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An ab initio and DFT conformational analysis of unsubstituted and ω-substituted ethyl-benzene: ($Ph–CH_2–CH_2–Z$; $Z = –H$, $–F$, $–NH_3^+$, $–CH_3$)

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Abstract

A series of compounds of $Ph–CH_2–CH_2–Z$, with substituents $Z = –H$, $–F$, $–NH_3^+$, and $–CH_3$, were subjected to conformational analysis. Conformational potential energy surfaces were generated and their minima were geometrically optimized at three levels of theory. The relative stabilities of the minima correlated with the electron withdrawing nature of the substituents (Z). © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Biogenic amines; Conformational analysis; $Ph–CH_2–CH_2–Z$; Hartree–Fock; MO; DFT

1. Preamble

There are numerous biogenic amines in which the backbone consists of an aryl-ethylamine with vicinally arranged substituents:

$$Ar–\overset{\alpha}{C}H_2–\overset{\beta}{C}H_2–NH_2$$

In the biogenic amines, the basic backbone may be modified. Either the aromatic ring or the ethyl side chain (in the α or benzylic position) or both may be hydroxylated. The phenolic hydroxyl groups, resulting from such oxidation of the aromatic ring, are sometimes methylated. The terminal nitrogen could be also methylated or acetylated. Some drugs or other biologically active amines may also carry an additional methyl group attached to the β-carbon, which also carries the amino nitrogen. These biogenic amines are formed by metabolization [1] of two important amino acids, tryptophan (Trp) and tyrosine (Tyr), as shown in Fig. 1. We might mention, in passing, that Trp and the precursor of Tyr, namely phenylalanine (Phe), are essential amino acids. These amino acids must be present in the diet in sufficient quantities for proper functioning of the human body. We should also note that there are numerous

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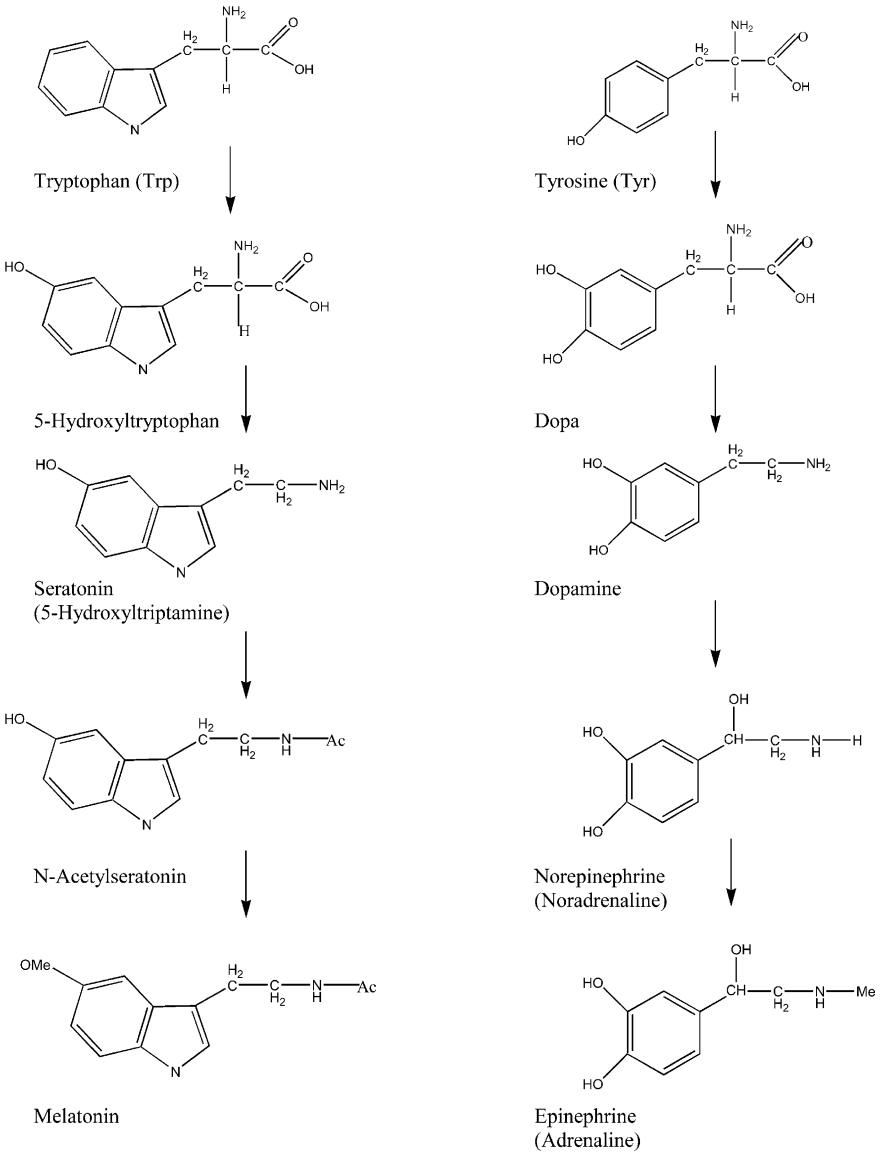

Fig. 1. A schematic representation of the metabolism of aromatic amino acids (Trp and Tyr) to biogenic amines that have crucial functions in the central nervous system (CNS).

bio-active variants of aryl-ethylamines, some of which are included in Fig. 2.

Naturally occurring neurotransmitters, which are aryl-ethylamines, are linked to mood. Most mood altering drugs (i.e. antidepressants) act either as enzyme-inhibitors or as receptor agonists/antagonists. These biogenic amines may be oxidized further by one of the monoamine oxidize enzymes (MAO-A or MAO-B). Such oxidation of selected biogenic amines is illustrated in Fig. 3. It may be interesting to note, that selegiline (cf. Fig. 2) is a MAO-B inhibitor. Hallucinogens also act at the same or similar sites where these biogenic amines form complexes with enzymes or receptors.

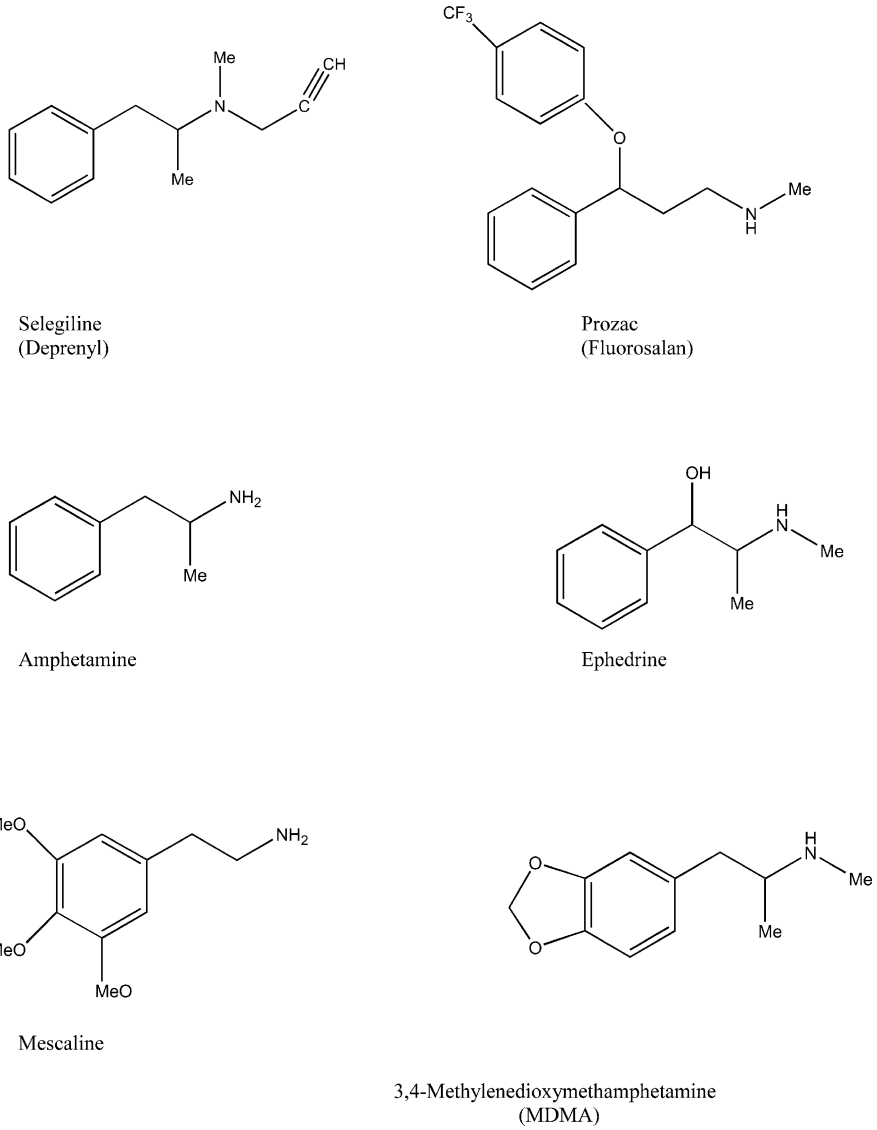

Fig. 2. Selected drugs and hallucinogens containing a β-phenyl-ethyl-amine skeleton.

2. Introduction

One of the cornerstones of both chemistry and biology is that structure predetermines function (i.e. physical, chemical, and biological properties). A relationship between function and structure may be qualitative or quantitative. For example, in pharmacology and in drug design, structure–activity-relationship (SAR) usually represent a qualitative, or at best, a semi-quantitative comparison. In contrast, we see more and more often the use of QSAR, which represents quantitative-structure–activity-relationship.

In studying chemical reactivity, structure–reactivity-relationship [2], such as the Hammett equation (for substituted aromatic rings), or the Taft equation (for substituted aliphatic chains) are frequently called

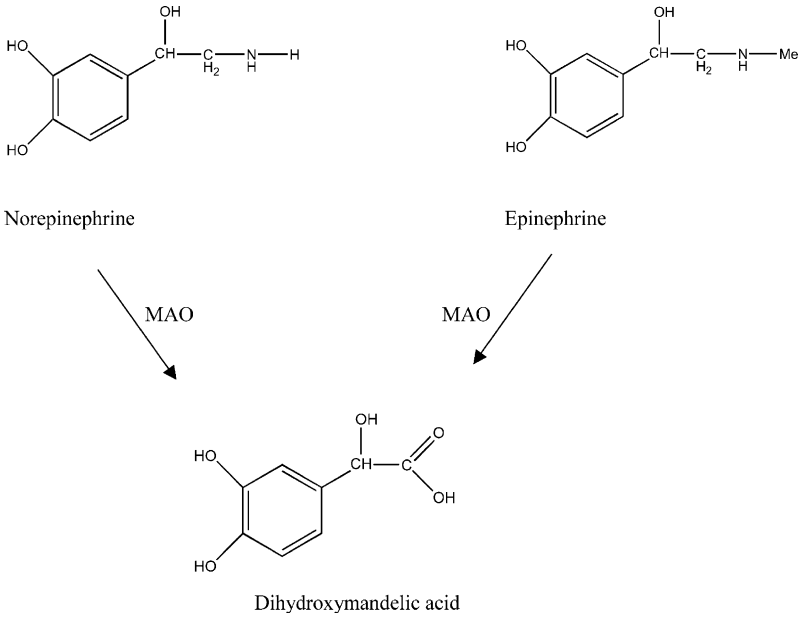

Fig. 3. Schematic representation of MAO-A catalyzed oxidation of selected biogenic amines.

linear-free-energy-relationships (LFERs):

$$\Delta G_Z = \rho\sigma + \Delta G_R, \qquad y = mx + b$$

In such a relationship, the dependent variable ΔG_Z measures the relative free energy value for the Z-substituted compound and ΔG_R is the corresponding quantity for the reference compound (R may be –H or $-CH_3$). The independent variable σ is called the substituent constant and it quantifies the structure, or more precisely, the structural change with respect to the reference substituent R. Finally, ρ is the reaction constant; as the slope of the straight line, ρ measures the steepness of the function, and therefore measures the susceptibility of the process to electron withdrawing, or electron releasing nature of substituent Z with respect to R.

When a systematic change is made by substitution, one would expect that such a change would manifest itself in the potential energy surface (PES). It may alter the appearance of the surface, or even its topology as well as the location and energy values of the optimized minima. Consequently, one would anticipate that the relative energy values would show, at least, a crude correlation using the above LFER. Even a crude correlation would indicate that there is at least a trend which would be in agreement with the basic premise.

3. Computational method

The molecular structure, stereochemistry, and geometry of ethyl-benzene, *n*-propyl-benzene, 2-phenyl-fluoroethane, and protonated 2-phenyl-ethyl-amine, were exclusively defined in terms of their *z*-matrix internal co-ordinate system. PES were calculated with 144 points at 30° increments at the RHF/3-21G level of theory. Potential energy curve (PEC) cross-sections, as well as the full PES, were plotted using Axum 5.0. Corresponding minima from the PES were selected and full optimizations were carried out successively at the RHF/3-21G, RHF/6-31G(d), and B3LYP/6-31G(d) level of theory. The GAUSSIAN 98 [3] program was used to carry out all the computations.

4. Results and discussion

The four compounds studied conformationally

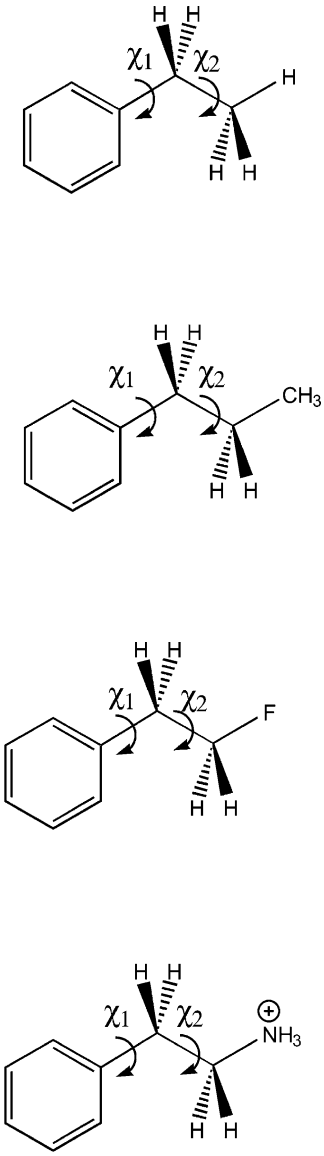

Fig. 4. Structures of the four compounds studied: Ph–CH_2–CH_2–Z [Z = –H, –CH_3, –CH_2F, and –NH_3^+].

in the present work are shown in Fig. 4. All of them were treated as double rotors. Torsional angle χ_1 was associated with the rotation of the phenyl group, while torsional angle χ_2 was associated with the rotation of the –CH_2Z group. Accumulated experience suggested that when χ_2 is varied, one observes $g+$, a, and $g-$ conformers. However, when a planar moiety is rotated about a tetrahedral moiety (χ_1), only $g+$ and $g-$ conformers may be expected in the vicinity of 90 and $-90°$, respectively.

Conformational PECs along these tortional modes (i.e. χ_1 and χ_2) are shown for the four compounds in Fig. 5. The four PECs at the right-hand side of Fig. 5 can be described by the equation $E = E(\chi_2)$.

All show the presence of the three minima as expected. The unsubstituted compound Z = H shows a fully symmetric PEC with triple degeneracy. One of the three not fully symmetric cases (Z = CH_3) shows the frequently expected *anti*-effect (i.e. *anti* is more stable than *gauche*). In contrast, the remaining two (Z = –F and –NH_3^+) exhibit the *gauche*-effect (i.e. *gauche* is more stable than *anti*).

The four PECs at the left-hand side of Fig. 5 can be described by the equation $E = E(\chi_1)$.

The global minima are located at $\pm 90°$ as has been shown before [4]. Nevertheless, one can only wonder if the two torsional modes (i.e. χ_1 and χ_2) are coupled or not. For this reason, the conformational PES as described by the equation $E = E(\chi_1, \chi_2)$ was computed and plotted for each of the four compounds. The graphical representation of the four PESs associated with Z = –H, –CH_3, –F, and –NH_3^+ are shown in Figs. 6–9, respectively.

These plots clearly indicate that the $g+$ and $g-$ minima of χ_2 are shifting noticeably, in the opposite directions, with respect to the *anti* conformer. The shift is analogous for Z = –NH_3^+ and –CH_3, but opposite for Z = –F. The location of the minima exhibited by these surfaces can be used as a guide for geometry optimizations.

The conformational and energetic characteristics of the optimized structures of Ph–CH_2–CH_2–Z are summarized in Tables 1–4. Note that the relative energies were calculated with respect to the $g+a$ or the equivalent $g-a$ conformations, so that

$$E[g+a] = E[g-a] = 0.00$$

As a result of the *gauche* or *anti* effect, the relative energies for the *gauche* conformers turned out to be either positive or negative. For example, at the B3LYP/6-31G(d) level of

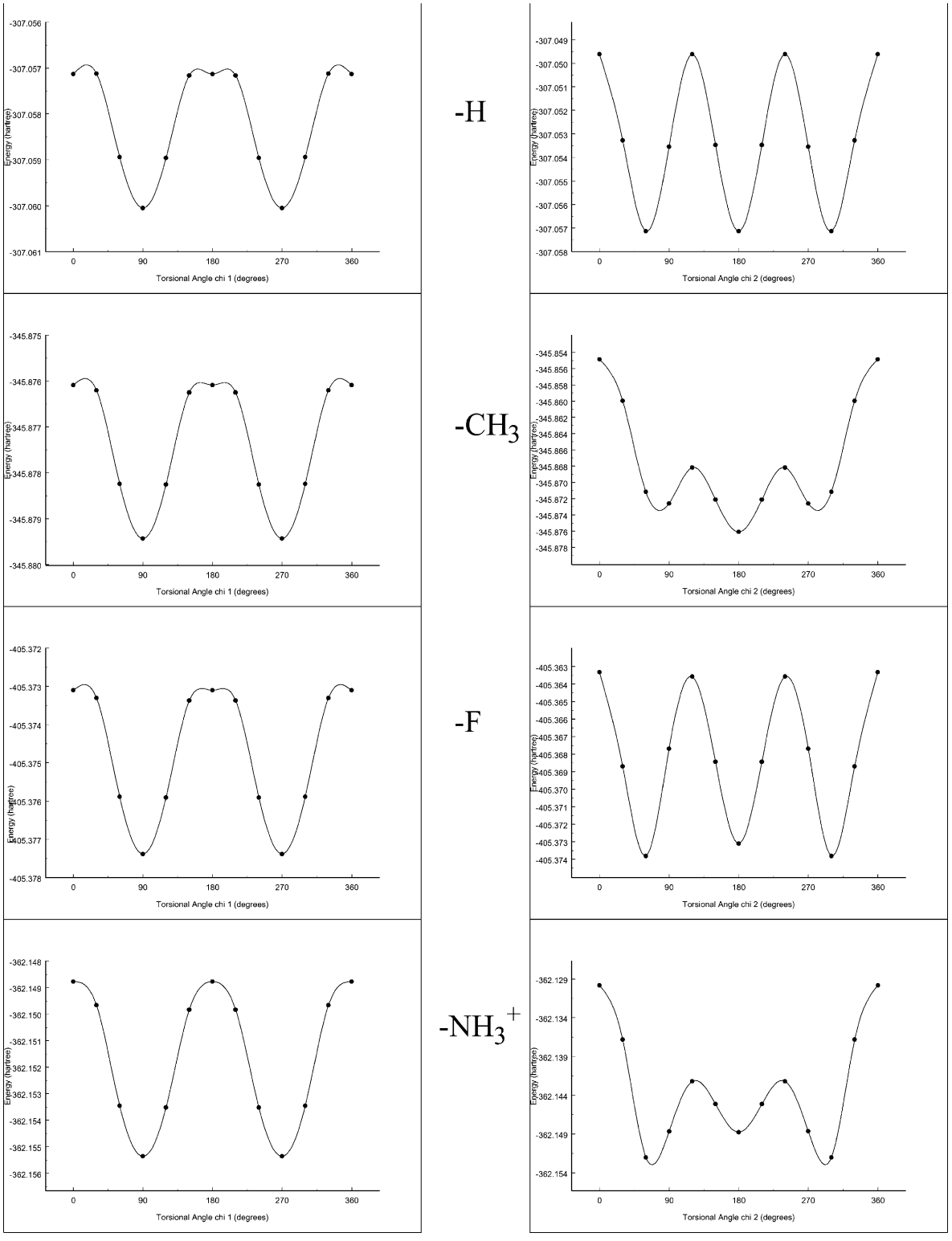

Fig. 5. Conformational PECs for the four compounds computed at the HF/3-21G level of theory.

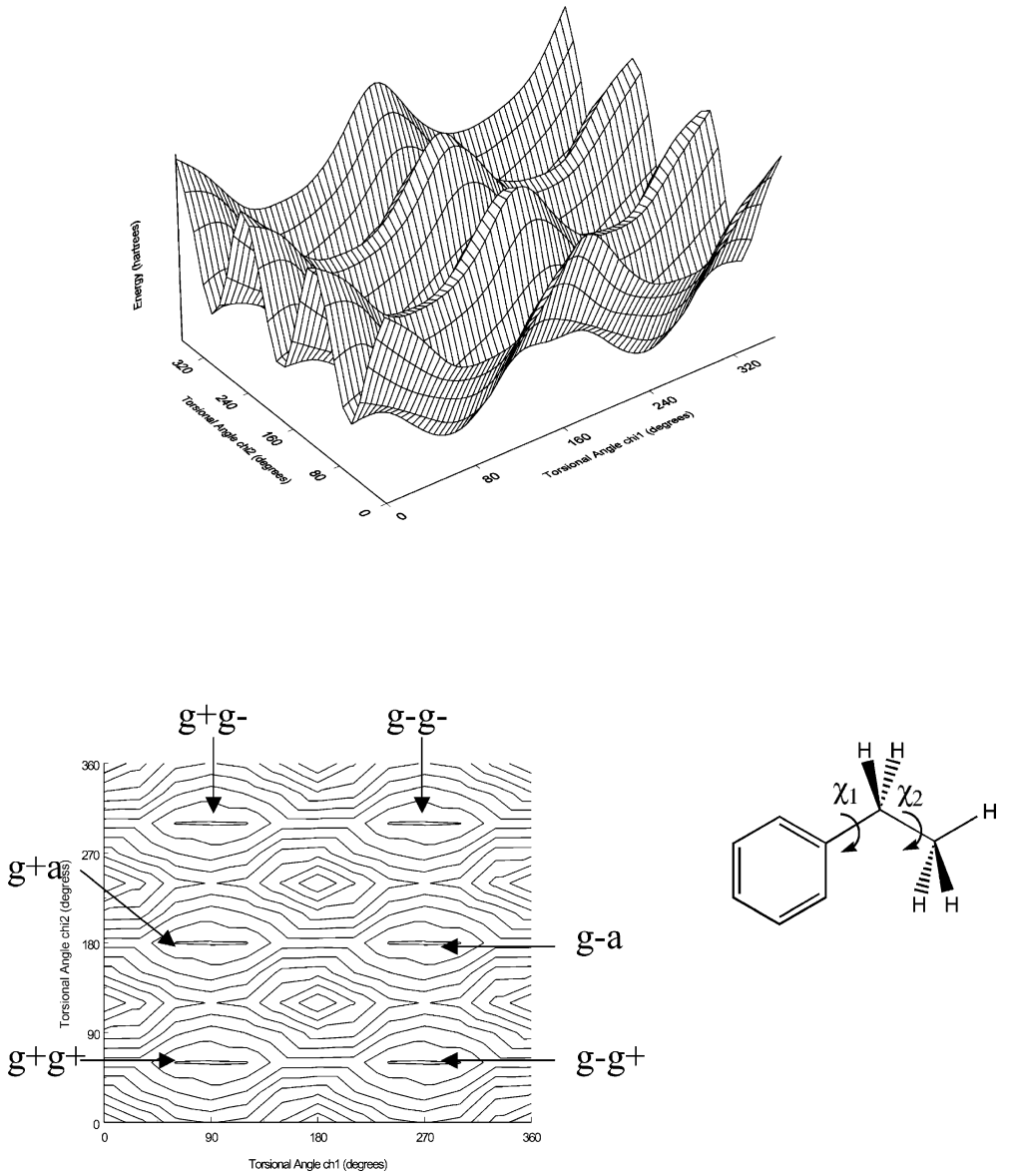

Fig. 6. Ethyl-benzene conformational surface (top) and contour (bottom).

theory:

$$\Delta E(\text{–Z} = \text{–CH}_3) = E[g + g+] - E[g + a] = 0.51,$$

$$\Delta E(\text{–Z} = \text{–F}) = E[g + g+] - E[g + a] = -0.19,$$

$$\Delta E(\text{–Z} = \text{–NH}_3^+) = E[g + g+] - E[g + a] = -3.93$$

These ΔE values are measuring the *gauche* versus the *anti* stability along χ_2, i.e. the rotation about the C–C bond in the CH_2–CH_2–Z moiety while χ_1 is relaxed.

The relative energy (ΔE) and associated conformational shifts ($\Delta\chi_1$ and $\Delta\chi_2$) for the $g+$ conformations

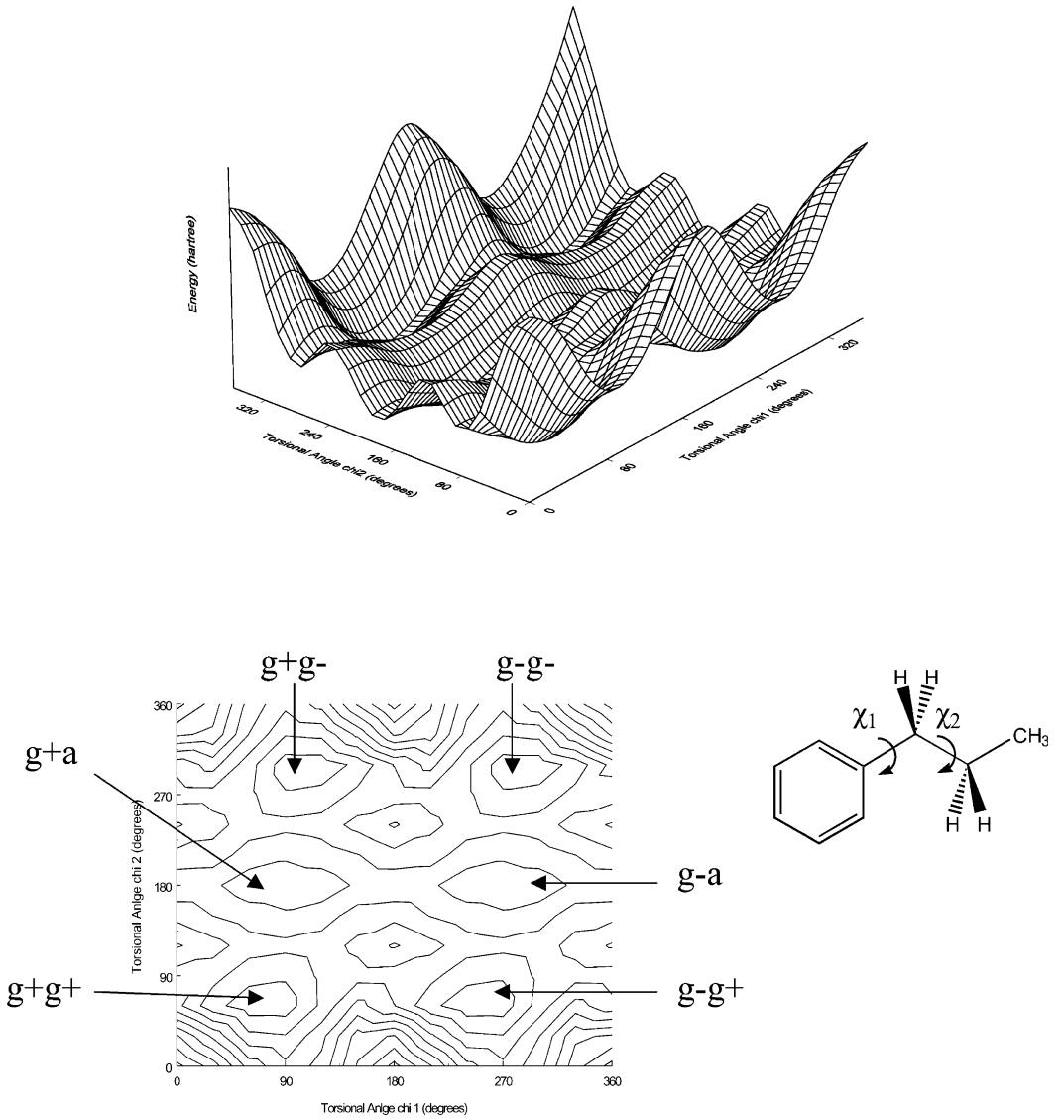

Fig. 7. *n*-Propyl-benzene conformational surface (top) and contour (bottom).

are summarized in Table 5.

$$\Delta\chi_1(Z) = \chi_1(Z) - \chi_1(H),$$

$$\Delta\chi_2(Z) = \chi_2(Z) - \chi_2(H)$$

An attempt was made to correlate the ΔE values with the electron withdrawing nature of substituent Z. Several parameters were tried but the classical Hammett-substituent constant (σ_p) gave the best correlation (see Fig. 10). The negative slope of the line indicates that the greater the electron withdrawing nature of the substituent, the more stable the *gauche* conformer. In other words, in the case of electron withdrawing groups, the *gauche*-effect will dominate the conformational energetics. Needless to say, future work will be done on the relative conformer stabilities in solvated mediums.

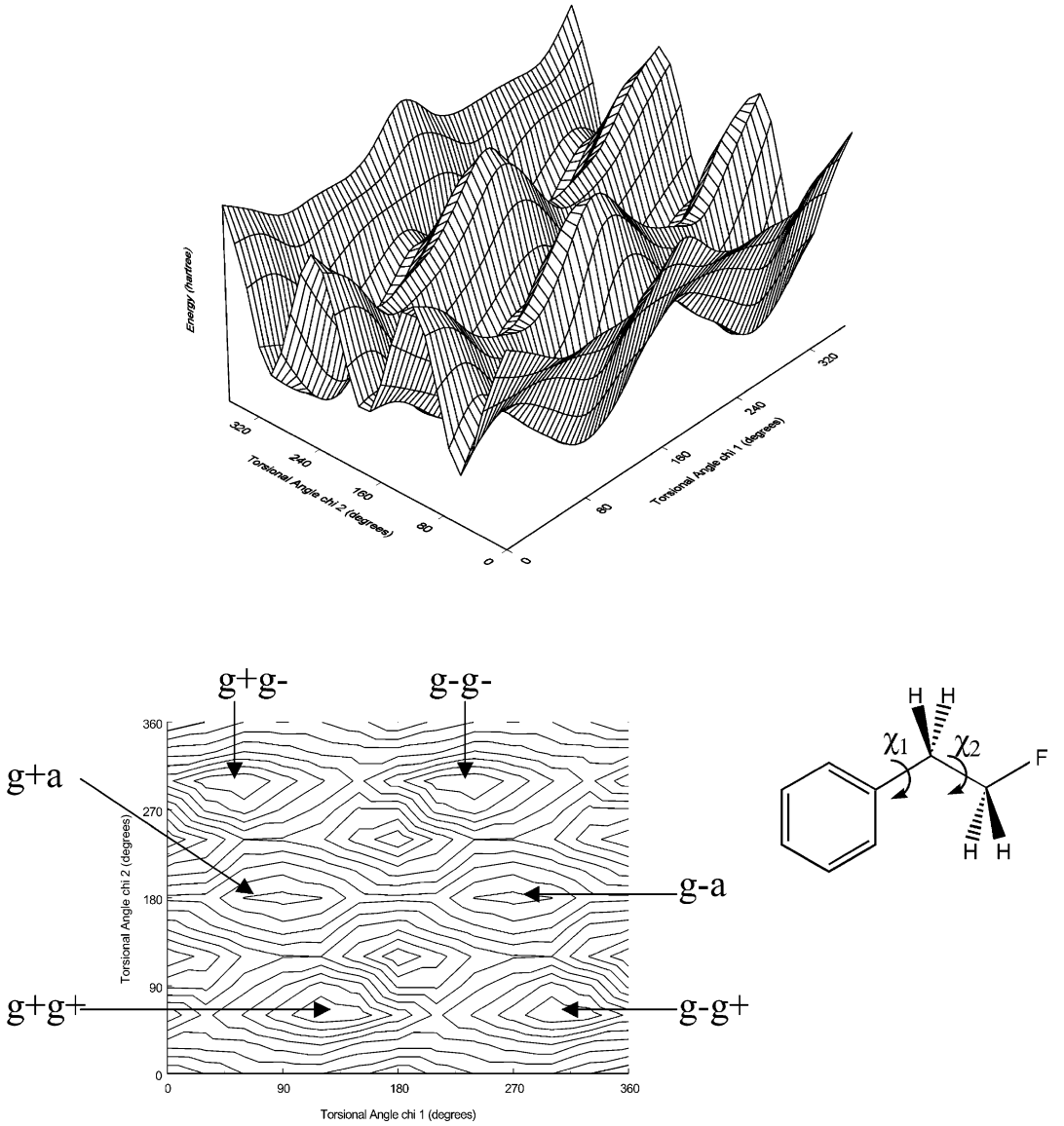

Fig. 8. 2-Phenyl-fluoroethane conformational surface (top) and contour (bottom).

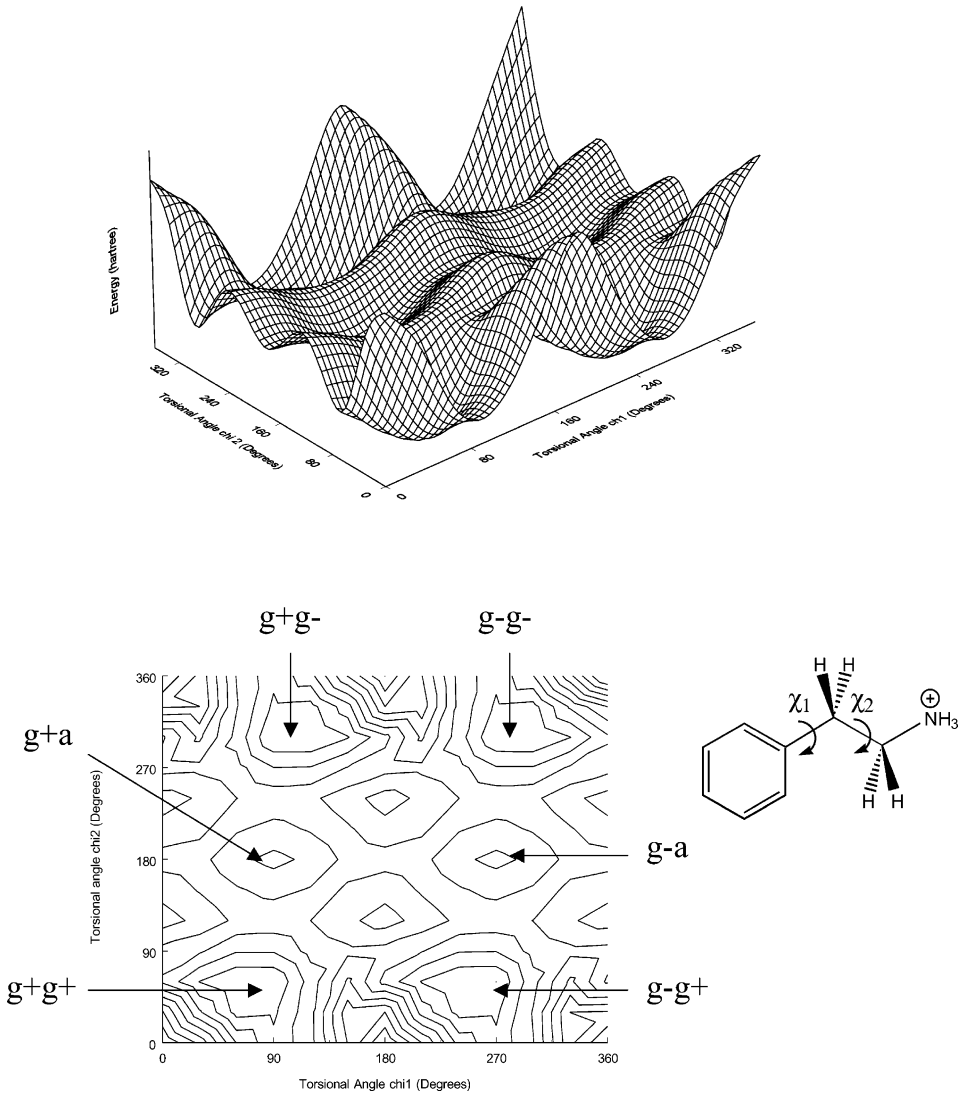

Fig. 9. Protonated 2-phenyl-ethyl-amine conformational surface (top) and contour (bottom).

Table 1
Optimized minima for ethyl-benzene

Conformer		χ_1 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	χ_2 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	RHF/3-21G energy (hartree)	RHF/6-31G(d) energy (hartree)	B3LYP/6-31G(d) energy (hartree)	Relative energy for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (kcal mol^{-1})
$g+$	$g+$	89.09, 89.41, 89.19	59.67, 59.89, 59.78	−307.060051710	−308.774779880	−310.880250443	0.00, 0.00, 0.00
$g+$	a	88.94, 89.38, 89.18	179.99, 180.00, 180.00	−307.060051669	−308.774779878	−310.880250444	**0.00**, **0.00**, **0.00**
$g+$	$g-$	88.94, 89.38, 89.18	−59.70, −59.87, −59.78	−307.060051669	−308.774779878	−310.880250444	0.00, 0.00, 0.00
$g-$	$g+$	−89.17, −89.45, −89.21	59.67, 59.88, 59.78	−307.060051686	−308.774779873	−310.880250444	0.00, 0.00, 0.00
$g-$	a	−88.96, −89.38, −89.18	180.00, 180.00, 180.00	−307.060051671	−308.774779878	−310.880250444	**0.00**, **0.00**, **0.00**
$g-$	$g-$	−88.94, −89.38, −89.19	−59.70, −59.88, −59.78	−307.060051668	−308.774779878	−310.880250444	0.00, 0.00, 0.00

Table 2
Optimized minima for *n*-propyl-benzene

Conformer		χ_1 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	χ_2 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	RHF/3-21G energy (hartree)	RHF/6-31G(d) energy (hartree)	B3LYP/6-31G(d) energy (hartree)	Relative energy for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (kcal mol^{-1})
$g+$	$g+$	75.86, 74.96, 74.61	65.95, 65.28, 65.25	−345.878973539	−347.808761587	−350.193464614	0.29, 0.62, 0.51
$g+$	a	88.89, 89.34, 89.02	180.01, 180.00, 180.00	−345.879428191	−347.809746806	−350.194284891	**0.00**, **0.00**, **0.00**
$g+$	$g-$	103.65, 104.93, 104.72	−65.94, −65.28, −65.24	−345.878973587	−347.808761577	−350.193464343	0.29, 0.62, 0.51
$g-$	$g+$	−103.58, −104.92, −104.71	65.93, 65.28, 65.24	−345.878973560	−347.808761583	−350.193464348	0.29, 0.62, 0.51
$g-$	a	−88.87, −89.36, −89.00	179.99, 180.00, 180.00	−345.879428152	−347.809746803	−350.194284924	**0.00**, **0.00**, **0.00**
$g-$	$g-$	−75.79, −74.79, −74.60	−65.95, −65.27, −65.25	−345.878973590	−347.808761584	−350.193464607	0.29, 0.62, 0.51

Table 3
Optimized minima for protonated 2-phenyl-ethyl-amine

Conformer		χ_1 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	χ_2 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	RHF/3-21G energy (hartree)	RHF/6-31G(d) energy (hartree)	B3LYP/6-31G(d) energy (hartree)	Relative energy for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (kcal mol^{-1})
g +	*g* +	75.16, 75.65, 81.29	55.15, 56.06, 55.92	−362.162263230	−364.171039203	−366.596808686	−4.33, −3.55, −3.93
g +	*a*	89.26, 89.23, 88.99	179.98, 180.00, 180.0	−362.155361220	−364.165703630	−366.590546041	**0.00**, **0.00**, **0.00**
g +	*g*−	103.43, 104.90, 95.74	−55.23, −56.04, −55.69	−362.162263436	−364.171039248	−366.596809731	−4.33, −3.55, −3.93
g−	*g* +	−103.40, −104.90, −95.61	55.18, 56.04, 55.75	−362.162263430	−364.171039249	−366.596809473	−4.33, −3.55, −3.93
g−	*a*	−89.22, −89.23, −89.01	179.95, −179.97, 179.99	−362.155361254	−364.165703659	−366.590546053	**0.00**, **0.00**, **0.00**
g−	*g*−	−75.13, −73.63, −89.29	−55.17, −56.05, −55.92	−362.162263396	−364.171039224	−366.596808682	−4.33, −3.55, −3.93

Table 4
Optimized minima for 2-phenyl-fluoroethane

Conformer		χ_1 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	χ_2 for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (°)	RHF/3-21G energy (hartree)	RHF/6-31G(d) energy (hartree)	B3LYP/6-31G(d) energy (hartree)	Relative energy for RHF/3-21G, RHF/6-31G(d), B3LYP/6-31G(d) (kcal mol^{-1})
g +	*g* +	131.90, 105.11, 114.88	70.68, 66.50, 68.03	−405.378078850	−407.623175983	−410.106976566	−0.44, 0.42, −0.19
g +	*a*	88.69, 89.37, 88.78	180.00, 179.99, 180.00	−405.377381250	−407.623838439	−410.106678480	**0.00, 0.00, 0.00**
g +	*g*−	49.35, 74.35, 64.56	−70.66, −66.52, −68.04	−405.378078878	−407.623175971	−410.106976832	−0.44, 0.42, −0.19
g−	*g* +	−49.39, −74.39, −64.56	70.62, 66.52, 68.04	−405.378078916	−407.623175931	−410.106976828	−0.44, 0.42, −0.19
g−	*a*	−89.11, −89.22, −88.76	180.03, 179.97, 180.00	−405.377381566	−407.623838545	−410.106678470	**0.00**, **0.00**, **0.00**
g−	*g*−	−131.62, −105.06, −114.88	−70.61, −66.55, −68.02	−405.378078904	−407.623175950	−410.106976569	−0.44, 0.42, −0.19

Table 5
Relative energy values (ΔE) w.r.t. ethyl/benzene g^+g^+ and selected conformational shifts for Ph–CH_2–CH_2–Z ($\Delta\chi_1$) as a function of substituent electronic effect (σ_p) (taken from Ref. [2])

Z	σ_p	ΔE (kcal mol^{-1})	{$z[g + g +]$} (°)	
			$\Delta\chi_1$	$\Delta\chi_2$
$-CH_3$	−0.14	0.51	−14.58	5.47
–H	0.00	0.00	0.00	0.00
–F	0.15	−0.19	25.69	8.25
$-NH_3^+$	0.60	−3.93	−7.90	−3.86

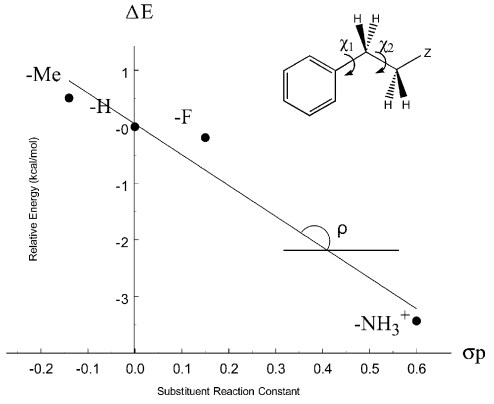

Fig. 10. LFER type correlation for relative conformational energies (ΔE versus σ_p) for Ph–CH_2–CH_2–Z [Z = –H, $-CH_3$, –F, and $-NH_3^+$].

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