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Combined *Ab initio* SCF and Molecular Mechanics Studies of Propionic and Isobutyric Acids and Their Indole Derivatives Related to the Phytohormone Auxin (Indole-3-acetic Acid)

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Detailed conformational analyses of propionic and isobutyric acids were performed to contribute to a better understanding of the stereochemical characteristics of biologically active indole-3-aliphatic acids. The studies are based on *ab initio* SCF (RHF/6-31G*) and molecular mechanics (force fields used: MM2, MM3, CFF91, AMBER, CVFF, ESFF) methods. The results obtained with the CFF91 and MM3 force fields revealed the best agreement with the experimental values and those from *ab initio* calculations.
Normal mode frequencies in the harmonic oscillator approximation were calculated for the geometry optimized conformers with C_s symmetry of these compounds as well as of indole-3-acetic acid (IAA) and some of its biologically important derivatives (4-Cl-IAA, 6-Cl-IAA, 7-Cl-IAA, 4-Me-IAA) and indole-3-isobutyric acid (IIBA). The influence of the indole ring on the C=O and O–H stretching frequencies was analyzed. A small decrease of the C=O frequency was determined in the indole-3-acetic acid derivatives and a larger one in indole-3-isobutyric acid.

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INTRODUCTION

Phytohormone auxins belong to a chemically diverse group of compounds, most of which have an aromatic ring system with a carboxyl group attached to the end of the main side chain. We mostly focused on those containing an indole ring. Indole-3-acetic acid (IAA) and its alkylated and halogenated derivatives were studied by the X-ray structure analysis,[1–4] IR spectroscopy[5] and computational chemistry methods (*ab initio* SCF, molecular mechanics and molecular dynamics simulations).[6,7] In this series of compounds, the influence of the substituent at the benzene part of the indole ring on the potential energy surface of the molecules was analyzed. However, the substituent effect at the C3 site (Scheme I) is pronounced and also strongly influences auxin activity. It is known that alteration of the indole side chain from a linear aliphatic chain to a branched one changes the biological activity of some synthetic auxins to antiauxin activity.[8,9] For example, 5,7-Cl_2-IAA showed weak stimulating activities in the elongation tests with *Avena* coleoptiles, whereas 5,7-dichloroindole-3-isobutyric acid (5,7-Cl_2-IIBA) produced no coleoptile elongation for the entire range of concentrations tested, *i.e.* it completely lost auxin activity (Hatano *et al.* [9]). According to Ray's investigations,[10] the values of the protein binding constant Pk_d for indole-3-acetic acid (IAA), indole-3-propionic acid (3-IPA) acid and 4-indole-3-butyric acid (4-IBA) are 5.4, 5.2 and 5.0, respectively, while that of indole-3-isobutyric acid is only 3.8. The results of bioassays using *Avena* coleoptiles revealed a decreasing elongation activity of indole-3-acetic acid, 4-indole-3-butyric acid and indole-3-propionic acid, but no activity of 3-indole-3-butyric acid (3-IBA) and 4,4,4-trifluoro-3-indole-3-butyric acid (TFIBA),[11] compounds with the CH_3 and CF_3 groups attached to the C8 atom in the side chain (Scheme I). While 3-IBA showed only weak promoting activity at a concentration of 10^{-4} M, the novel fluorinated regulator TFIBA has a pronounced antiauxin activity: it inhibits *Avena* coleoptile elongation but promotes root growth in rice, Chinese cabbage and lettuce, which is an antiauxin characteristic.

The different biological response of the indole compounds discussed above could be understood as a result of at least three phenomena: a) differences in the fit of the various side chains to the receptor binding site, b) different orientations of COOH group towards the indole ring, and c) the ability of the ligand to undergo a conformational change simultaneously with the receptor after binding, as it was discussed in the so-called conformational change theory that was formulated 20 years ago by Kaethner.[12] According to this theory, auxin binds in the so called “recognition” conformation and after the binding, changes to the “modulation” one.

As building blocks of many auxins, indole and non-indole, propionic and isobutyric acid were studied to check the reliability of different force fields to be used in future studies of auxins.

We also compared the rotational freedom of the carboxyl group and the C=O and O–H normal mode frequencies in IAA derivatives and IIBA with those in free propionic and isobutyric acids. The present work should be understood as a study preceeding a QSAR analysis of auxin related compounds.

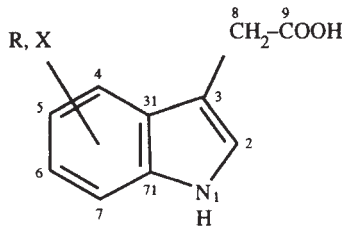
RESULTS

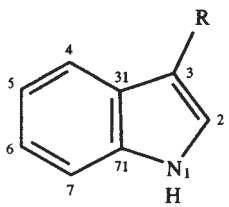
Ab initio MO-SCF Study

Geometry optimizations were carried out for a number of propionic and isobutyric acid conformers and for the C_s conformers of indole-3-isobutyric acid (IIBA), IAA, 4-Cl-IAA, 4-Me-IAA, 6-Cl-IAA and 7-Cl-IAA with both C2–C3–C8–C9 and C3–C8–C9=O2 dihedrals (see Scheme I) equal to 0°.

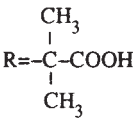
The conformational search of propionic and isobutyric acid was performed by rotating the central C–C bond in steps of 30°, which is adequate for small molecules without major intramolecular interactions. All calculations were performed with the GAMESS[13] program on a variety of machines. The well known RHF formalism[14] was used with the 6-31G* basis set.

All structures were fully optimized to the remaining root mean square (rms) gradient less than $0.3 \cdot 10^{-4}$ Hartree/Bohr. The nature of all minima





R=H	IAA	R=$\overset{8}{C}H_2$–$\overset{9}{C}H_2$–COOH	3-IPA
CH_3	4-Me-IAA	R=CH_2–CH_2–CH_2–COOH	4-IBA
X=Cl	4-Cl-IAA		
	6-Cl-IAA		
	7-Cl-IAA		



IIBA

Scheme I. Atom numbering for indole compounds.

was verified *via* computation of the eigenvalues of the Hessian matrix. All the conformers analyzed had the *synperiplanar* conformation of the COOH group, *i.e.* H–O–C=O about 0°. According to the results obtained by Nagy *et al.*[15] for the free acids at the MP2/6-31G* and HF/6-31G* level, the conformers with the *antiperiplanar* acid group have about 30–40 kJ/mol higher energy than those with *synperiplanar*. A similar conclusion can be drawn from the *ab initio* structure investigations of a large number of amino and hydroxyl acids performed by Ramek, Flock and Seebacher.[16–18]

The propionic and isobutyric acid PESs: $E = f$(C–C–C=O) determined by this work are given in Figures 1 and 2. The energy profiles for the internal rotation of the C–C–C=O dihedral are similar to those obtained by Siam *et al.*[19] with the 4-31G basis and Wiberg[20] with the 3-21G basis. However, energy differences determined by us in the 6-31G* basis are about 2 kJ/mol (≈ 30%) smaller than those determined in 4-31G.[19]

For propionic acid, the global minimum (E = –266.846548 Hartree) is the C_s symmetrical conformer with the *synperiplanar* conformation of the dihedral C–C–C=O, which is in accord with the results obtained by micro wave spectroscopy.[21] The conformers with C–C–C=O about ±120° are local minima, while those with C–C–C=O about ±75° are barriers of the internal rotation of this dihedral (Figure 1).

For isobutyric acid there are two C–C–C=O dihedrals, defined towards the two methyl groups. The isobutyric acid conformers with an *anticlinal* orientation (±120°) of one C–C–C=O dihedral and the *synperiplanar* (0°) of the other are the global minima (E = –305.8806179 Hartree), while the C_s

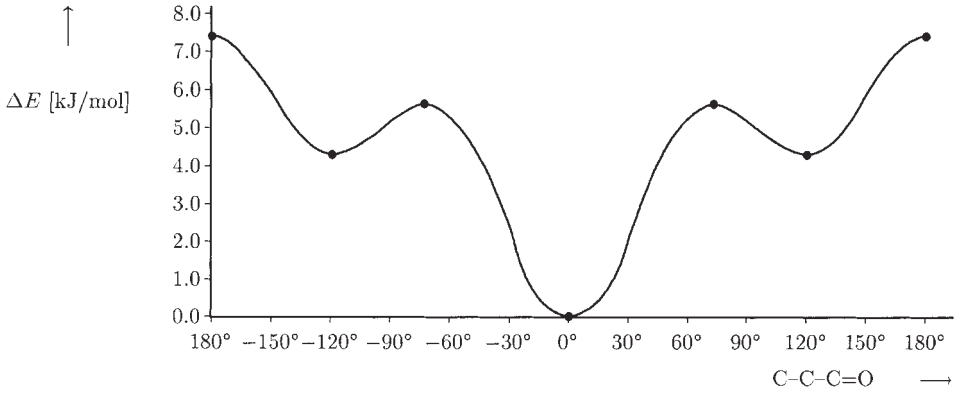


Figure 1. Energy profile (kJ/mol) for propionic acid obtained by *ab initio* RHF/6-31G* optimizations, as a function of the torsion angle C–C–C=O. The positions of the minima and the first order saddle points are marked by circles. Zero relative energy has been chosen to correspond to global minimum, with absolute energy of –266.846548 Hartree.

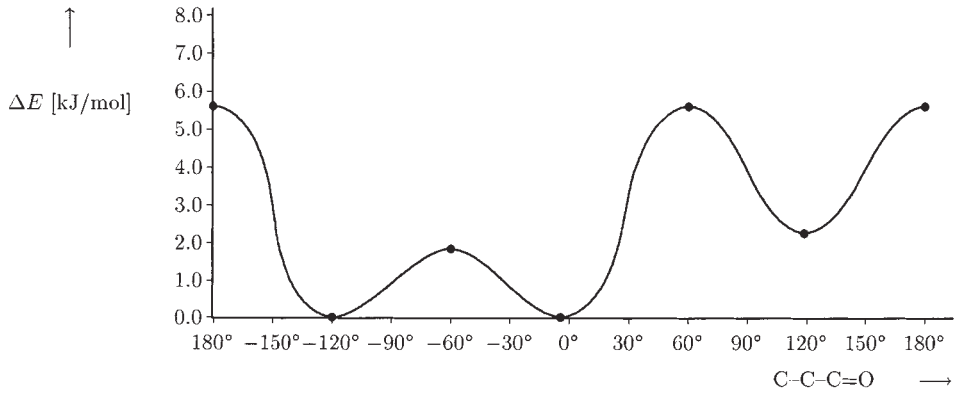


Figure 2. Energy profile (kJ/mol) for isobutyric acid obtained by *ab initio* RHF/6-31G* optimizations, as a function of the torsion angle C–C–C=O. The positions of the minima and the first order saddle points are marked by circles. Zero relative energy has been chosen to correspond to global minimum, with absolute energy of –305.8806179 Hartree.

conformer with both dihedrals C–C–C=O about ±120°, *i.e.* H–C–C=O equal to 0°, is a local minimum for the internal rotation of the central C–C bond. The energy of the latter (*E* = –305.8797505 Hartree) is about 2 kJ/mol above the energy of the global minima and about 0.4 kJ/mol above the mirror symmetrical saddle point (Figure 2).

From previous *ab initio* calculations of IAA[6] and 4-Cl-IAA[7] it is known that the most stable conformation for both compounds is planar, *i.e.* the one with the dihedrals C2–C3–C8–C9 and C3–C8–C9=O equal to 0° (for the atom numbering see Scheme I). However, there are a few local minima with the side chain tilted to the indole ring plane (C2–C3–C8–C9 about 100°) for each compound. The one with the *synperiplanar* orientation of the dihedral C–C–C=O is common for both compounds, only for IAA it is the highest in energy and for 4-Cl-IAA the second lowest in energy. It is noteworthy that, in the crystal phase, both compounds have a conformation similar to this one. The other minima with a tilted side chain are: for IAA those with ±*anticlinal* orientation of the dihedral C–C–C=O and for 4-Cl-IAA the conformer with *antiperiplanar* orientations of C–C–C=O. For all the compounds with the indole ring moiety analyzed, *i.e.*: IIBA, IAA, 4-Cl-IAA, 6-Cl-IAA, 7-Cl-IAA, and 4-Me-IAA, the planar conformer with C2–C3–C8–C9 and

C–C–C=O equal to 0° is a minimum on the molecule PES. From these results, it seems that the *synperiplanar* orientation of the dihedral C–C–C=O determined in the free (unsubstituted) acids as the most populated is to some extent preserved in the indole compounds analyzed. Similarly, the conformer with C–C–C=O *anticlinal* is a local minimum on the IAA PES.

It is accepted that the carboxyl group in the auxins is one of the auxin-receptor interaction centers,[8,12,22–24] so we compared O–H and C=O frequencies in different compounds. The values are listed in Table I together with experimental values of the C=O frequency.[5,25] In all the compounds analyzed, the unscaled O–H frequency is in the range between 4055 and 4058 cm^{-1}. Regarding the IAA derivatives, the highest value of this frequency occurs in the compounds with the substituent at position 4 of the indole ring (4-Me-IAA 4057.2 and 4-Cl-IAA 4057.1). The range of the calculated C=O stretching frequency is broader, with slightly lower values determined in the compounds with the indole ring than in the free acids. The calculated C=O frequencies are scaled according to the ratio of isobutyric acid frequencies, measured in gas and calculated (Table I). Although the values of such scaled frequencies for indole-3-acid derivatives are similar to those measured in polar solution, their trend agrees well with those measured in non-polar solution. The highest C=O frequency of all IAA derivatives analyzed was determined for 7-Cl-IAA and the lowest for 4-Cl-IAA, about 10 cm^{-1} lower than for propionic acid.

TABLE I

H-bond orders, H-bond distances (Å) and C=O and O–H streching frequencies (cm^{-1}), as determined by RHF/6-31 G* calculations and the C=O frequences measured in the polar (first entry) and non-polar solvent (second entry).

Compund	H-bond order[27] 6-31G*	H-bond (Å)	Calculated frequencies			Measured frequencies
			C=O (cm^{-1})		O–H (cm^{-1})	C=O (cm^{-1})
			a)	b)		
IAA	0.016	2.391	2028.5	1775	4056.7	1740.8[5] 1710.9[5]
4-Cl-IAA	0.019	2.315	2024.2	1771	4057.1	1744.2[5] 1710.8[5]
6-Cl-IAA	0.016	2.385	2028.9	1775	4055.3	1740.6[5] 1711.1[5]
7-Cl-IAA	0.016	2.384	2029.3	1776	4055.1	1741.0[5] 1713.1[5]
4-Me-IAA	0.018	2.329	2028.2	1775	4057.2	1742.5[5] 1711.1[5]
IIBA	0.020	2.223	2011.9	1760	4058.0	
Propionic acid			2034.0	1780	4055.4	
Isobutic acid			2030.8	1777	4055.8	1776.6 (gas)[25] 1706.6 (neat)[25]

a) unscaled
b) scaling factor for frequencies = 0.875

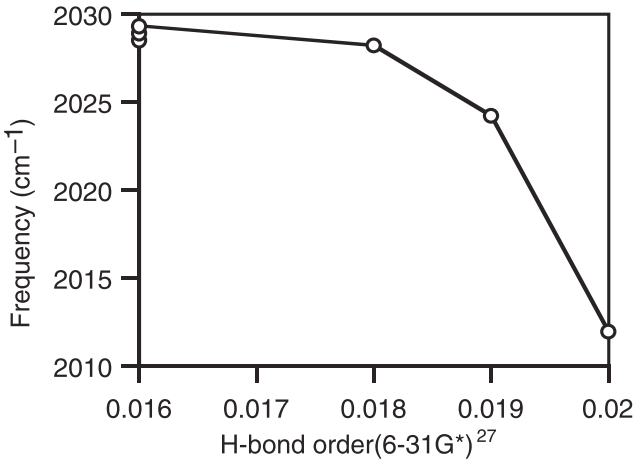


Figure 3. The C=O frequency (cm^{-1}) *vs.* H-bond order, determined for indole compounds.

Inspection of the electron densities of the C2–H2···O2=C9 interaction showed the existence of a critical point with one positive and two negative eigenvalues of the Hessian matrix between atoms H2 and O2 in all the indole compounds analyzed. A critical point of this nature is structually associated with a chemical bond,[26] hence these interactions have to be classified as weak intramolecular hydrogen bonds. The distance in the indole-3-acetic acid derivatives is in the range 2.3–2.4 Å, while in the C_s conformers of propionic and isobutyric acid the corresponding interatomic distance is 2.8 Å. The bond orders[27] and the distances between the atoms participating in these hydrogen bonds are also given in Table I. The C=O frequency in the indole compounds, analyzed *vs.* the H-bond order, is shown in Figure 3. IIBA has the lowest C=O frequency and the strongest C2–H2···O2=C9 hydrogen bond and because of that deserves more attention. In this molecule, the decrease of the C=O frequency is mostly due to the van der Waals interactions of the hydrogen atoms of methyl groups. The repulsive interaction of these atoms and the hydrogen atom at position 4 of the indole ring results in an increase of the valence angles H–C4–C31, C4–C31–C3, C31–C3–C8, and C3–C8–C9. They are consistently 1–2° larger in IIBA than IAA, forcing the C=O group closer to C2–H2 in the former.

Molecular Mechanics (MM) Conformational Analysis

The conformational analyses of propionic and isobutyric acids have also been performed using the MM method with the following force fields: CVFF,[28] CFF91,[29] ESFF,[30] AMBER,[31,32] MM2,[33,34] and MM3.[35,36] Calcula-

tions were performed to find out which force fields produce satisfactory results for these molecules. This part of investigations is important for the future calculations on larger systems: derivatives of acetic, propionic and isobutyric acids.

The molecules were 'built' by the computer program INSIGHT.[37] Parameterization was performed in the desired force fields and the molecular geometry of the starting, planar conformation, was optimized before further analysis. Internal rotations of the central C–C bond were performed in steps of 10° or 15° from –180° to 180° (lowering the stepsize of the rotation from 15° to 10° had no influence on the shape of PES). Each step was followed by an optimization of the rest of the molecule. Calculations were performed by the computer programs DISCOVER,[38] MM2,[39] and MM3.[40]

Results for propionic acid:

In the CVFF force field, only the conformers with C–C–C=O ≈ ±100° (mirror images) were recognized as minima (Figure 4a). Calculations in AMBER and ESFF yielded the minima found by *ab initio* calculations, but the conformers with the dihedral C–C–C=O in *anticlinal* orientation are energetically more favourable (about 1.5 kJ/mol) than the one with C–C–C=O *synperiplanar* (Figures 4b and c). In the CFF91, MM2 and MM3 force fields the latter was determined as the global minimum and those with the *anticlinal* conformation of the C–C–C=O dihedral (in CFF91 and MM2 about ±100°, and in MM3 about ±120°) as local minima (Figures 4 d–f). The relative energies of the barriers and the local minima for the internal rotation of the C–C–C=O dihedral determined in CFF91 are similar to those found by *ab initio* calculations (Figure 4d).

Results for isobutyric acid:

The conformational analysis performed in CVFF revealed the mirror symmetrical conformers (C–C–C=O ≈ ±60°, and C–C–C=O ≈ ±120°) as minima with similar conformational energies (Figure 5a). In AMBER and ESFF (Figures 5b, c), the same minima were determined as by *ab initio* calculations, but in these force fields the conformer with C_s symmetry (C–C–C=O ≈ ±120°) is the main minimum, and those with one C–C–C=O *synperiplanar* and the other *anticlinal* are local minima with about 1 kJ/mol (AMBER, Figure 5b) and 2 kJ/mol (ESFF, Figure 5c) higher conformational energy, respectively.

The PESs determined in CFF91 and MM3 (Figures 5d, e) are similar to those determined by *ab initio* calculations, *e.g.* the barrier between the global minima (the C–C–C=O dihedrals equal 0° and ±120°) is the mirror symmetrical conformer (C–C–C=O ≈ ±60°) with a relative conformational energy of about 1 kJ/mol (CFF91) and 4 kJ/mol (MM3). The energy of the local

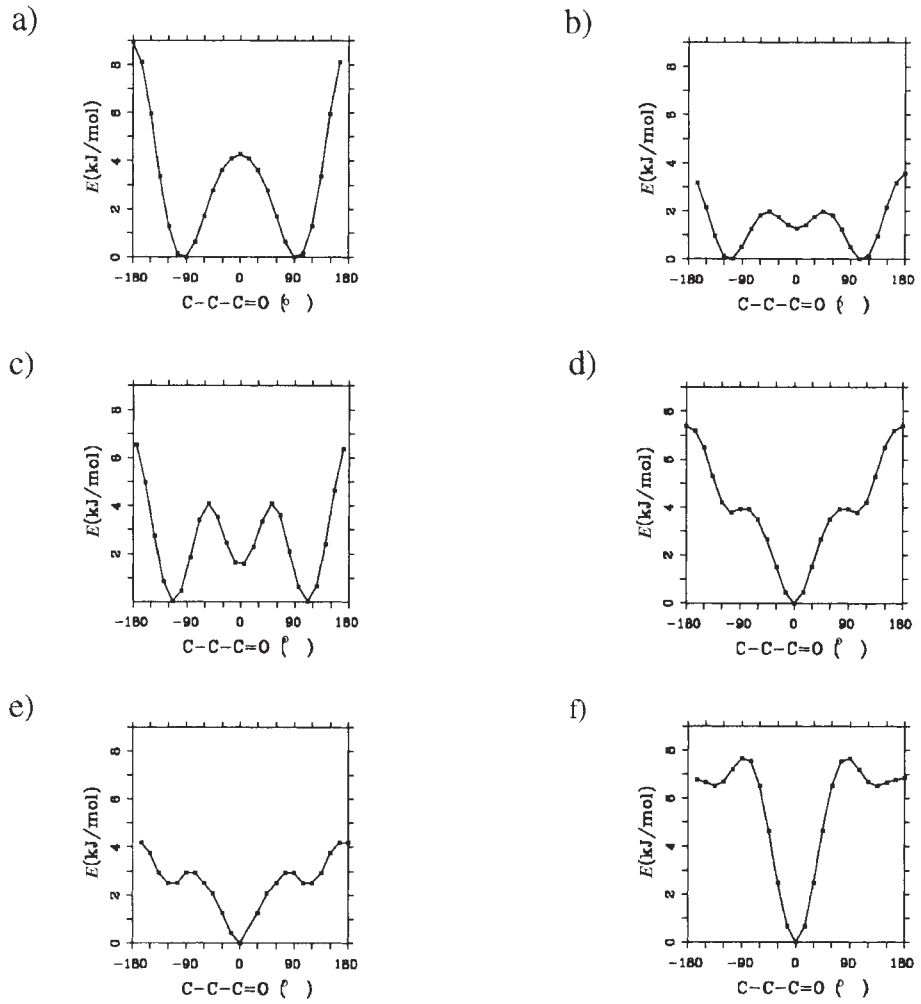


Figure 4. The relative conformational energy (kJ/mol) for propionic acid as a function of the C–C–C=O dihedral determined in various force fields: a) CVFF, b) AMBER, c) ESFF, d) CFF91, e) MM2, f) MM3.

minimum (C–C–C=O ≈ ±120°) is in CFF91 about 3 kJ/mol and in MM3 about 2 kJ/mol above the barrier.

The conformational energy components, which most significantly change during the rotations differ substantially from one force field to another. Changes of valence angle and non-bonded (van der Waals + electrostatic) energy are dominant in CVFF; in the MM2 and MM3 force fields, changes of valence angle and torsion energy terms prevail, while in the ESFF and AMBER force fields those of torsion and non-bonded energy. Besides, in CFF91,

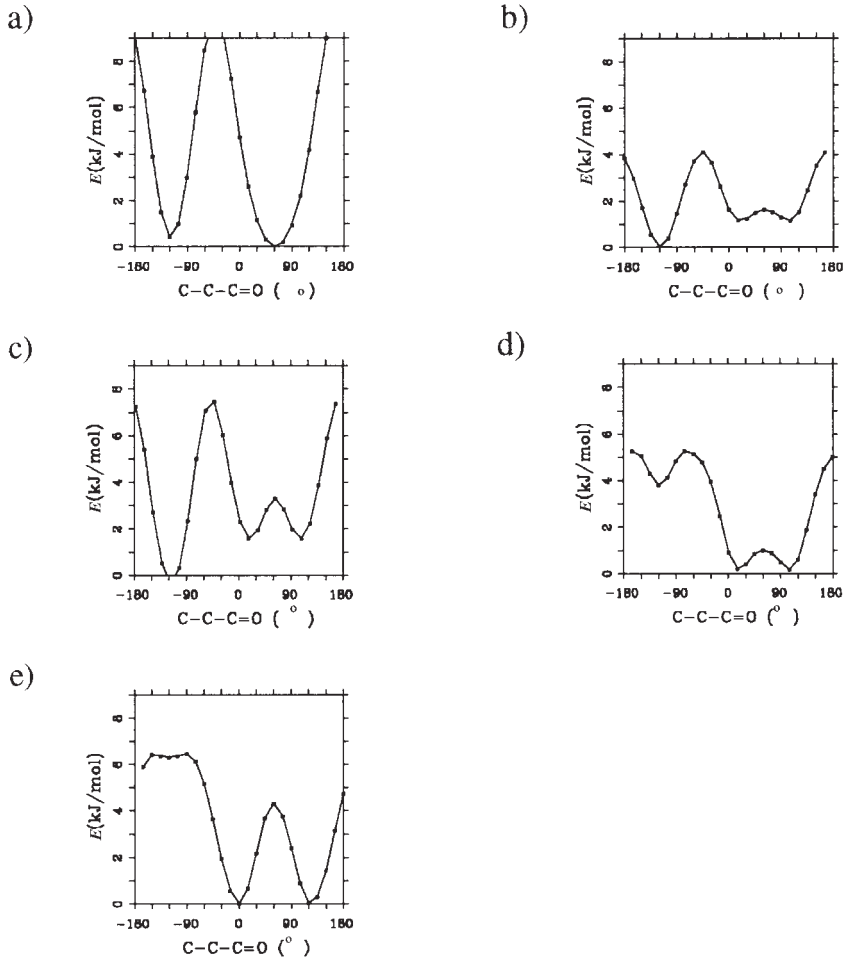


Figure 5. The relative conformational energy (kJ/mol) for isobutyric acid as a function of the C–C–C=O dihedral determined in various force fields: a) CVFF, b) AMBER, c) ESFF, d) CFF91, e) MM3.

the shape of the PES (C–C–C=O) is determined by the cross valence angle-torsion energy term as well.

Results for IAA, 3-IPA, 3-IBA and IIBA:

Conformational analyses were performed in CFF91, and the two dimensional PESs, for the internal rotation of the two bonds in the side chain,

were determined, see Figures 6a–d. For IAA and IIBA, this comprises the first and the second bond in the side chain. The related 2D PES for these compounds are similar (Figures 6a, b). For the internal rotation of the C3–C8 bond (for numbering see Scheme I), three minima were determined, with C2–C3–C8–C *synperiplanar* and ± *anticlinal*, and saddle points at about ±60° and 180°. Because of the methyl groups attached to C8, the relative energy of the saddle points at ±60° is about two times higher for IIBA than for IAA (Figures 6a, b). For 3-IBA and 3-IPA, rotations were performed about the second and the third bonds in the side chain (Figures 6c, d). For the rotation about the C8–C9 bond, three minima were determined with the dihedral C3–C8–C9–C about 180° and ±60° (for numbering see Scheme I). The barriers of rotation at 0° and ±120° have only about 2 kJ/mol higher en-

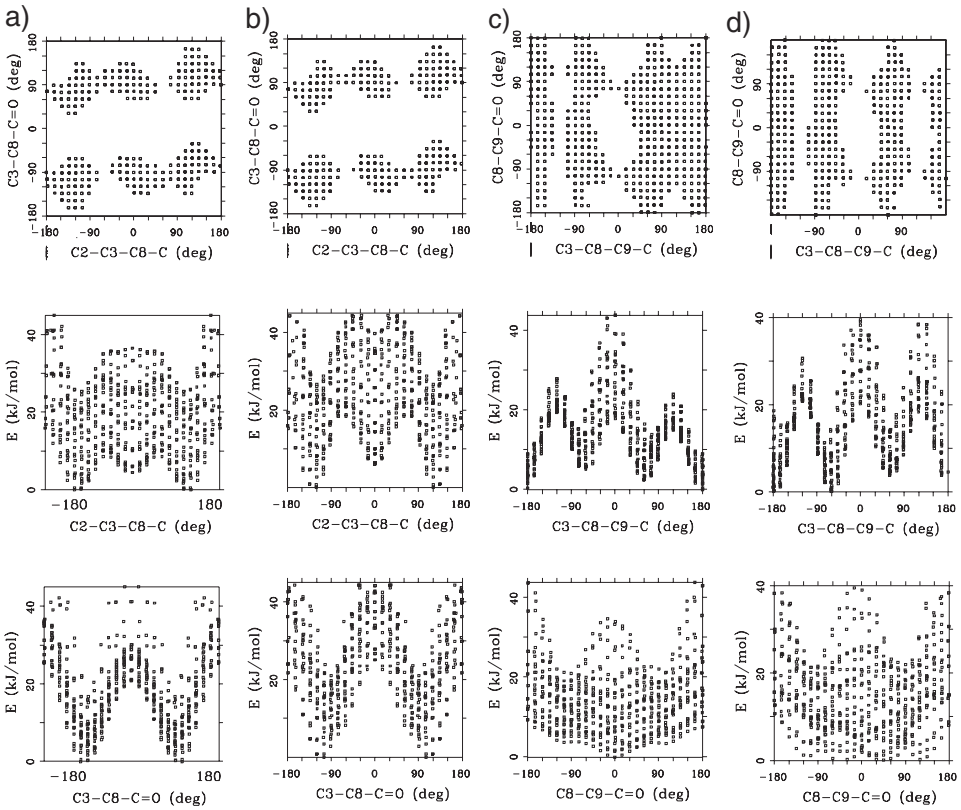


Figure 6. From top to bottom: conformations of the two neighbouring torsion angles in the side chain with relative energies up to 20 kJ/mol (shaded areas), energy profiles (kJ/mol) as functions of these torsion angles, as specified on *x*-axes, for: a) IAA, b) IIBA, c) 3-IPA, d) 3-IBA, determined in CFF91. For numbering see Scheme I.

ergy for 3-IBA than for 3-IPA. For these two compounds, there are two preferable conformations of C2–C3–C8–C9: *synperiplanar* and *anticlinal*. The PESs for the rotation of the carboxyl group in these compounds are similar to those obtained for propionic and isobutyric acids. The conformations determined for propionic and isobutyric acids are preserved in 3-IPA and 3-IBA, respectively. However, the conformational search, as already noticed before,[6] did not reveal the planar conformer of IAA and IIBA, which are minima in *ab initio* calculations.

DISCUSSION

Various theoretical structure investigation methods were applied to propionic and isobutyric acids and several derivatives of indole acetic acid. The methods employed were: *ab inito* RHF and the molecular mechanics with the empirical force fields MM2, MM3, CFF91, CVFF, ESFF, and AMBER. With the exception of AMBER, these are general purpose force fields that are not intended for a specific class of compounds; AMBER was originally developed for proteins and nucleic acids, but has been used for other compounds too.[41, 42]

A major aspect of the collection of results presented here is a comparison of the methods. According to the experimental and *ab initio* results, MM3 and CFF91 give the most reliable results among the force fields used for the specific class of compounds with the –C–CH_2–COOH and –C$(CH_3)_2$COOH groups. This is not suprising because CFF91 is parameterized on the basis of *ab initi*o calculation, and lately this has also been the case for the MM3 force field.[43] The results obtained with the other force fields are similar to those obtained by Teixeira-Dias, Fausto, and Batista de Carvalho[44] for compounds in which the carbonyl oxygen atom is replaced by sulfur. Their *ab initio* calculations with the 3-21G and 3-21G+d(S) basis sets on the $CH_3CH_2C(=X)YH$ series of molecules showed that in compounds with X=S, the lowest energy conformations occur for the dihedral C–C–C=S between 100° and 120°, while in compounds with X=O, the dihedral C–C–C=O preferentially adopts the *synperiplanar* conformation (C–C–C=O= 0°).

Interest in the indole acetic acid derivatives is due to their role as plant growth regulators, and efforts to correlate structural features with the hormone activity. The large scatter of the force field results, and their inability to locate some conformers, found both experimentally and by *ab initio* calculations, lead to one important conclusion: structure-activity assumptions should not rely on molecular mechanics calculations only, but should be accompanied by experimental measurements and/or *ab initio* calculations.

The fact that the bulky methyl group(s) attached to the C8 atom (see Scheme I) does not hinder molecular planarity, but is responsible for antiauxin behaviour of these compounds,[8,9] is important from the biological as-

pect. The current results on indole compounds lead to the following assumptions. The size and shape of the side chain are important for biological activity, but the importance of the orientation of the side chain towards the indole ring cannot be neglected. It is also possible that this group(s) reduce or even block the ability of the receptor + hormone system to adopt the active conformation once the hormone is bound to it. However, a clear correlation between the structure and auxin activity could not be obtained from the results of isolated species, hence a detailed conformational study of the molecules in a surrounding similar to the receptor active site will be unavoidable once this active site is identified.

Supplementary Material

The optimized geometries (Cartesian coordinates) of the molecules analyzed are available on request *via* e-mail (tomic@rudjer.irb.hr).

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SAŽETAK

Kombinirana *ab initio* SCF i molekulsko-mehanička studija propionske i izomaslačne kiseline i njihovih indolskih derivata u svezi s biljnim hormonom auksinom (indol-3-octenom kiselinom)

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Provedena je detaljna konformacijska analiza propionske i izomaslačne kiseline što doprinosi boljem razumijevanju stereokemijskih osobina biološki aktivnih indol-3-alifatskih kiselina. Izučavanja su temeljena na *ab initio* (RHF/6-31*) pristupu i metodi molekulske mehanike (korištena su polja sila: MM2, MM3, CFF91, AMBER, CVFF, ESFF). Rezultati dobiveni uporabom polja sila CFF91 i MM3 najbliži su eksperimentalnim vrijednostima i rezultatima *ab initio* računa.

Frekvencije normalnih načina titranja izračunane su za utočnjene, zrcalno simetrične konformere navedenih spojeva, indol-3-octene kiseline (IAA) i nekih njenih biološki važnih derivata (4-Cl-IAA, 6-Cl-IAA, 7-Cl-IAA, 4-Me-IAA) te za odgovarajući C_s konformer indol-3 izomaslačne kiseline korištenjem aproksimacije harmonijskog titrala.

Proučavan je utjecaj indolskog prstena na frekvencije istezanja C=O i O–H. Utvrđeno je malo povećanje frekvencije C=O kod derivata indol-3-octene kiseline i veće kod indol-3-izomaslačne kiseline.