Molecular structures of β-amino-α-bromovinyl trifluoromethyl ketones

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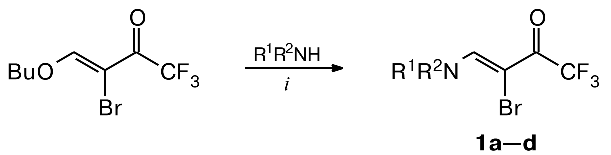
The molecular structures of β-amino-α-bromovinyl trifluoromethyl ketones was studied by UV, IR, ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy and using the density functional (B3LYP/6-31G(d,p) and PBE/QZ3P) and *ab initio* riMP2/cc-pVTZm quantum-chemical calculations. Factors affecting stabilization of the *EZE*-conformation of the molecules, which is atypical of analogous unsubstituted amino enones, are considered.

Key words: α,β-unsaturated trifluoromethyl ketones, molecular structure, isomerism, hydrogen bond.

β-Amino enones are starting compounds in various, sometimes poorly predictable chemical transformations. They are considered as convenient synthons in the design of heterocyclic systems. Various aspects of chemistry of these compounds have been the subject of numerous reviews.[1—7] Nevertheless, perfluoro-substituted β-amino enones are still little studied in spite of increasing interest in organofluorine compounds. Polydentate character and high reactivity make fluorinated enones attractive and valuable building blocks in organic synthesis.[8] In the present work, we studied the molecular structures of β-amino-α-bromovinyl trifluoromethyl ketones[9—11] (Scheme 1).

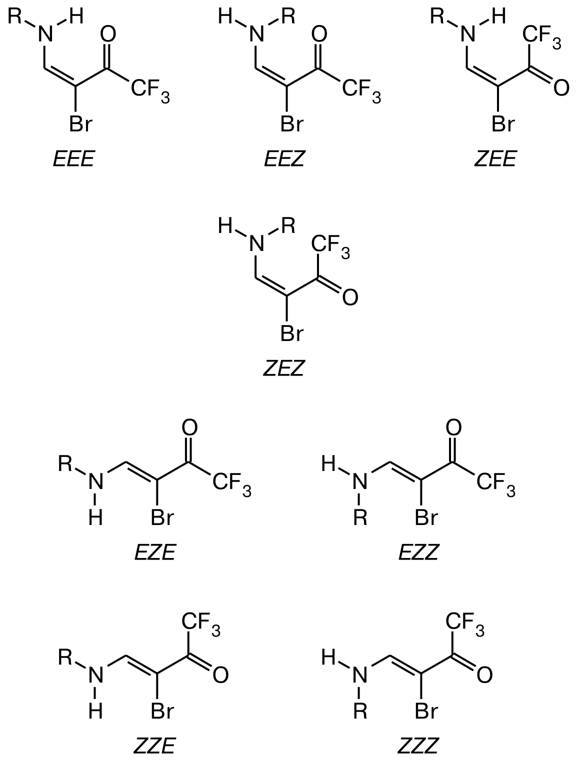
Scheme 1



R^1 = H, R^2 = Me (**a**), Bn (**b**), $HOCH_2CMe_2$ (**c**); R^1 = R^2 = Et (**d**)

i. Et_2O or THF, 25 °C.

Amino enones **1** containing a secondary amino group can have eight diastereomers and rotamers.



Unlike unsubstituted β-trifluoroacetyl(amino)alkenes, which usually exist as mixtures of geometric isomers,[12—14] β-amino-α-bromo enones **1a—c** exist as single isomers. Determination of the configuration of these compounds with only one olefinic proton is a non-trivial task. Therefore, in addition to ^{1}H, ^{13}C, and ^{15}N NMR spectra, in this work we also analyzed the UV and IR spectra of these compounds and the results of quantum-chemical calcula-

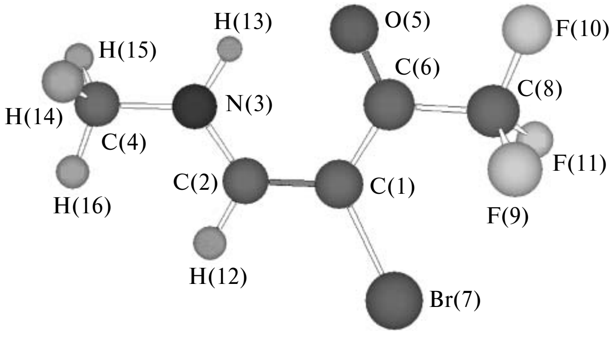
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 102—106, January, 2005.

tions carried out by the B3LYP/6-31G(d,p), PBE/QZ3P, and riMP2/cc-pVTZm methods.

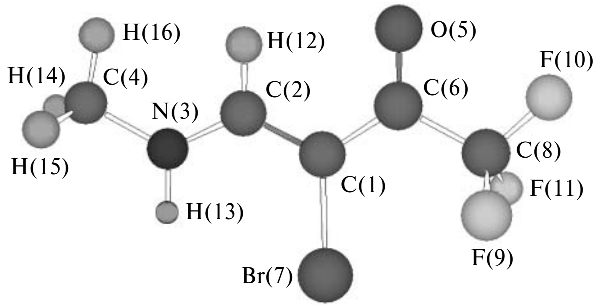
The long-wavelength absorption band in the UV spectrum of a solution of compound **1a** (MeCN, 32700 cm^{-1}) is on the border separating intervals characteristic of the antiperiplanar (ap, ap) (35100—32800 cm^{-1}) and synperiplanar (sp, sp) (33300—31250 cm^{-1}) conformations of amino enones.[1,15] This complicates the determination of the molecular conformation based on the UV spectroscopy data. The intensity ratio observed for the C=O (1670 cm^{-1}, w) and C=C (1620 cm^{-1}, vs) stretching bands in the IR spectra of the solutions of **1a** in $CHCl_3$, CH_2Cl_2, or MeCN suggests an sp-orientation of bonds in the C=C—C=O fragment and excludes the *ZEE*, *ZEZ*, *ZZE*, and *ZZZ* rotamers with the ap-arrangement of the carbonyl group and the double bond[2,16] from consideration.

Analysis of NMR spectra even more reduces the number of possible structures. The vicinal coupling constant between the carbonyl C atom and the olefinic proton is known to be smaller for the sp-isomer than for the ap-isomer (0—6 and 9—14 Hz, respectively).[14,17,18] The $^3J_{C-H}$ constants of the β-amino-α-bromo enones containing tertiary or secondary amino groups lie between 1 and 4 Hz. The *E*- and *Z*-isomers of their structural analog, 4-(4-ethoxyanilino)-1,1,1-trifluorobut-3-en-2-one existing in DMSO-d_6 solution as a 2 : 1 mixture of geometric isomers, are characterized by the $^3J_{C-H}$ values of 3.6 and 9.6 Hz, respectively.[10] The results obtained point to the *Z*-configuration of β-amino-α-bromo enones **1a—c** and rule out the structures *EEE* and *EEZ*.

Among the remaining two rotamers, *EZZ* and *EZE*, the latter can be preferred based on the $^3J_{H-H}$ vicinal constant. In the case of β-methylaminovinyl trifluoromethyl ketone, the coupling constant between the olefinic proton and amino group proton increases from 7.8 Hz for the *ZZZ*-rotamer to 13.9 Hz for the *EZE*-rotamer.[14] The corresponding constants of β-amino-α-bromo enones **1a—c** vary within a narrow interval from 13.7 to 14.4 Hz, which unambiguously indicates the *EZE*-configuration of the molecules under study, being consistent with the results obtained earlier.[11]



EEE



EZE

Fig. 1. PBE/QZ3P (I) and riMP2/cc-pVTZm (II) calculated structures of *EEE* and *EZE* rotamers of molecule **1a**

Parameter	*EEE*		*EZE*	
	I	II	I	II
Distance		*d*/Å		
H(13)...O	1.811	1.810	—	—
H(13)...Br	—	—	2.604	2.621
N—H(13)	1.033	1.020	1.020	1.010
N...O	2.628	2.610	—	—
N...Br	—	—	3.114	3.109
H(12)...Br	2.858	2.847	—	—
H(12)...O	—	—	2.412	2.373
Angle		θ/deg		
N—H(13)...O	133.3	132.6	—	—
N—H(13)...Br	—	—	110.7	109.7

This configuration of molecules **1a—c** is atypical of α-unsubstituted amino enones. Its stability can be explained by the influence of several factors including the presence of intramolecular hydrogen bond NH...Br. To confirm this assumption, we carried out a theoretical study of the diastereomers and rotamers of molecule **1a** by the B3LYP/6-31G(d,p), PBE/QZ3P, and riMP2/cc-pVTZm methods. According to calculations, the *EEE* and *EZE* geometric isomers containing chelate rings closed by the NH...O or NH...Br bond (Fig. 1) are the most stable structures in the isolated state (Table 1). The total energy difference (ΔE_t) between them is 1.4 (PBE/QZ3P) and 1.5 kcal mol^{-1} (riMP2/cc-pVTZm). The PBE/QZ3P calculated total energy differences (ΔE) suggest that the *EZE* isomer can be additionally stabilized through the intramolecular hydrogen bond NH...Br (Fig. 2). At first glance, this seems to be a matter of opinion. Indeed, the NH...O=C bond belongs to moderately strong bonds with energies lying between 5 and 10 kcal mol^{-1}. Therefore, it seems unlikely that the NH...Br bond can compete with the NH...O=C bond provided that some factors do not weaken the intramolecular interaction NH...O=C or counteract it. The results obtained show that the NH...O=C bond in the *EEE* isomer is actually rather strong, because the energy of its formation is nearly 10 kcal mol^{-1} (see Fig. 2). However, among the two geometric isomers (*EEZ* and *EZZ*) containing no hydrogen

Table 1. Relative energies (E_t) of isomers of molecule **1a** calculated by different methods

Isomer	E_t/kcal mol^{-1}			
	PBE /QZ3P	PBE /QZ3P(ZPVE)	riMP2 /cc-pVTZm	B3LYP /6-31G(d,p)
ZEE	7.8	7.8	8.0	—
ZEZ	14.4	14.7	13.5	—
ZZE	0.0	0	0	—
ZZZ	6.1	6.4	5.4	—
EEE	0	0.1	0.3	0
EEZ	9.7	10.0	9.1	10.4
EZE	1.4	1.4	1.8	1.1
EZZ	7.4	7.6	6.9	6.3

bonds, the latter is more stable (by ~2.3 kcal mol^{-1}), which suggests that the antiplanar rotamers are preferable. The hydrogen bond NH...Br, which is weaker than the NH...O bond, is also involved in stabilization of molecules **1a—c**.

In addition, we performed a topological analysis of the electron density distribution in the *EZE* and *EEE* conformers of molecule **1a** according to Bader.[19] In these cases, the presence of hydrogen bond must cause the appearance of ring critical points with (3, 1) signature in additon to the bond critical points with (3, −1) signature, as follows from the Poincaré—Hopf relationship[19] relating the number of atomic nuclei and chemical bonds to the number of the ring and cage critical points. In calculating the *EEE* conformer a bond critical point was located in the region between the oxygen atom and amino group H atom. The electron density and electron density Laplacian values (separated by a slash in the text below) at this critical point are characteristic of hydrogen bonds, being equal to 0.03954/0.12291 (PBE/QZ3P) and 0.03987/0.12623 (riMP2/cc-pVTZm). A ring critical point with the parameters 0.01846/0.10926 (PBE/QZ3P) and 0.01849/0.11311 (riMP2/cc-pVTZm) was located in the region confined by the atoms O(5)—C(6)—C(1)—C(2)—N(3)—H(13), which clearly indicates the formation of an H-bond. Calculations of the *EZE* conformer revealed a bond critical point in the region between the Br atom and amino group H atom with the parameters 0.01630/0.05268 (PBE/QZ3P) and 0.01536/0.05940 (riMP2/cc-pVTZm) and a closely lying ring critical point in the region Br—C(1)—C(2)—N(3)—H(13) with the parameters 0.01602/0.06683 (PBE/QZ3P) and 0.01535/0.06399 (riMP2/cc-pVTZm). Similar electron density values at the critical point of the H...Br hydrogen bond and at the ring critical point for the *EZE* conformer calculated by the PBE/QZ3P and riMP2/cc-pVTZm methods and close proximity between these points indirectly confirm a rather weak interaction between the Br atom and the amino H atom.

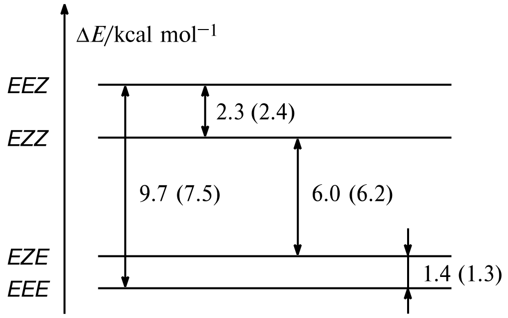


Fig. 2. PBE/QZ3P calculated energy differences (Δ*E*). The Δ*E* with inclusion of zero-point vibrational energy (ZPVE) correction.

Thus, enhanced stability of the *EZE* conformer of molecule **1a** is due to at least two reasons, namely, energy factors that favor stabilization of the ap,sp-conformer and an additional energy gain owing to possible formation of a weak intramolecular bond NH...Br. Stabilization can also be due to the 1,3-interaction (CH...O=C), which is favored by a shortened contact between the olefinic proton and the carbonyl O atom (see Fig. 1).

^{1}H and ^{15}N NMR spectroscopy and IR spectroscopy also confirm the existence of a weak intramolecular bond NH...Br in molecule **1a**. It is known[2] that the position of the amino proton resonance in intramolecularly hydrogen-bonded chelates varies over a wide range (from δ 5 to 20), the magnitude of the chemical shift δ(NH) being a bond strength indicator. The δ(NH) values (relative to Me_4Si) calculated for different isomers of molecule **1a** by the B3LYP/6-31G(d,p) and PBE/QZ3P methods are listed in Table 2. The experimental δ(NH) value for **1a** (δ 6.2; $CDCl_3$) is much closer to that calculated for the *EZE* isomer (see Table 2).

^{15}N NMR spectra also indirectly confirm the existence of intramolecular hydrogen bond NH...Br in the molecules of compounds **1a,b**. A high-field shift of the nitrogen resonance in tertiary β-amino enones by ~10—20 ppm compared to their analogs containing a primary or secondary amino group was attributed to the

Table 2. Chemical shift of amino group calculated for different conformers of molecule **1a**

Isomer	δ(NH), ppm	
	PBE/QZ3P	B3LYP/6-31G(d,p)
ZEE	6.07	—
ZEZ	4.67	—
ZZE	5.48	—
ZZZ	4.33	—
EEE	11.48	9.56
EEZ	4.97	4.07
EZE	5.62	4.52
EZZ	4.57	3.70

Table 3. ^{15}N NMR chemical shifts in molecules of β-amino-α-bromo enones **1** ($CDCl_3$)

Amino enone	δ(^{15}N), ppm
1a	104.7
1b	114.8
1d	127.3

effect of an intramolecular hydrogen bond NH...O.[2] For the same reason, $E \rightarrow Z$-isomerization of amino enones $R^1NH—CH=CH—C(O)R^2$ is accompanied by deshielding of the N atom, thus leading to a low-field shift of the amino group resonance by ~10 ppm. A comparison of the parameters of the ^{15}N NMR spectra of the amino enones containing tertiary (**1d**) and secondary amino group (**1a,b**) shows that nitrogen atoms in the last two compounds are deshielded and their signals are shifted by 12—22 ppm toward lower fields (Table 3). Taking into account structural similarity of the compounds under study and identical conditions for recording NMR spectra, we can state that a possible reason for this chemical shift difference can be the intramolecular hydrogen bond NH...Br.

The IR spectrum of a saturated solution of compound **1a** in $CHCl_3$ exhibits two absorption bands with maxima at 3250 and 3380 cm^{-1} in the region of N—H stretching vibrations. The peak intensity ratio of these bands strongly depends on solution concentration. Similarly to the solid phase, the low-frequency component of the doublet (3250 cm^{-1}) characterizes the stretching vibrations of the amino group involved in the intermolecular H-bond NH...O=C. At rather high dilution, the IR spectrum exhibits only the high-frequency stretching band (3380 cm^{-1}) of the NH group involved in the intramolecular bond NH...Br. This frequency is lower than the stretching vibration frequencies of a free NH group in various amino enones including those containing the CF_3 group (3440—3490 cm^{-1}).[20—22] Note that introduction of the halogen atom influences the interaction between the nitrogen atom and the enone π-system, leading to an increase in the ν(NH) frequency by ~10 cm^{-1}.[16] Our calculations show (Table 4) that the ν(NH) vibrational frequencies of the *EZE* and *ZZE* rotamers are 70—115 cm^{-1} lower than the frequencies of those rotamers where contact between the Br atom and amino H atom is impossible. In addition, the ν(NH) vibrational frequency of the *EEE* rotamer indicates the formation of a hydrogen bond with the carbonyl O atom, approaching the frequency of the low-frequency component of the doublet in the region of N—H vibrations for the solid phase. Therefore, the low-frequency shift of the band in question can be explained only by the presence of a weak intramolecular hydrogen bond NH...Br.

Table 4. PBE/QZ3P calculated vibrational frequencies (ν(NH)) and intensities (*I*) of molecule **1a**

Conformer	ν(NH)/cm^{-1}	*I*/km mol^{-1}
ZEE	3527.4	83.972
ZEZ	3551.9	86.616
ZZE	3454.2	42.529
ZZZ	3567.6	84.256
EEE	3245.2	92.626
EEZ	3557.5	87.211
EZE	3453.4	39.297
EZZ	3564.0	82.242

Thus, in contrast to α-unsubstituted amino enones, the molecules of their α-bromo-substituted analogs exist in dilute solutions as the *EZE*-isomers stabilized by conformational factors and through a weak NH...Br bond.

Experimental

IR and UV spectra of solutions of the compounds under study were recorded on Specord 75 IR and Specord UV—VIS spectrophotometers, respectively. Room-temperature ^{1}H, ^{13}C (with Me_4Si as reference), and ^{15}N (with NH_3 as reference) NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 400, 100 and 40 MHz, respectively, in $CDCl_3$. Signals in the ^{13}C NMR spectra were assigned using the DEPT technique.

Quantum-chemical calculations of isomers of molecule **1a** were carried out with full geometry optimization using two density functional methods, B3LYP/6-31G(d,p) and PBE/QZ3P, and by the riMP2/cc-pVTZm method. The cc-pVTZm basis set is based on the well-known Dunning-type correlation-consistent basis set cc-pVTZ with the same number of the basis functions but with another contraction pattern: {6,7,8/2,3/2} for the H atom, {9,10,11,12/6,7,8/2,3/2} for the C, N, O, F atoms, and {17,18,19,20,21,22/12,13,14,15,16/8,9,10/2} for the Br atom. The contraction pattern for the QZ3P basis set was as follows: {5,3×1/3×1/2×1} for the H atom, {7,7×1/5,3×1/3×1/2×1} for the C, N, O, F atoms, and {8,17×1/6,13×1/6,8×1/3×1} for the Br atom. PBE/QZ3P calculations were followed by calculations of the Hessian and vibrational analysis of the structures obtained (all of them were found to correspond to local minima on the potential energy surfaces). B3LYP/6-31G(d,p) calculations were carried out using the GAUSSIAN-98 [23] suite. PBE/QZ3P [24] and riMP2/cc-pVTZm calculations and analysis of structures under study according to Bader were performed using the PRIRODA program.[25] riMP2 is an accelerated version of the MP2 method. It is based on the approximation of two-electron four-center integrals.[26] The synthesis of amino enones **1a—d** was reported in our earlier studies.[9,10]

The authors express their gratitude to Prof. V. A. Lopyrev for help in performing calculations with GAUSSIAN-98, to Dr. D. N. Laikov for providing access to the PRIRODA program and basis sets and halpful discussions. The authors also express gratitude to the Research Computing Center at the M. V. Lomonosov Moscow State University for providing computing time and help in employment of computational resources.

This work was carried out with the financial support from the Russian Foundation for Basic Research (Project No. 02-03-32547).

References

1. J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.
2. U. Kuckländer, in *The Chemistry of Enamines*, Ed. Z. Rappoport, Wiley, New York, 1994, 523.
3. Ya. F. Freimanis, *Khimiya enaminoketonov, enaminoiminov, enaminotionov* [*Chemistry of Enamino Ketones, Enamino Imines, and Enamino Thiones*], Zinatne, Riga, 1974, 276 pp. (in Russian).
4. H. E. Gottlieb, in *The Chemistry of Enones*, Eds S. Patai and Z. Rappoport, Wiley, New York, 1989, 129.
5. Yu. V. Smirnova and Zh. A. Krasnaya, *Usp. Khim.*, 2000, **69**, 1111 [*Russ. Chem. Rev.*, 2000, **69** (Engl. Transl.)].
6. P. Lue and J. V. Greenhill, *Adv. Heterocycl. Chem.*, Ed. A. R. Katritzky, 1997, **67**, 207.
7. C. Cimarelli and G. Palmieri, *Recent Res. Dev. Org. Chem.*, 1997, 179.
8. V. G. Nenajdenko, A. V. Sanin, and E. S. Balenkova, *Usp. Khim.*, 1999, **68**, 483 [*Russ. Chem. Rev.*, 1999, **68**, 437 (Engl. Transl.)].
9. A. Yu. Rulev, D.Sc. (Chem.) Thesis, A. E. Favorskii Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk, 2002, 299 pp. (in Russian).
10. A. Yu. Rulev, S. V. Fedorov, V. G. Nenajdenko, E. S. Balenkova, and M. G. Voronkov, *Izv. Akad Nauk. Ser. Khim.*, 2003, 2164 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 2287].
11. I. I. Gerus, L. M. Kacharova, and S. I. Vdovenko, *Synthesis*, 2001, 431.
12. I. I. Gerus, M. G. Gorbunova, S. I. Vdovenko, Yu. L. Yagupol´skii, and V. P. Kukhar´, *Zh. Org. Khim.*, 1990, **26**, 1877 [*J. Org. Chem. USSR*, 1990, **26** (Engl. Transl.)].
13. A. L. Krasovskii, V. G. Nenajdenko, and E. S. Balenkova, *Izv. Akad Nauk. Ser. Khim.*, 2001, 1329 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1395].
14. J. Wójcik, W. Domalewski, K. Kamieńska-Trela, L. Stefaniak, S. I. Vdovenko, I. I. Gerus, and M. G. Gorbunova, *Magn. Res. Chem.*, 1993, **31**, 808.
15. J. Gavronski, in *The Chemistry of Enones*, Eds S. Patai and Z. Rappoport, Wiley, New York, 1989, 55.
16. L. J. Bellamy, *Advances in Infrared Group Frequences*, Methuen, London, 1968, 304 pp.
17. P. E. Hansen, *Progr. in NMR Spectroscopy*, 1981, **14**, 175.
18. J. L. Chiara and A. Gomez-Sanchez, *NMR Spectra*, in *The Chemistry of Enamines*, Ed. Z. Rappoport, Wiley, New York, 1994, 279.
19. R. F. W. Bader, *Atoms in Molecules — A Quantum Theory*, Oxford University Press, Oxford, 1990, 458 pp.
20. J. Dabrowski, K. Kamieńska-Trela, and L. Kania, *Tetrahedron*, 1976, **32**, 1025.
21. L. Kania, K. Kamieńska-Trela, and M. Witanowski, *J. Mol. Struct.*, 1983, **102**, 1.
22. S. I. Vdovenko, I. I. Gerus, and M. G. Gorbunova, *J. Chem. Soc., Perkin Trans. 2*, 1993, 559.
23. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, *GAUSSIAN 98, Revision A.6*, Gaussian, Inc., Pittsburgh (PA), 1998.
24. J. P. Perdew, K. Burke, and M. Ernzerhof, *Phys. Rev. Lett.*, 1996, **77**, 3865.
25. D. N. Laikov, *Chem. Phys. Lett.*, 1997, **281**, 151.
26. R. A. Kendall and H. A. Fruchtl, *Theor. Chim. Acta*, 1997, **97**, 158.

Received September 30, 2004;
in revised form January 9, 2005