fact that the bonding maxima found for III are too low [see (3)], the experimental results for II and III show that, as expected, the bonding maxima increase in the order  $C-C < C=C < C\equiv C$ . For single  $C-C$  bonds the maxima for  $C(sp^3)-C(sp^3)$  tend to be lower than for  $C(sp^2)-C(sp^2)$  and  $C(sp)-C(sp^3)$ .

### Conclusions and prospects

The results obtained so far lead to the following conclusions:

(1) Detection of small differences (of the order of  $0.05 \text{ e \AA}^{-3}$ ) between bonding maxima is easier to achieve within one crystal than for molecules in different crystals. In the latter case care should be taken that the experimental data are measured and worked out in the same way. Experimental precautions have been discussed by van der Wal (1979).

(2) Correct evaluation of the experimental data becomes increasingly difficult with increasing thermal motion. When possible, compounds with small thermal motion should be selected and/or the temperatures should be kept as low as possible.

(3) If only X-ray data are available, full-angle multipole refinements do not give correct values for the scale  $K$ . When the region of moderately strong reflections is restricted due to large thermal motion, correct determination of the scale factor  $K$  is hampered by correlation between  $K$ ,  $U_{ii}$ , the populations and the type of radial function used (van Nes & van Bolhuis, 1979). If a sufficient number of moderately strong high-order reflections are available, scale and overall thermal motion are adjusted predominantly to the high-order

range (van der Wal & Vos, 1979a). In this case these quantities are influenced by systematic errors due to thermal diffuse scattering and possible errors in the intensities due to an incorrect choice of the profile-analysis method (van der Wal, de Boer & Vos, 1979). The close agreement between theory and experiment for the  $D(HO', \mathbf{r})$  values of  $II. \frac{1}{2}H_2O$  shows that the mixed high-order-full-angle refinement procedure has worked well for this compound. The analysis of the X-ray data can be improved by correction for systematic errors, application of better (flexible) radial functions in the multipole refinements and by combination of the multipole refinements with the high-order-full-angle procedure. Checks must be made by neutron diffraction studies and by direct accurate experimental determination of the scale, if possible to within 0.5%.

(4) The above comparisons of experiment with theory indicate that, for simple systems, theoretical errors in bonding maxima due to the use of a small basis set are of the same order as experimental errors due to systematic effects (it is assumed that random errors are kept small). In view of this, electron density studies are most promising for complicated systems for which no reliable quantum-theoretical calculations are available. An example of a more complicated situation is the hydrogen bonding discussed by van der Wal (1979) and by van der Wal & Vos (1979b).

The above remarks refer to electron density distributions. There are better prospects for the mapping of the electric-potential function  $V(\mathbf{r})$  or of electric forces  $F(\mathbf{r})$  (Stewart, 1977). In comparison with the Fourier amplitudes  $F(\mathbf{H})$  of density maps, for  $V(\mathbf{r})$  and  $F(\mathbf{r})$  maps, the amplitudes (which still need to be on the correct absolute scale) are reduced in weight for the high-order reflections. For  $V(\mathbf{r})$  maps the amplitudes  $F(\mathbf{H})$  are multiplied by  $(\sin \theta/\lambda)^{-2}$  and for  $F(\mathbf{r})$  maps by  $(\sin \theta/\lambda)^{-1}$ . Electric-field gradients, on the other hand, again require unmodified  $F(\mathbf{H})$  amplitudes in the Fourier series in addition to associated Legendre functions for the directional dependence. The advantages of the mapping of  $V(\mathbf{r})$  and  $F(\mathbf{r})$  show that further attention should be paid to the deduction of physical properties from diffraction data.

Part of the work has been supported by the Foundation for Fundamental Research of Matter with X-rays and Electron Rays (FOMRE) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

### References

- HELMHOLDT, R. B. & VOS, A. (1977). *Acta Cryst.* **A33**, 456-465.  
 NES, G. J. H. VAN & VAN BOLHUIS, F. (1979). *Acta Cryst.*  
 To be published.

NES, G. J. H. VAN & VOS, A. (1979). *Acta Cryst.* To be published.  
 STEWART, R. F. (1977). *Isr. J. Chem.* **16**, 124–131.  
 STEWART, R. F., BENTLEY, J. & GOODMAN, B. (1975). *J. Chem. Phys.* **63**, 3786–3793.  
 WAL, H. R. VAN DER (1979). Thesis, Univ. of Groningen.

WAL, H. R. VAN DER, DE BOER, J. L. & VOS, A. (1979). *Acta Cryst.* **A35**, 685–688.  
 WAL, H. R. VAN DER & VOS, A. (1979a). *Acta Cryst.* **B35**, 1793–1804.  
 WAL, H. R. VAN DER & VOS, A. (1979b). *Acta Cryst.* **B35**, 1804–1809.

*Acta Cryst.* (1979). **B35**, 1812–1819

## Opiacés Peptidiques: Structure et Conformation de Deux Fragments d'Enképhalines, Tyr-Gly-Gly-Phe et Gly-Gly-Phe-Leu

PAR THIERRY PRANGÉ ET CLAUDINE PASCARD

*Laboratoire de Cristallogénie, Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif sur Yvette, France*

(Reçu le 23 octobre 1978, accepté le 23 avril 1979)

### Abstract

The crystal structures of two enkephalin fragments, Tyr-Gly-Gly-Phe (TGGP),  $C_{22}H_{26}N_4O_6$ , and Gly-Gly-Phe-Leu (GGPL),  $C_{19}H_{28}N_4O_5$ , have been determined by direct methods. TGGP is orthorhombic, space group  $P2_12_12_1$  with  $a = 12.912$  (4),  $b = 21.730$  (5),  $c = 10.760$  (4) Å,  $V = 3019.0$  Å<sup>3</sup>,  $D_x = 1.20$  Mg m<sup>-3</sup>,  $Z = 4$ ; GGPL is monoclinic, space group  $P2_1$  with  $a = 9.110$  (3),  $b = 6.200$  (2),  $c = 19.760$  (4) Å,  $\beta = 102.6$  (1)°,  $V = 1089.9$  Å<sup>3</sup>,  $D_x = 1.25$  Mg m<sup>-3</sup> and  $Z = 2$ . Refinements with least-squares methods led to  $R = 8.2\%$  with 2396 reflections (TGGP) and  $R = 7.3\%$  with 1719 reflections (GGPL) [ $I > 2\sigma(I)$ ]. The conformations of the chains are rather different; TGGP undergoes a  $GG\beta$  turn, while GGPL exhibits mainly a bent conformation without intramolecular head-to-tail interaction. These structural features are compared to those of Leu-enkephalin and discussed in terms of possible conformational influence on the biological response for the peptide.

La découverte de petits peptides responsables d'une puissante activité analgésique, de type morphinique, dans le cerveau des mammifères (Hughes, Smith, Kosterlitz, Fothergill, Morgan & Morris, 1975), a soulevé un intérêt considérable quant à leur utilisation potentielle en thérapeutique humaine. Cependant, si ces espoirs ont été rapidement déçus,\* l'intérêt pour les études structurales des sites récepteurs des dérivés opiacés a rebondi. Il s'agit en effet de toute une famille

\* A cause du phénomène d'accoutumance que l'on aurait pu croire absent, du fait de la nature endogénique des produits.

de substances dont il est possible de faire varier la composition, suivant les possibilités de la synthèse peptidique, et de comparer leur pouvoir morphinique, afin de préciser la nature et la topologie de ces sites récepteurs. Ainsi, depuis la découverte des deux pentapeptides responsables de l'activité endogénique, Tyr-Gly-Gly-Phe-Met ('Met-Enk') et Tyr-Gly-Gly-Phe-Leu ('Leu-Enk'), de nombreux dérivés ont été obtenus (Bajusz, Ronai, Szekely, Dunai-Kovacs & Graf, 1976; Terenius, Wahlström, Lindberg, Karlsson & Ragnarsson, 1976; Morgan, Smith, Waterfield, Hughes & Kosterlitz, 1976; Dulla, Gormley, Hayward, Morlay, Shaw, Stacey & Turnbull, 1977). Ils ont permis de dégager, pour le maintien de l'activité, les principaux caractères suivants:

– La Tyr<sup>1</sup>, amino acide N-terminal, est essentielle, ainsi que le résidu Gly<sup>3</sup>.

– L'acide aminé C-terminal (Leu<sup>5</sup> ou Met<sup>5</sup>) est assez peu sélectif, mais son élimination entraîne une perte importante de l'activité.

– Le remplacement du résidu Gly<sup>2</sup> par un autre amino acide peut induire une augmentation notable de son pouvoir analgésique, surtout s'il s'agit d'un résidu D qui entraîne un surcroît de résistance aux peptidases (Pert, Pert, Chang & Fong, 1976; Hambrook, Morgan, Rance & Smith, 1976; Yamashiro, Tseng, Doneen, Loh & Li, 1977; Walker, Berntson, Sandman, Coy, Schally & Kastin, 1977).

– La modification du quatrième résidu (Phe) n'est pas très importante, tant que l'on respecte le stéréomimétisme (groupe N-benzyle...); l'activité disparaît rapidement dans les autres cas.

L'analyse de ces relations mène à faire plusieurs remarques: (1) La présence des deux phényles est primordiale (ceci rejoint les conclusions structurales de