Amino Acids (1995) 8: 271–289

Amino
Acids

Ab-initio SCF investigation of γ-aminobutyric acid

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Accepted October 27, 1993

Summary. The potential energy surface of the neutral form of γ-aminobutyric acid was investigated by means of ab-initio 4-31G SCF calculations. Geometries, energies, and selected wave numbers of all 62 symmetry unique local minima are reported. Intramolecular interactions and all reactions, which involve the intramolecular hydrogen bond, are discussed and compared with those present in the homologues β-alanine and glycine.

Keywords: Amino acids – GABA, H-Bond – Intramolecular – Structure – Ab-initio

Abbreviations: GABA: γ-aminobutyric acid; PES: potential energy surface; RHF: Roothaan-Hartree-Fock; SCF: self consistent field.

Introduction

Amino acids are of interest to biological chemists as well as structure chemists. The interest of biological chemists is, of course, mainly oriented towards α-amino acids, although β- or γ-amino acids are biologically active too. GABA in particular is a neurotransmitter substance of widespread interest.

The interest of structure chemists in amino acids results from the fact, that amino acids form zwitterions $H_3N^{\oplus}-R-COO^{\ominus}$ in the solid state or in a polar environment. In gas phase or in matrix isolation, however, isolated molecules in the neutral form $H_2N-R-COOH$ are more stable. Whereas the solid state structure is easily accessible by X-ray methods, the investigation of isolated molecules is experimentally extremely difficult, since most amino acids decompose before melting. GABA is no exception: crystals of zwitterions $H_3N^{\oplus}-(CH_2)_3-COO^{\ominus}$ form the solid state (Jönsson and Kvick, 1972) which decompose at 203° C (Weast et al., 1985).

Quantum chemical calculations, which conceptually deal with isolated molecules, are therefore an important tool for structure investigations of the neutral

form of amino acids. The case of glycine (Suenram and Lovas, 1978; Sellers and Schäfer, 1978; Schäfer et al., 1980) has to be recalled in this context: the global minimum of the neutral glycine potential energy surface was first predicted by means of ab-initio calculations, and later detected experimentally with the help of the predicted rotation constants. Due to the biological importance of α-amino acids, quantum chemical work so far was mostly oriented towards these compounds. Compared to the numerous work which was, e.g., published on glycine (Vishveshwara and Pople, 1977; Clementi et al., 1977; Palla et al., 1980; Wright and Borkman, 1980; Förner et al., 1981; Voogd et al., 1981; Laurence and Thomson, 1981; Peters and Peters, 1981; Dykstra et al., 1981; Laurence and Thomson, 1982; Oie et al., 1982; Wright et al., 1982; Oie et al., 1983; Luke et al., 1984; Siam et al., 1984; Bonaccorsi et al., 1984; Tranter, 1985a, b; Sukumar and Segal, 1986; Masamura, 1987; Liegener et al., 1987; Alagona et al., 1988; Ramek, 1990a; Ramek et al., 1991; Jensen and Gordon, 1991; Ramek and Cheng, 1992; Ding and Krogh-Jespersen, 1992) almost nothing has been done on β-, γ-, or higher amino acids. GABA in particular appeared in ab-initio work so far only in supporting roles for comparison with other compounds. Fugler-Domenico et al. (1988) gave three conformations, which they reported to be energetically low and optimized in RHF calculations with the 6-31G basis set (Hehre et al., 1972). One other GABA conformer is given in a discussion of one aspect of the ab-initio study of ω-amino acids and related compounds, which was performed in our group in the last years (Ramek, 1990a).

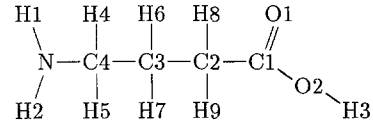
We have investigated the PES of neutral GABA in detail as part of this study and report the main results in this contribution.

Methods

The RHF formalism (Roothaan, 1951) and the 4-31G basis set (Ditchfield et al., 1971) were employed in all calculations for the reasons outlined previousely (Ramek, 1990b; Kelterer and Ramek, 1991). All conformers were fully optimized with the program GAMESS (Schmidt et al., 1990) to remaining maximum and root mean square gradients less than 5×10^{-4} and 1.67×10^{-4} H/Bohr, respectively. All local minima were verified to have positive eigenvalues of the Hessian matrix only. Due to the limitations on the computational facilities, which are available to the authors, the Hessian matrix had to be calculated by numerical differentiation of analytically computed gradients.

According to the conclusions which can be drawn from both, the correlation influence on the results of glycine and N-formyl alanine amide (Frey et al., 1992) and the basis set dependence of the glycine SCF results (Ramek and Cheng, 1992), the structures obtained in this way are quite reliable. The energy differences, however, may change to some degree upon either basis set variation or the inclusion of electron correlation.

The following atom numbering will be used throughout.



Results

Local minima

According to the present study the PES of neutral GABA contains a total of 122 local minima. Two of these minima have C_S symmetry, the other form 60 pairs of mutually mirror symmetrical conformers of C_1 symmetry. In accordance to earlier work the condition of a positive value of the dihedral angle C–C–C–N was chosen as the criterion for symmetry uniqueness. This leads to 62 symmetry unique local minima, which are labelled **I**, **II**, etc. in the following. Whenever necessary, the mirror images of these conformers are denoted by the superscript "m". In addition, the PES of neutral GABA contains 4 pairs of mutually mirror symmetrical stationary points of inflexion, which are labelled **LXIII–LXVI**. Such stationary points of inflexion may be considered as special cases of local minima, namely ones without an energy barrier in one reaction path (Mezey,

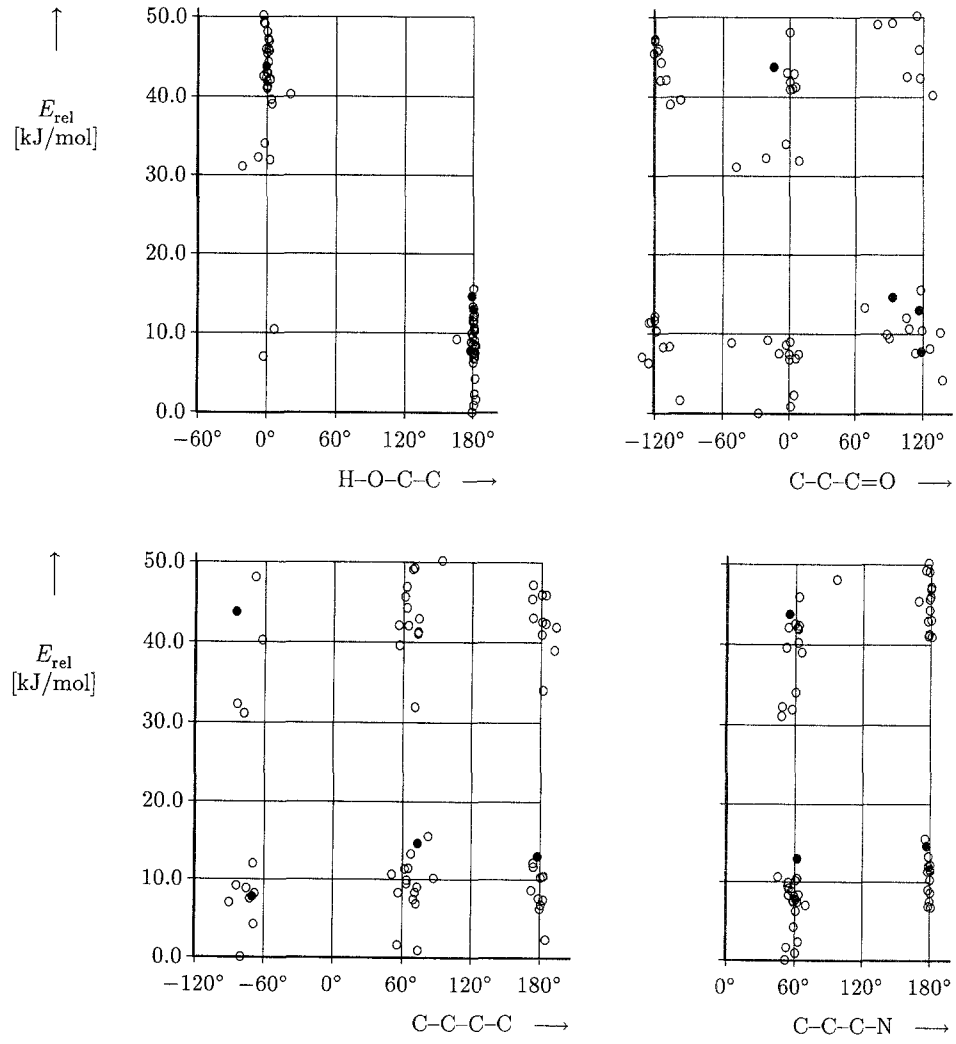


Fig. 1. The relative energy of all local minima (o) and stationary points of inflexion (•) as a function of the dihedral angles of the molecular backbone N–C–C–C–COOH

1987). In the GABA conformers discussed here this reaction path is the internal rotation of the $-NH_2$ group (**LXIII**, **LXIV**) or the internal rotation of the –COOH group (**LXV**, **LXVI**).

A complete list of the geometry data (bond lengths, valence and torsion angles) of all symmetry unique local minima and stationary points of inflexion, which includes the calculated vibration wave numbers, rotational constants, and vibrational zero point energies, is available from the authors upon request.

Figure 1 shows the relative energy of all symmetry unique local minima and stationary points of inflexion in correlation to the various dihedral angles of the nuclear backbone N–C–C–C–COOH. These displays indicate two standard values for the dihedral angle H–O–C–C and three standard values for the dihedral angles C–C–C–N, C–C–C–C, and C–C–C=O. Only minor deviations occur from the values 0° and 180° for H–O–C–C and from the values +60° and 180° for C–C–C–N. (C–C–C–N $\approx -60°$ is excluded by the criterion for symmetry uniqueness.) For the dihedral angles C–C–C–C and C–C–C=O the pattern is significantly different: the deviations from the mean values −75°, 66°, and 179° for C–C–C–C are considerable, and for C–C–C=O the scatter is so large that for some minima the assignment to one of the (ideal) values −120°, 0°, and 120° is almost arbitrary. The various positions of the amino group are indicated in Fig. 2. Roughly three "standard" orientations may be distinguished: −160°/70°, −80°/70°, and −80°/140°, with considerable scatter in the orientation of the amino group relative to the carbon chain, but at the same time remarkable constant H–N–H angles. Fig. 3 displays a scheme, which categorizes all symmetry unique local minima and stationary points of inflexion with respect to the dihedral angles of the molecular backbone.

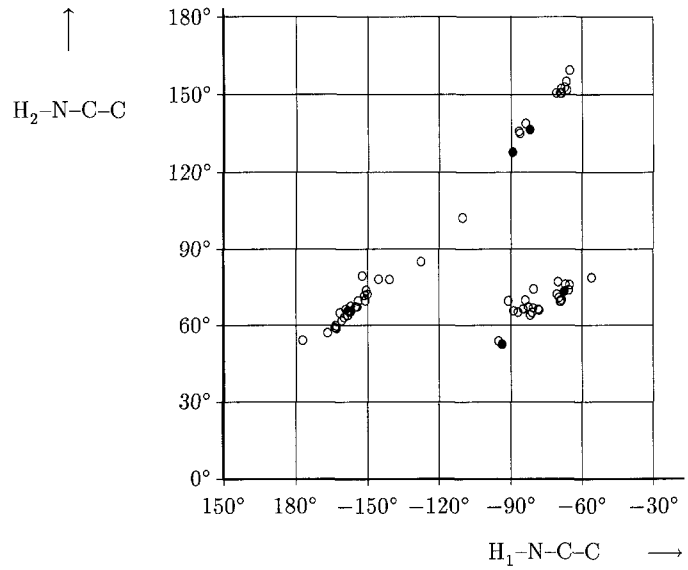


Fig. 2. Plotting the two dihedral angles H–N–C–C of all local minima (o) and stationary points of inflexion (●) in the GABA PES versus each other shows that roughly three different orientations of the $-NH_2$ group occur: 70°/−160°, 70°/−80°, and 140°/−80°. One conformation (**XLI**, H2–N–C–C/H1–N–C–C = −110.45°/102.14°) cannot be assigned to any of these three "standard" orientations

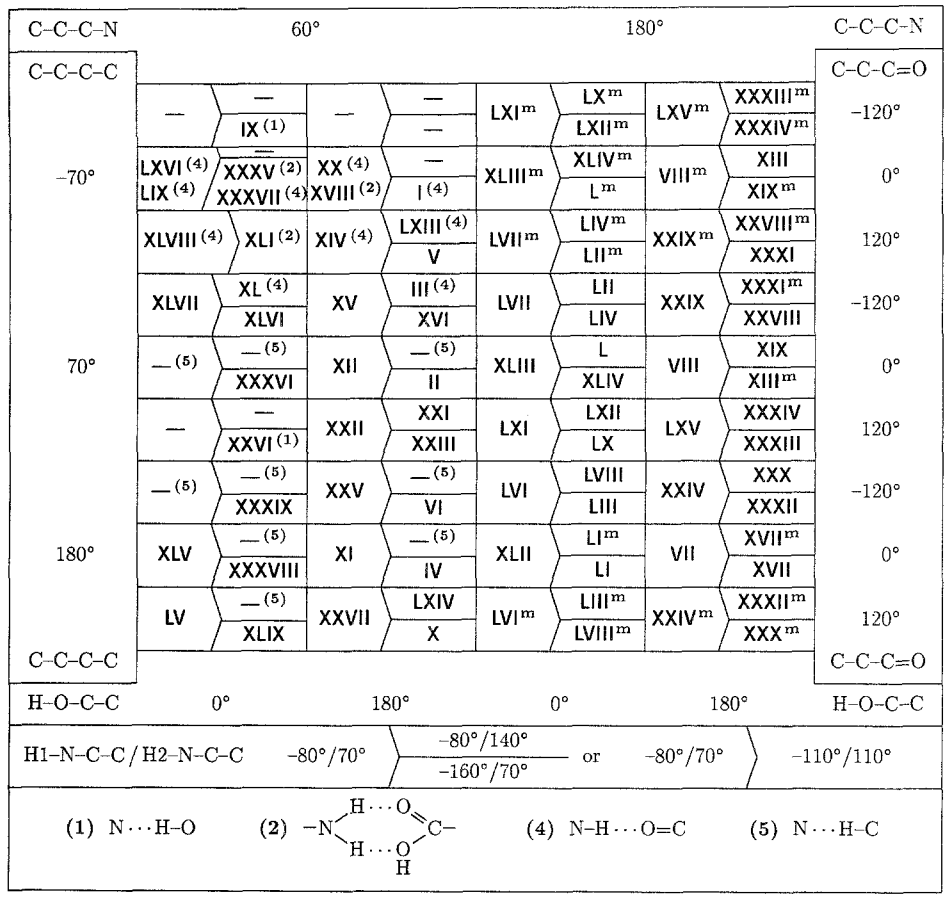


Fig. 3. The local minima in the PES of neutral GABA may be classified according to their dihedral angles. All vacancies are due to intramolecular interactions

The global minimum of the PES of neutral GABA (**I**) reflects this behaviour: the value of the dihedral angle H–O–C–C is 178.6°, the C–C–C–N value is 51.8°, the C–C–C–C value is −80.4°, and the C–C–C=O value is −27.9°. The values of the dihedral angles H1–N–C–C and H2–N–C–C are −163.43° and 59.84°. The exact geometry of this conformer is shown in Fig. 4.

Several other local minima with low energies are present in the PES of neutral GABA: **II** (E_{rel} = 0.84 kJ/mol), **III** (E_{rel} = 1.57 kJ/mol), **IV** (E_{rel} = 2.26 kJ/mol), and **V** (E_{rel} = 4.20 kJ/mol). Except for the syn-clinal orientation of the N–C–C–C fragment and the syn-periplanar orientation of the groups C=O and O–H these conformers do not show specific regularities. If zero point corrected energies are considered, the conformers **I–IV** are almost equal in energy: $E_{ZP,I}$ = 387.595 kJ/mol, $(E_{rel} + E_{ZP})_{II}$ = 387.312 kJ/mol, $(E_{rel} + E_{ZP})_{III}$ = 387.977 kJ/mol, and $(E_{rel} + E_{ZP})_{IV}$ = 387.970 kJ/mol.

The intramolecular N···H–O hydrogen bond

Figure 1 allows the distinction of two sets of local minima: a low energy set (E_{rel} < 16 kJ/mol) and a high energy set (E_{rel} > 30 kJ/mol). Fig. 1 also shows

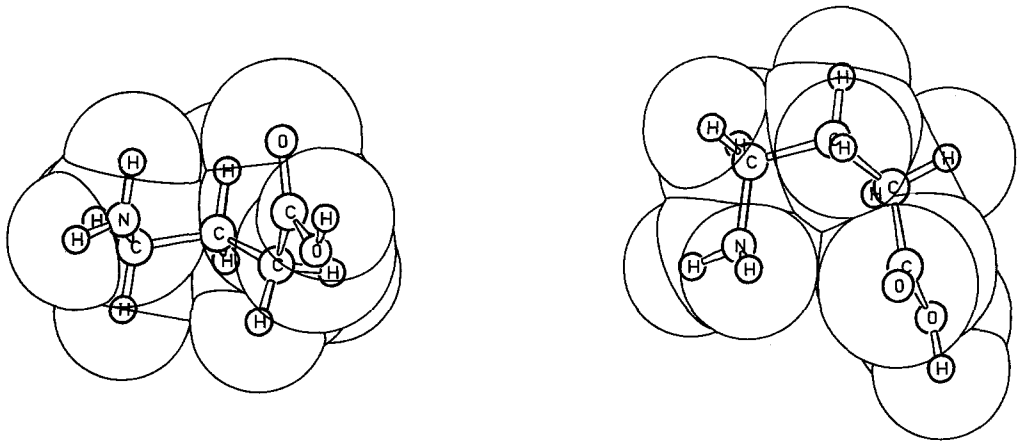


Fig. 4. Ball and stick model of the global minimum in the PES of neutral GABA overlayed with fused spheres of the corresponding van der Waals radii, seen from two different directions

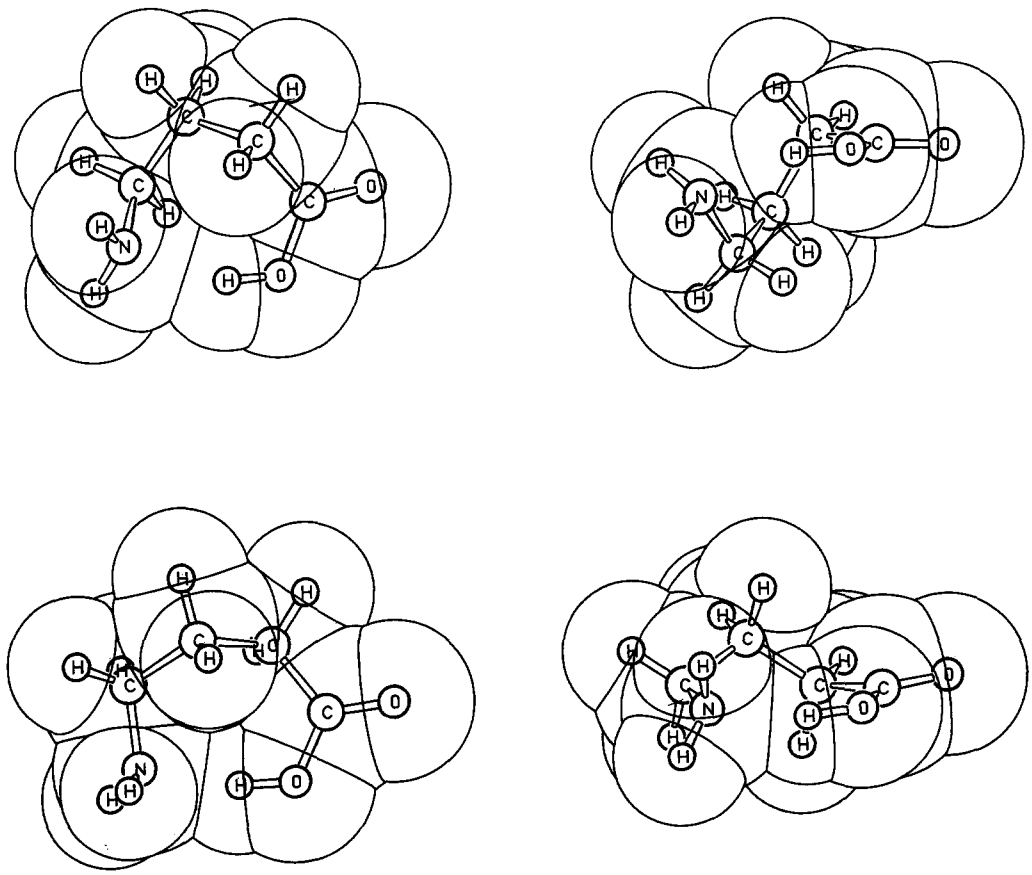


Fig. 5. Ball and stick models of the conformers **XXVI** (top) and **IX** (bottom) overlayed with fused spheres of the corresponding van der Waals radii, seen from two different directions. The N···H–O interaction is visualized by the strong overlap of the respective spheres

that these two sets correlate almost perfectly with the orientation of the –COOH group: all conformers with syn-periplanar orientation of the groups C=O and O–H are in the low energy set, and all but two conformers with anti-periplanar orientation are in the high energy set. The two conformers with low energy and anti-periplanar O=C–O–H orientation are **IX** and **XXVI**. Both of them exhibit a cyclic arrangement of the molecular backbone N–C–C–C–CO–O–H, in which the groups $-NH_2$ and –OH come close enough to form an intramolecular hydrogen bond N···H–O. In both cases a seven membered ring is formed which includes this hydrogen bond. In **IX** this ring is of the envelope type: the atoms N, C4, C2, and the COOH group are located in one (slightly distorted) common plane while the β-carbon atom C3 sticks out of this plane. The geometry of **XXVI** can be described similarily: most atoms of the molecular backbone lie in one distorted plane, but this time the β- and the γ-carbon atom (C3 and C4) stick out of this plane. **XXVI** may best be characterized as a distorted boat form. The exact geometries of **IX** and **XXVI** are depicted in Fig. 5.

The distance between the nitrogen atom and the carboxylic hydrogen atom is 1.765 Å in **IX** and 1.884 Å in **XXVI**. Both values are considerably smaller than the sum of the van der Waals radii, which is a criterion that is often used for hydrogen bonds (Hasenein and Hinchliffe, 1990). The presence of an intramolecular hydrogen bond N···H–O in **IX** and **XXVI** is also confirmed by the significant weakening of the O–H bond in both conformers, which is visualized by the data shown in Fig. 6. The lesser stability of the H-bond in **XXVI**, which

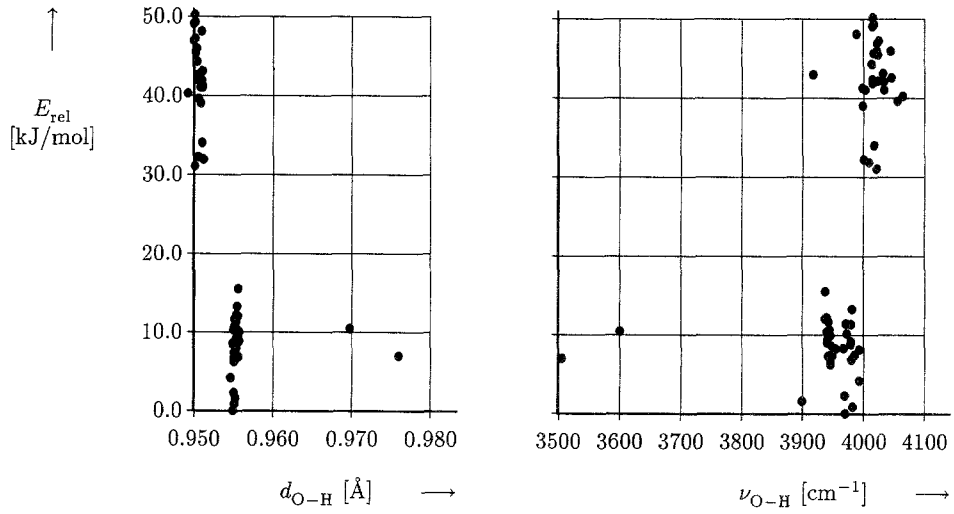


Fig. 6. The O–H bond length is considerably increased in the two conformers **IX** and **XXVI**. The values of the calculated vibration frequency show a matching decrease of more than 300 cm^{-1}, which is typical for hydrogen atoms that are involved in hydrogen bonds. Both sets of data indicate that the H-bond in **IX** is stronger than that in **XXVI**. Furthermore, the data of the remaining local minima (•) show remarkable constant values of the O–H bond length in the low energy set but a significant reduction of approximately 40 cm^{-1} for the O–H frequencies of some of these conformers. In most cases this discrepancy is caused by intramolecular C–H···OH interactions

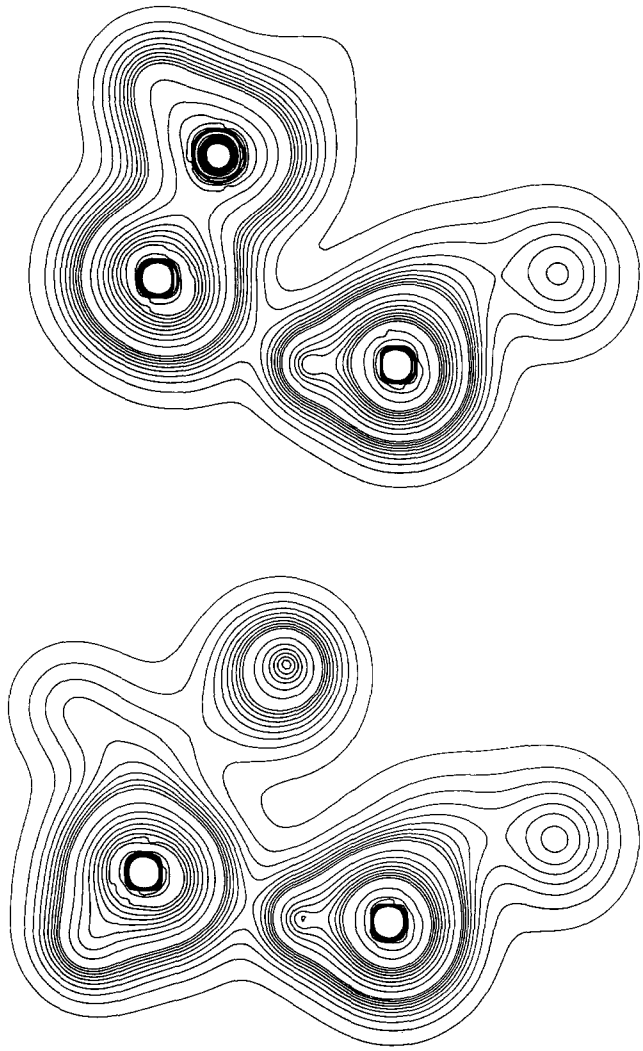
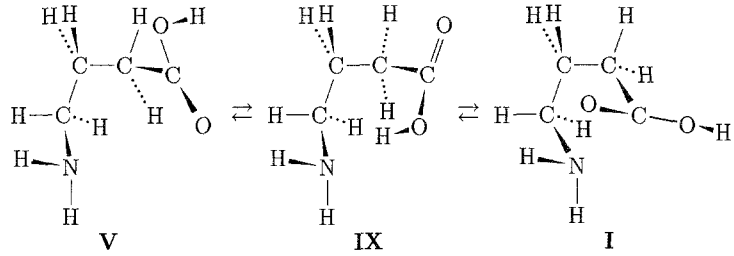


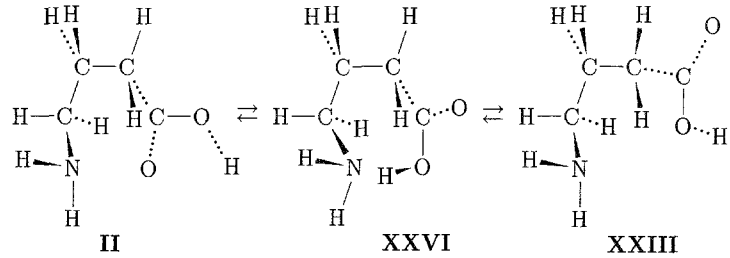
Fig. 7. Contour maps of the electron density along the intramolecular N···H–O hydrogen bond in **XXVI** (top) and **IX** (bottom). Both maps show the plane defined by the fragment $N\cdots H-O$ (in approximately this orientation). Contour lines are drawn for the electron density values 0.01, 0.02, .., 0.10, 0.15, 0.20, ..., 0.50, 0.75, 1.00, ..., 2.75. The distorted contour lines for high electron densities are an artefact of the curve fitting algorithm, which is based on previousely calculated values on a regular grid (Kurnig, 1983)

is indicated by these data, is verified by the stationary point in the electron density along the N···H connection line of both conformers as shown in Fig. 7. It is also reflected by the energies ($E_{\text{rel, IX}} = 6.690$ kJ/mol and $E_{\text{rel, XXVI}} = 10.425$ kJ/mol), by the angle N···H–O (which is 165.0° in **IX** and 151.4° in **XXVI**), and also by the fact that all conformers with a N–C–C–C–COO arrangement similar to the one present in **IX** collapse to **IX**, while there are three stable local minima (**XXII**, **XXI**, and **XXIII**) which have a heavy atom framework similar to the one present in **XXVI** but different orientations of the groups –OH and $-NH_2$.

Similar to the hydrogen bonds, which are present in the previously studied systems (Ramek, 1990b; Kelterer et al., 1992), the intramolecular H-bonds combine the internal rotations of the groups –OH and –COOH in the reaction paths **V** ⇌ **IX** ⇌ **I** and **II** ⇌ **XXVI** ⇌ **XXIII**.

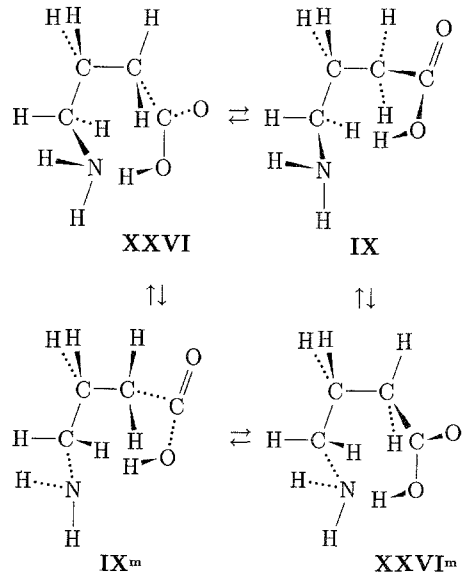


V **IX** **I**



II **XXVI** **XXIII**

In addition there is a reaction path **XXVI** ⇌ **IX** ⇌ **XXVI**^{m} ⇌ **IX**^{m} ⇌ **XXVI** which connects all local minima that contain the intramolecular hydrogen bond N···H–O. Starting from **XXVI**, it is induced by an increase of the dihedral angle C–C–C=O which combines the internal rotations of the two CH_2–CH_2 bonds and the counter-clockwise rotation of the $-NH_2$ group. The hydrogen bond is preserved along this reaction cycle: the N···H length is 1.743 Å in the transition state **XXVI** ⇌ **IX** and 1.778 Å in the transition state **IX** ⇌ **XXVI**^{m}.



XXVI **IX**

IX^{m} **XXVI**^{m}

Table 1. Relative energies (kJ/mol) and attractive intramolecular interactions (Å) for all symmetry unique local minima in the PES of neutral GABA. The absolute energy of conformer **I** is −360.3670756 Hartree

Conformer	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
Energy	0.000	0.840	1.571	2.263	4.197	6.207	6.734	6.849
O1–H1	2.6306							
O2–H1					2.9214			
O1–H2			2.6969					
H8–N						2.6256		
H9–N	2.9812	2.5776	2.6519	2.6206				
O1–H4								2.6438
O1–H5		2.6290	2.9407					
O1–H6	2.5400			2.7182			2.7825	
O2–H6					2.5428	2.5781		
O1–H7		2.6896		2.8722			2.7825	2.6906
O2–H7			2.9247					

Conformer	**IX**	**X**	**XI**	**XII**	**XIII**	**XIV**	**XV**	**XVI**
Energy	6.960	7.281	7.382	7.398	7.473	8.132	8.273	8.290
N–H3	1.7645							
O1–H2						2.8056		
H9–N		2.6308	2.7588	2.7249			2.7670	2.6170
O1–H5				2.6390	2.7100			2.9356
O1–H6			2.7721					
O2–H6	2.9687	2.6700				2.5928		
O1–H7			2.8207	2.7123	2.6668			
O2–H7							2.7077	2.7015

Conformer	**XVII**	**XVIII**	**XIX**	**XX**	**XXI**	**XXII**	**XXIII**	**XXIV**
Energy	8.604	8.808	8.969	9.161	9.428	9.905	10.157	10.272
O1–H1				2.7555				
O2–H2		2.8320			2.6576	2.6765		
H9–N					2.6423	2.7494	2.5149	
O1–H4			2.6288					
O2–H5					2.7707	2.7632	2.4577	
O1–H6	2.9468	2.6785		2.5290				
O2–H6								2.6192
O1–H7	2.6891		2.7119					
O2–H7							2.8675	

Conformer	**XXV**	**XXVI**	**XXVII**	**XXVIII**	**XXIX**	**XXX**	**XXXI**	**XXXII**
Energy	10.393	10.425	10.654	11.352	11.435	11.640	11.995	12.152
H3–N		1.8836						
H9–N	2.7436	2.7607	2.7641					
O1–H5							2.9636	
O2–H5		2.6764						
O2–H6					2.6289	2.6881	2.7570	2.7169
O2–H7	2.6187		2.6537	2.6220				

Table 1 (continued)

Conformer	XXXIII	XXXIV	XXXV	XXXVI	XXXVII	XXXVIII	XXXIX
Energy	13.245	15.499	31.019	31.913	32.231	34.017	39.022
O1–H1			2.8387		2.5457		
H8–N			2.9579				
H9–N				2.5507	2.8548	2.5956	2.5817
O2–H4	2.9390	2.5259					
O1–H5				2.5991			
O1–H6			2.5540		2.4610	2.7705	
O2–H6							2.7676
O1–H7	2.8395			2.6687		2.7705	

Conformer	XL	XLI	XLII	XLIII	XLIV	XLV	XLVI	XLVII	XLVIII
Energy	39.604	40.239	40.987	41.059	41.277	41.902	42.048	42.117	42.370
O1–H2	2.6663	2.9824						2.9094	2.6461
H9–N	2.6093					2.7439	2.6257	2.7395	
O1–H4				2.6164	2.6717				
O1–H5	2.9288								
O1–H6			2.7530			2.7351			
O2–H6		2.8331							
O1–H7			2.7530	2.6674	2.6677	2.7904			
O2–H7	2.9967						2.7868	2.8691	2.7619

Conformer	XLIX	L	LI	LII	LIII	LIV	LV	LVI
Energy	42.567	42.930	43.072	44.296	45.418	45.681	45.942	45.961
H9–N	2.6393						2.7600	
O1–H4		2.6379						
O1–H6			2.9111					
O2–H6					2.8368			2.7678
O1–H7		2.6551	2.6642					
O2–H7	2.8543			2.8103		2.7845	2.7921	

Conformer	LVII	LVIII	LIX	LX	LXI	LXII
Energy	46.944	47.193	48.105	49.099	49.263	50.181
O1–H2			2.2544			
O2–H4				2.7909	2.7252	2.7041
O1–H6			2.8035			
O2–H6		2.8115				
O1–H7				2.9149		
O2–H7	2.7584					

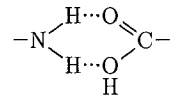
Other intramolecular interactions

Various intramolecular interactions are present in the PES of neutral GABA besides the intramolecular hydrogen bond N···H–O. The strongest of these interactions occurs in the syn-periplanar orientation of the groups C=O and O–H. It causes the separation of a low energy set and a high energy set of local minima by a gap of more than 15 kJ/mol, which has already been mentioned. The interaction of these groups is of electrostatic origin, as recently discussed in detail for the GABA homologue β-alanine (Ramek et al., 1992). Comparison of otherwise identical conformations (e.g., **VII** and **XLII**) allows to estimate the stabilization due to this interaction as 34 ± 3 kJ/mol.

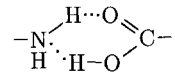
Attractive interactions N–H···O=C, N–H···OH, C–H···O=C, C–H···OH, N–H···H–C are present in practically every GABA conformer, as the data in Table 1 show. The unusual C–C–C–N angle in **LIX** (95.8°) should be noted explicitely as a consequence of the interaction N–H···O=C. In **XXVI** the interactions C2–H···N and C4–H···OH are in competition with the intramolecular hydrogen bond O–H···N, which is probably the most significant reason why the hydrogen bond in **XXVI** is weaker than in **IX**.

None of these interactions has an influence on bond lengths, but some of them have an influence on vibration frequencies (see Fig. 6). Inspection of the electron densities shows that only the N–H···O=C interaction in **LIX** has some H-bond character; this H-bond character is again in accordance with the criterion that the bond length has to be significantly less than the sum of the van der Waals radii: in **LIX** the H···O distance accounts to 86% of this sum.

Two noteworthy interactions between the amino group and the carboxy group can be figured out from the data collected in Fig. 1 and Fig. 2. The first of these is of the type



It occurs in **XVIII** and is responsible for the extreme value of the angle C–C–C=O (−52.0°). The other of these interactions is of the type



It occurs in **XXXV** and **XLI** and causes the extreme C–C–C=O angle in **XXXV** (−48.1°) and the unusual orientation of the groups $-NH_2$ and –COOH in **XLI**. Fig. 8 shows the exact geometries of these three conformers.

The scheme shown in Fig. 3 proved to be very helpful to detect all intramolecular interactions by pointing out all sets of conformers, in which the amino group is present only in one or two of the three typical orientations. In most cases this is due to the intramolecular interactions discussed above. In the

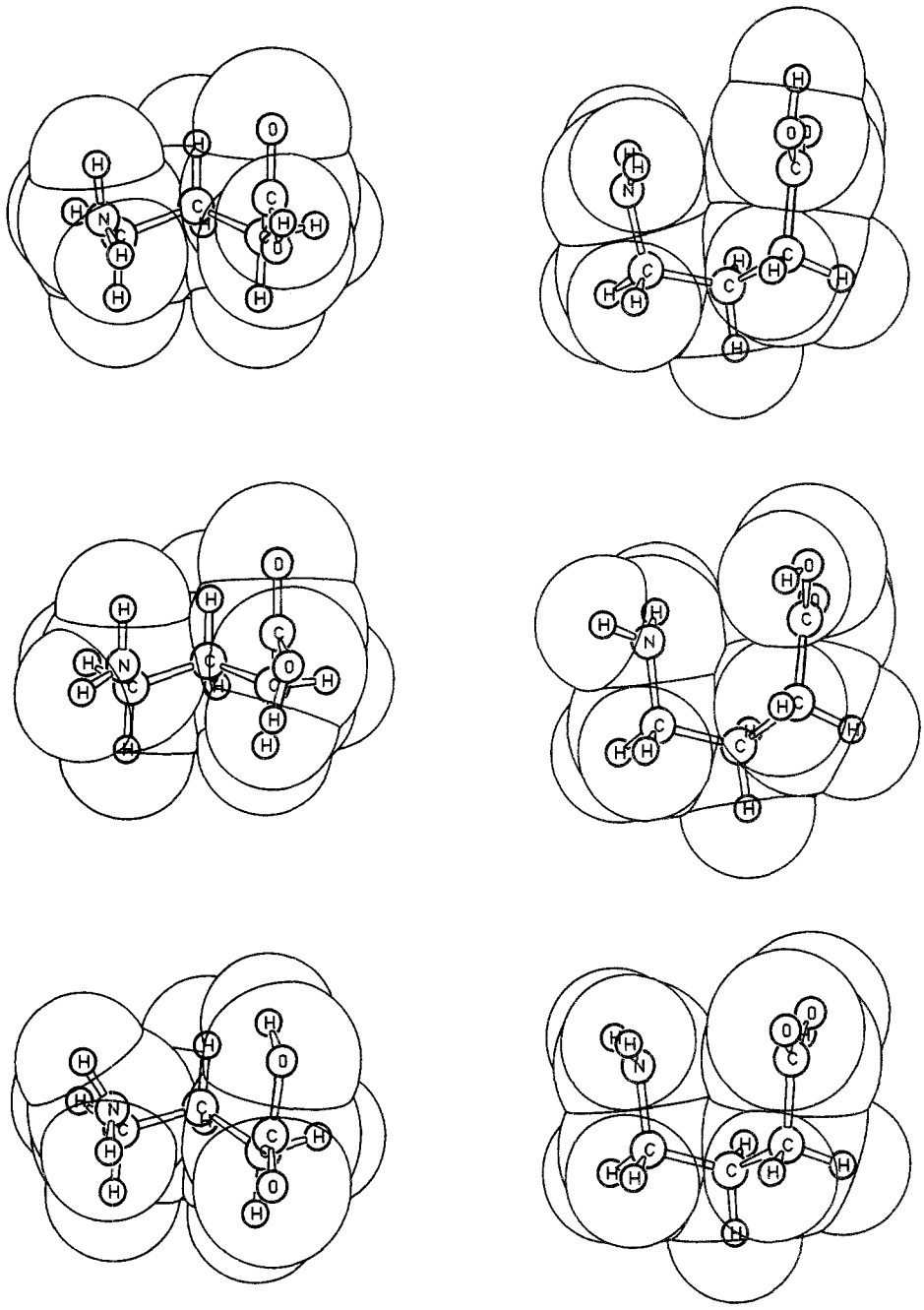


Fig. 8. Ball and stick models of the conformers **XVIII** (top), **XXXV** (middle), and **XLI** (bottom), overlayed with fused spheres of the corresponding van der Waals radii, seen from two different directions. All three of these conformers exhibit two electrostatic interactions between the groups $-NH_2$ and $-COOH$

following conformers, however, one or two orientations of the amino group are missing because of N···H–C related steric hinderings: **XXXVI**, **II/XII**, **XXXVIII/XLV**, **IV/XI**, **XXXIX**, **VI/XXV**, and **XLIX/LV**, **X/XXVII**. These

N···H–C related steric hinderings thus turn out to be a significant feature in the PES of GABA.

Discussion

Comparison with previous work on GABA

None of the three geometries, which were described by Fugler-Domenico et al. (1988) as RHF/6-31G optimized structures (labelled there **1a**, **1b**, and **1c**), could be correlated with any of the local minima described here. These three conformations were therefore reoptimized with the 6-31G basis set but free of the constraints imposed by Fugler-Domenico et al. Subsequent frequency calculations revealed that these conformations are transition states with the imaginary frequencies 35 i cm^{-1} (**1a**), 159 i cm^{-1} (**1b**), and 170 i cm^{-1} (**1c**), which are linked to the present work as follows: **1b** is the transition state of the reaction **IX** $\rightleftharpoons$ **XXVI**^{m}, which was discussed above; **1a** is the transition state **II** $\rightleftharpoons$ **XVI**, and **1c** is the mirror symmetrical transition state **XVII** $\rightleftharpoons$ **XVII**^{m}. Obviousely Fugler-Domenico et al. did not examine the eigenvalues of the Hessian matrix for any of their structures although such a check was a standard procedure highly recommended (Schlegel, 1987) at that time already.

Comparison with glycine and β-alanine

Figure 9 displays plots of the relative energy versus the dihedral angles of the molecular backbone for glycine; the corresponding plot for β-alanine is given in Fig. 4 of Ramek (1990b). Together with Fig. 1 these figures show that the GABA conformers are much more flexible than those of β-alanine or glycine. This parallels the influence of the ring size on the intramolecular hydrogen bond N···H–O, which has already been shown to increase in the series glycine,

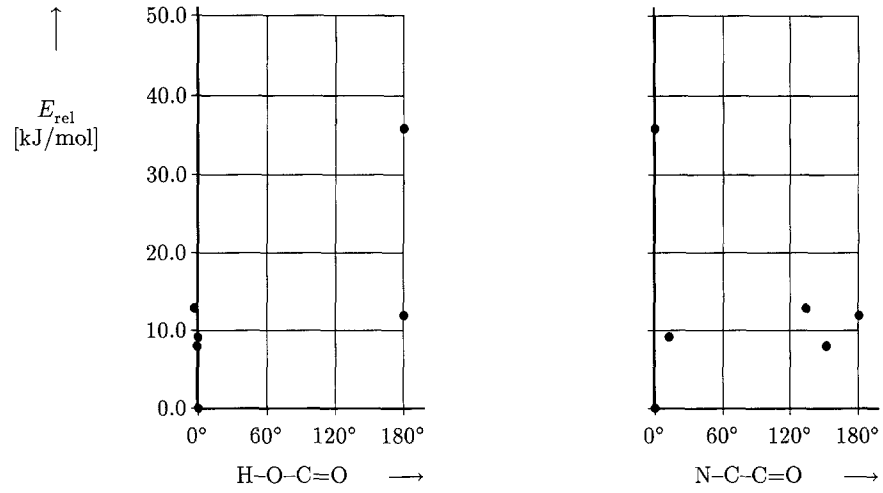


Fig. 9. The relative energies for all glycine conformers as a function of the dihedral angles of the molecular backbone N–C–COOH

β-alanine, and GABA (**IX**) according to the N···H and O–H distances and the O–H vibration frequencies (Ramek, 1990a). Hence the intramolecular H-bond in GABA is less constrained, and the stabilization due to this H-bond must be larger in GABA than in β-alanine.

It is interesting to compare this conclusion with the simple estimate for the H-bond stabilization based upon the energy differences between corresponding conformers in which the groups C=O and O–H are in syn-periplanar and in anti-periplanar orientation. This estimate is 34.8 ± 2.5 kJ/mol for β-alanine (Ramek, 1990b) but, opposed to the above conclusion, only 30.5 ± 4.3 kJ/mol for the GABA conformer **IX**. This contradiction must be attributed mainly to the greater flexibility of the GABA conformers, which, by allowing a large number of additional intramolecular interactions, causes this simple approach to fail.

In contrast, the analoguos estimates for the electrostatic interaction between the groups C=O and O–H in the syn-periplanar orientation are remarkably constant: 34.8 ± 2.5 kJ/mol for β-alanine and 34 ± 3 kJ/mol for GABA. This allows the conclusion that in this case the underlying interaction is confined to the –COOH group with only marginal influence on the rest of the molecule.

Considering the 4-31G optimized conformations with the intramolecular hydrogen bond N···H–O in the series glycine, β-alanine, and GABA, an inter-

Table 2. Final geometries and potential barriers E_a (kJ/mol) of all internal rotations starting from the two conformers with an intramolecular hydrogen bond N···H–O

Reaction	IX⇌	E_a	XXVI⇌	E_a
H–O–C–C decrease	**I**	30.91	**XXIII**	51.60
C–C–C=O increase	**XXXV**	24.09	**IX**	19.22
C–C–C–C decrease	**XXXIX**	32.20		
C–C–C–N increase	**LII^m**	43.97		
C–C–C–N decrease	**XXVI^m**	18.68	**IX^m**	15.21
H–N–C–C increase	**XXVI**	22.69		
C–C–C–C increase				
H–N–C–C decrease	**LIX**	49.80	**LI**	43.63
H–O–C–C increase	**V**	29.83	**II**	41.20
C–C–C=O decrease			**XXXVI**	24.39

esting progression can be noted: one (mirror symmetrical) glycine conformer, two (mutually mirror symmetrical) β-alanine conformers, and four GABA conformers contain this interaction.

The potential barriers for the reactions of the two GABA conformers, which are stabilized by the intramolecular N···H–O hydrogen bond, are collected in Table 2. Not surprisingly the lowest potential barriers are the ones for the reaction cycle **XXVI** ⇌ **IX** ⇌ **XXVI**^{m} ⇌ **IX**^{m} ⇌ **XXVI**, which preserves the H-bond: 18.68 kJ/mol for **IX** and 15.21 kJ/mol for **XXVI**. The lowest potential barriers for reactions which do not preserve the H-bond are 24.09 kJ/mol for **IX** and 24.39 kJ/mol for **XXVI**. The values for the corresponding β-alanine conformer with the intramolecular hydrogen bond are 28.66 kJ/mol for the H-bond preserving reaction and 36.42 kJ/mol for the H-bond breaking reactions. The comparison of the GABA and β-alanine values shows again the greater flexibility of GABA.

Concerning the interaction N–H···O=C it has to be noted that it is present in the global minima of the PES of glycine, β-alanine, and GABA. The H···O distances are 2.948 Å in glycine, 2.460 Å in β-alanine, and 2.632 Å in GABA. These values indicate already that no H-bond is involved. The electron densities of these three conformations, which are shown in Fig. 6 of Ramek et al. (1992) and in Fig. 10, confirm that no electronic interaction between the hydrogen atom of the amino group and the oxygen atom of the carbonyl group occurs in these conformers. The interaction N–H···O=C in the global minima therefore is purely electrostatic. This, however, cannot be generalized for all N–H···O=C interactions: in **LIX** this interaction definitely has some H-bond character. It should be noted that the PES of neither β-alanine nor glycine contains minima with an N–H···O=C H-bond as the one in **LIX**.

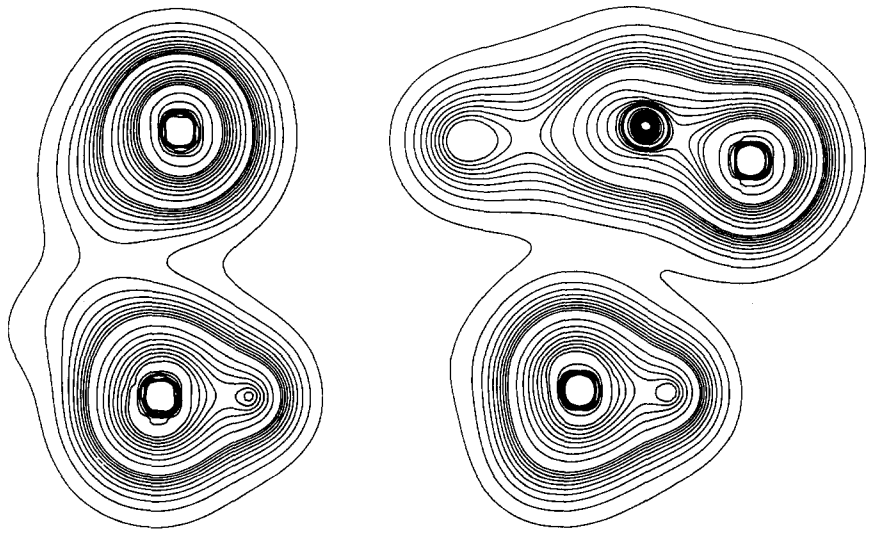


Fig. 10. Contour maps of the electron density of the global minima in the PES of glycine (left) and GABA (right). Both maps show the plane defined by the fragment O= ⋰ N–H in approximately this orientation). See Fig. 7 for technical details

Acknowledgement

This work was supported by the Austrian Fonds zur Förderung der wissenschaftlichen Forschung (project P 6856). Many calculations were done on the IBM 3090 VF operated by the EDV-Zentrum der Universität Wien within IBM's European Academic Supercomputing Initiative. The authors are grateful for this support and the constant support by the EDV-Zentrum der Technischen Universität Graz. Thanks are due to Dr. Mike W. Schmidt (Iowa State University) and to Dr. Egbert Keller (Universität Freiburg) for copies of the programs GAMESS and SCHAKAL.

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Received August 27, 1993