J. Phys. Chem. A **1999,** *103,* 4861−4864

Experimental and ab Initio Studies on Solid-State Hydrogen Isotope Exchange with Spillover Tritium

Yurii A. Zolotarev,*,† Yurii A. Borisov,‡ and Nikolai F. Myasoedov†

Institute of Molecular Genetics, Russian Academy of Sciences, 123182, Kurchatov sq., Moscow, Russia, and Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813, Vavilov st. 28, Moscow, Russia

Received: September 24, 1998; In Final Form: January 8, 1999

This study utilizes ab initio calculations to investigate the reaction of high-temperature solid-state catalytic isotope exchange (HSCIE) between amino acids and spillover tritium. The Hartree−Fock approximation and second-order Møller−Plesset perturbation theory in conjunction with 6-31G* and aug-cc-pVDZ basis sets were used to calculate potential energy surfaces for the interactions between CH_4, alanine, hydroxyproline, and the H_3O^+ ion. Ab initio calculations were used to estimate the activation energies and structures of the transition states of these reactions. The hydrogen exchange reaction occurs by a synchronous mechanism, with a transition state that is characterized by pentacoordinated carbon. The proposed one-center mechanism is in good agreement with observed retention of configuration of the asymmetric carbon atoms in the HSCIE reaction with spillover tritium in experiments. The regioselectivity and stereoselectivity of hydrogen isotope exchange in amino acids with spillover tritium can be predicted on the basis of ab initio calculations of interaction of this compound with a model acidic center, taking the H_3O^+ ion as an example.

Introduction

In the case of interaction with supported catalysts (metals of the platinum group) H atoms bound to the surface atoms migrate to the carrier. This effect is called hydrogen spillover.[1] Spillover hydrogen (SH) is capable of entering into almost all reactions typical of hydrogen activated on the surface of a platinum group metal. SH ensures hydrogenation of solid unsaturated organic compounds at room temperature.[2] Solid-state reactions between organic compound and SH have found a wide application in the synthesis of labeled compounds. The reaction based on high-temperature solid-state catalytic isotope exchange (HSCIE)[3] was proved to be especially effective. With HSCIE, it became possible to substitute hydrogen atoms for tritium almost completely in organic molecules of different classes. These uniformly labeled compounds were previously unavailable. At the same time, the nature of SH activated on the catalyst still remained undetermined and the mechanism of solid-state reactions was unknown.

There are hypotheses that SH can be either a solvated proton[4] or a proton−electron pair.[5] Hydrogen spillover over a carbon surface is accompanied by simultaneous electron and ion conductivity.[5] Ab initio calculations of hydrogen migration over a model graphite-like surface are in favor of the hypothesis about the protonic nature of SH.[6] At moderate temperature, a proton is always covalently bonded to one of the electron donor atoms. Migration of the proton over a surface containing bound water or hydroxyl groups can occur by a relay mechanism with an activation energy of 5 kcal/mol.[7] Water molecules adsorbed on the surface may participate in transport of SH. The acidic centers formed in this process can participate in the isotope exchange reaction. It has been shown that adsorbed water is a cocatalyst of SH migration.[4] The action of SH with the surface of the silica aluminas create Brønsted acidic sites. This process is accelerated in the presence of H_2O and H_2S.[8] It has been shown by IR spectroscopy that highly acidic Brønsted-type centers of the H^+ forms of zeolite were H_3O^+ ions bonded by hydrogen bonds to the silica aluminas.[9,10] These H^+ forms resulted from the decationization of zeolite via the treatment with aqueous HCl solution.[11]

In this communication, the interaction of the H_3O^+ ion with organic compounds was studied as a model for HSCIE reaction of amino acids with spillover hydrogen. The conventional hydrogen exchange mechanism implies the participation of two water molecules. This two-center mechanism provides for the synchronous transfer of H^+ from H_3O^+ to CH_4 and from CH_4 to another H_2O with a configuration reversal of the carbon atom taking place.[12] However, hydrogen isotope exchange in the HSCIE reaction proceeds with retention of the configuration of asymmetric carbon atoms.[13] Because of this, we made an attempt to find a mechanism of hydrogen substitution at the saturated carbon atom under the action of H_3O^+ ions, in which the initial configuration is retained. As a result, a new pathway has been found for the reaction of hydrogen substitution in methane under the action of H_3O^+ ions. Previously, a transition state for a one-center mechanism for hydrogen exchange between CH_4 and one H_3O^+ molecule was found by the HF/6-31G* method.[14] In this communication, we present a more detailed ab initio study of the new mechanism for hydrogen substitution at a saturated carbon atom for CH_4 using the IRC method and then apply this one-center mechanism to the analysis of HSCIE reactions between amino acids and SH.

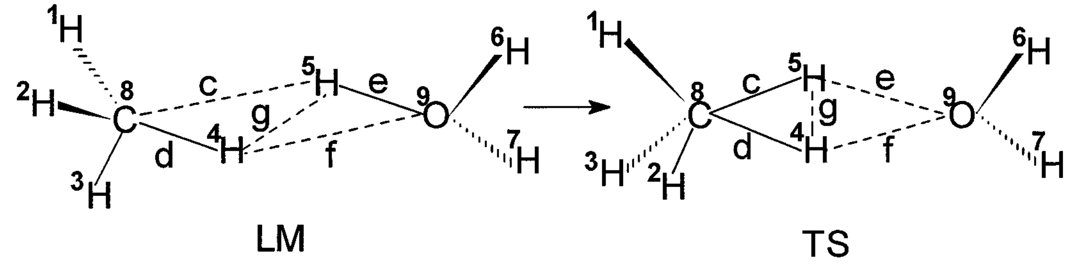
Results and Discussion

Ab initio calculations for hydrogen exchange between methane and hydroxonium ion were performed at the second-order level of Møller−Plesset perturbation theory[15] using 6-31G* basis sets (MP2/6-31G*). The transition state (TS) and

---

† Institute of Molecular Genetics.
‡ Nesmeyanov Institute of Organoelement Compounds.

10.1021/jp9838487 CCC: $18.00



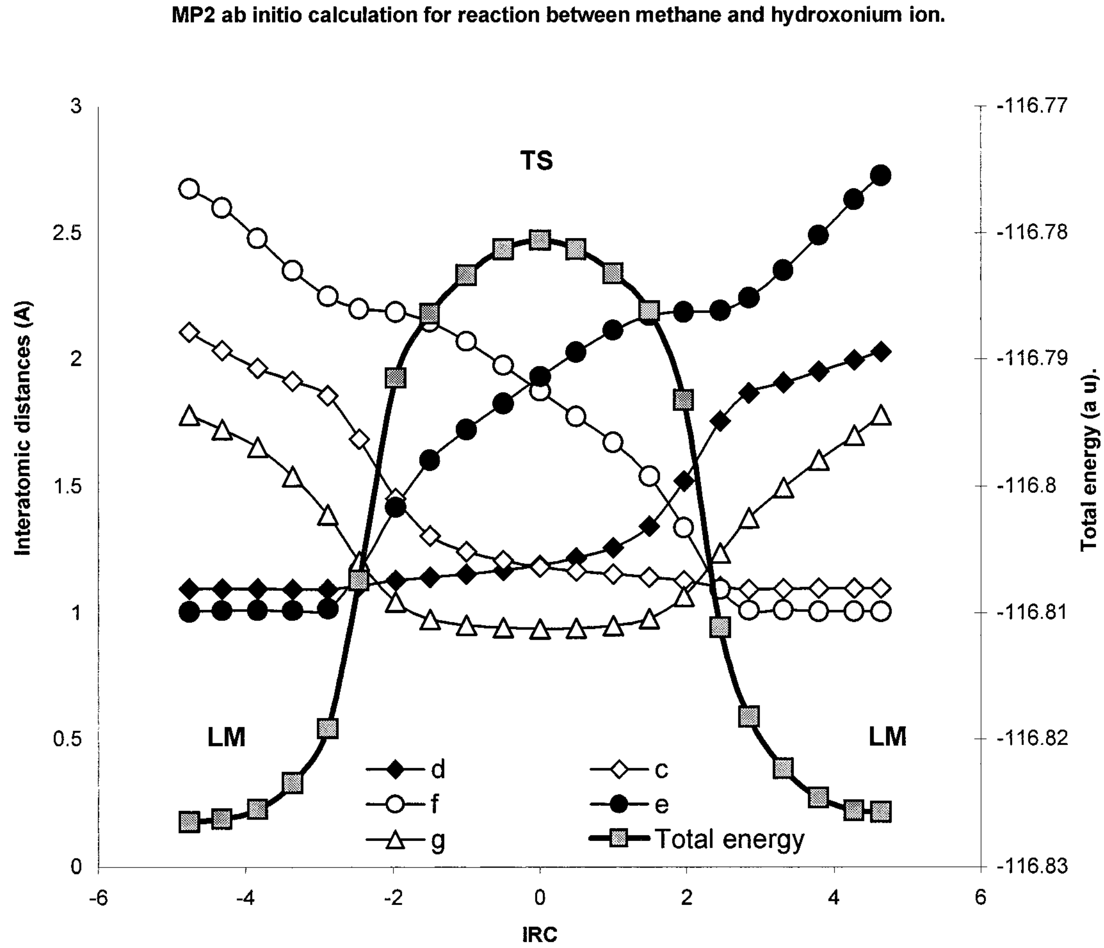


Figure 1. Ab initio IRC calculation of hydrogen exchange reaction between methane and model acidic center. The transition state (TS) and local minimum (LM) of the reaction between CH_4 and H_3O^+. The pathway of the reaction between CH_4 and H_3O^+. Change in the bond lengths (c, d, e, f, g) and in the total energy of the reaction according to MP2/6-31G* calculations.

local energy minimum (LM) on the potential energy surface were calculated with the MP2 method using Dunning's correlation consistent basis set[16] (aug-cc-pVDZ). The geometry for this calculation was taken from an MP2/6-31G* calculation. The methane−hydroxonium ion interaction is a strongly bound intermolecular complex (Figure 1). This complex is 9.2 kcal/mol (MP2/aug-cc-pVDZ) more stable than the initial compounds. The Mulliken effective charge of the CH_5 fragment of this complex is equal to +0.58.

Changes bond lengths and total energy for the one-center methane−hydroxonium ion interaction as computed in IRC calculations[18] are shown in Figure 1. It can be seen that hydrogen exchange occurs by a synchronous mechanism possessing a transition state with pentacoordinated carbon (Figure 1). The exchanged hydrogen atoms draw closer to one another, allowing a chemical interaction that leads to additional stabilization of the TS (Table 1). The CH_5 fragment of the TS geometry is close to that of the CH_5^+ ion at the MP2/6-31G*: the lengths of the $H_4{-}C_8$ and $H_4{-}H_5$ bonds are 1.184 and 0.938 Å in the TS and 1.183 and 0.949 Å in CH_5^+. A fully accomplished charge transfer from the acidic center to the CH_5 fragment is observed, as indicated by the effective (Mulliken) charge 1.01 (MP2/6-31G*). Formation of the CH_5^+ ion in the gas phase is precluded due to a large positive enthalpy of proton transfer from H_3O^+ to CH_5^+, 52 kcal/mol at the MP2/6-31G* is all. But the synchronous mechanism for hydrogen exchange with the formation of TS, whose geometry is similar to that of the CH_5^+ ion, is much more energetically favorable; the calculated E_{act} of H exchange on an acidic center is 21.3 and 14.5 kcal/mol at the MP2/6-31G* and MP2/6-31G*//MP2/aug-cc-pVDZ level, respectively. For comparison, the HF/6-31G* value is 27.7 kcal/mol.[14]

Quantum chemical calculations were also carried out for a hydrogen exchange in alanine at the HF/6-31G* level. The

TABLE 1: Geometric Parameters of the Transition State (TS) and Local Minima (LM) of the Hydrogen Exchange Reaction between CH_4 and H_3O^+ at the MP2/6-31G* Level[a]

bond	r/Å			r/Å	
	TS	LM		TS	LM
H_4-H_5	0.938	1.781	C_8-O_9	2.933	3.116
H_1-C_8	1.088	1.089	H_6-O_9	0.975	0.988
H_2-C_8	1.102	1.089	H_7-O_9	0.975	0.988
H_3-C_8	1.088	1.098	H_4-O_9	1.930	1.782
H_4-C_8	1.184	1.097	H_5-O_9	1.875	1.008
H_5-C_8	1.185	2.109			

bond angle	α/deg			α/deg	
	TS	LM		TS	LM
$H_1-C_8-H_2$	107.74	110.75	$C_8-O_9-H_2$	107.27	124.28
$H_3-C_8-H_2$	107.73	107.62	$H_6-O_9-C_8$	127.33	112.44
$H_4-C_8-H_2$	80.93	107.76	$H_7-O_9-C_8$	127.30	112.53
$H_5-C_8-H_2$	127.52	124.34	$H_4-C_8-H_5$	46.59	57.00

torsion angle	δ/deg			δ/deg	
	TS	LM		TS	LM
$H_3-C_8-H_2-H_1$	126.74	−117.31	$H_6-O_9-C_8-H_1$	−23.67	−22.46
$H_4-C_8-H_2-H_1$	−116.63	117.68	$H_7-O_9-C_8-H_1$	152.03	−148.66
$H_5-C_8-H_2-H_1$	−116.64	−179.88	$H_4-H_5-C_8-H_2$	0.00	90.22
$C_8-O_9-H_2-H_1$	−116.65	179.06	$H_4-H_5-C_8-H_1$	−120.50	−89.91

[a] The total energies of the separated $CH_4-H_3O^+$, LM, and TS are −116.8146, −116.8265, and −116.7806 au (MP2/6-31G*); 116.7336, −116.7430, and −116.7015 au with zero-point energy corrections (MP2/6-31G*); and −116.8975, −116.9121, and −116.8744 au, respectively (MP2/6-31G*//MP2/aug-cc-pVDZ). The transition state had one imaginary frequency i 403.3 cm^{-1} (MP2/6-31G*).

TABLE 2: Tritium Distribution in *L*-Hydroxyproline Synthesized by the HSCIE Reaction at 150 °C and ab Initio Calculation of the Activation Energy of Hydrogen Exchange by the HF/6-31G* Method[a]

position	tritium distribution, %	activation energy, kcal/mol
2α	9	23.59
3α	6	23.72
3*β*	1	26.17
4*β*	4	25.57
5α	59	18.07
5*β*	21	22.03

[a] For comparison, E_{act} of the hydrogen exchange reaction between CH_4 and H_3O^+ is 27.7 kcal/mol (HF/6-31G*).

activation energies of the hydrogen substitution reaction at the α-carbon atom and in the methyl group of alanine are 27.0 and 16.6 kcal/mol, respectively. The experimentally measured activation energies of the HSCIE reaction for the same positions of the alanine molecule agree well with this theoretical calculation, 25 kcal/mol for C_2 and 14 kcal/mol for C_3.[18]

Finally, the new one-center mechanism for the HSCIE reaction was also tested with *L*-hydroxyproline. Table 2 compares the results of an experimental study of isotope exchange in *L*-hydroxyproline with theoretical calculations. The TS structure was calculated at the HF/6-31G* level (Table 3, Figure 2).

It was found that the likelihood of H substitution occurring at a particular C atom in the HSCIE reaction correlates with the E_{act} value and with the presence of additional interaction between exchanged hydrogen atoms and O or N in the TS. The H_α atom bonded to the C_5 interacts with O_6 and N_1 atoms in TS 5α, and this H atom was found be the most reactive in the HSCIE reaction. The H_β atom at the same C_5 atom interacts only with the N_1 atom, and TS stabilization on the O_6 atom becomes impossible. Additional stabilization of TS 5α on the hydroxyl group at the C_4 atom may lead to observed stereoselectivity of hydrogen exchange reaction at the C_5 atom of *L*-Hyp. The H_α atom at the C_3 atom interacts with the O_6 atom, but the H_β atom at this C atom is located too far away from both the O and the N atoms to stabilize this TS 3*β*. Thus, the observed regioselectivity and stereoselectivity of H substitution in the HSCIE reaction in amino acids can be determined using one-center mechanism involving the interaction of C−H bonds with H_3O^+. The additional interaction between the H atoms and electron donor O and N atoms in the substitution process provides a secondary source of stabilization in amino acid transition states.

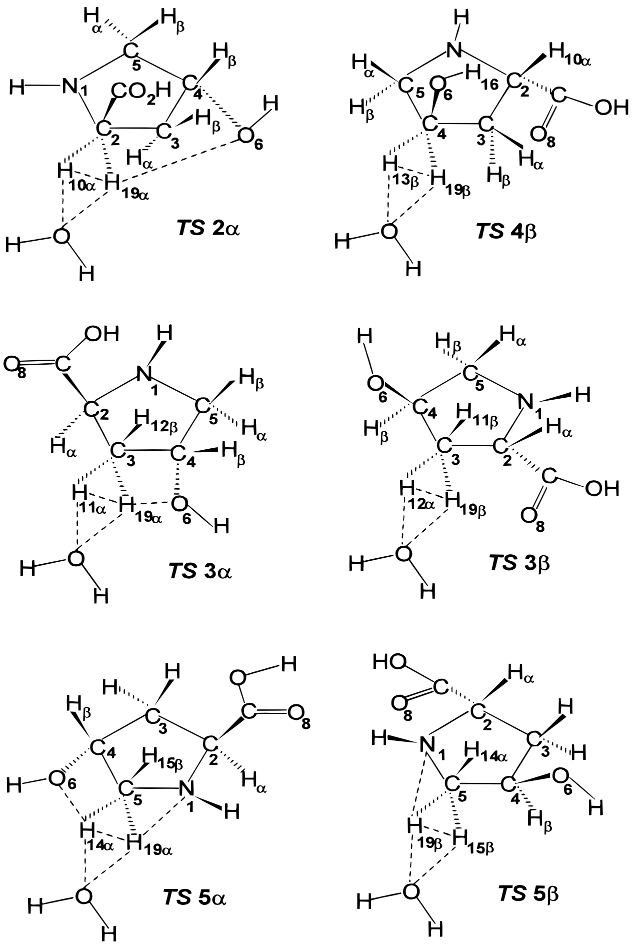


Figure 2. Structures of transition states of the hydrogen exchange reaction between *L*-Hyp and H_3O^+.

TABLE 3: Geometric Parameters of Hydroxyproline (Hyp) and Transition States (TS) of the Hydrogen Exchange Reaction between Hyp and H_3O^+ Calculated by the RHF/6-31G* Method

bond, Å	Hyp	TS 2α	TS 3α	TS 3*β*	TS 4*β*	TS 5α	TS 5*β*
N(1)−C(2)	1.44	1.41	1.44	1.48	1.51	1.47	1.47
C(2)−C(3)	1.53	1.59	1.53	1.52	1.52	1.55	1.54
C(3)−C(4)	1.54	1.52	1.56	1.58	1.59	1.52	1.53
C(4)−C(5)	1.55	1.53	1.55	1.55	1.59	1.59	1.59
N(1)−C(5)	1.45	1.48	1.47	1.48	1.46	1.42	1.42
C(4)−O(6)	1.41	1.45	1.44	1.43	1.42	1.44	1.42
C(7)−O(8)	1.19	1.19	1.19	1.19	1.22	1.19	1.19
N(1)−H(19)		2.06	3.27	2.66	3.21	2.12	2.10
O(6)−H(19)		1.86	1.96	3.47	2.12	1.81	3.14
O(8)−H(19)		2.98	3.85	3.60	2.51	4.79	4.40

Conclusion

This work describes a theoretical and experimental study of a new one-center HSCIE reaction between solid organic compounds and spillover hydrogen. The suggested mechanism of the substitution reaction at saturated carbon atoms is synchronous double proton migration. As demonstrated with *L*-hydroxyproline, it is consistent with the regioselectivity of tritium distribution in labeled amino acids and the stereochemistry of the H substitution in the HSCIE reaction. This mechanism allows the reactivity of organic compounds to be predicted in reactions with SH. Quantum chemical modeling of the HSCIE reaction indicates that the one-center mechanism is more realistic than the alternative two-center.

Technical Details

Methods of Calculation. The geometry of all systems was optimized with Hartree−Fock approximation (HF). Second-order Møller−Plesset perturbation theory (MP2) was used for the $CH_4-H_3O^+$ interaction. 6-31G* and aug-cc-pVDZ basis sets were used. All calculations of the molecular systems in their ground states were performed with the GAMESS program[19] running on DEC AXP 3000-400 and PENTIUM-266 computers (Nesmeyanov's Institute of Organoelement Compounds, Russian Academy of Science, Moscow, Russia). The calculations in their ground state were performed at full optimization of the energy with overall geometric parameters including interatomic distances and bond and dihedral angles. Changes in bond lengths and total energy for the hydrogen exchange reaction between CH_4 and H_3O^+ ion were found using the IRC method.[17] The ab initio calculation of the TS reaction between the H_3O^+ ion and amino acids is a very complicated task for the modern supercomputers. Therefore, the geometry of the $\langle CH_2O\rangle$ fragment in the TS of *L*-hydroxyproline with H_3O^+ ion was borrowed without optimization from the TS of a reaction between the H_3O^+ ion and CH_4 obtained by the same method (HF/6-31G*). The rest of the geometrical parameters were optimized for the total energy minimum. Additional calculations of the activation energy of hydrogen exchange in the alanine β-position were done with complete optimization of the geometry and with the frozen $\langle CH_2O\rangle$ fragment geometry in the same transition state. It was shown that divergences in the activation energies for these calculations do not exceed 1 kcal/mol. The electron density distribution in the molecules was analyzed according to Mulliken on the basis of calculations of neutral molecules of amino acids.

Solid-State Isotope Exchange of *L*-Amino Acids with Tritium. Activated carbon (Norit A, Serva) in an amount of 2S mg was mixed with 0.5 mL of a solution of 0.5 mg of *L*-amino acid. The water was removed under reduced pressure at 20 °C. Activated carbon containing preapplied amino acid in a 50:1 ratio and 10 mg of 5% rhodium-on-alumina catalyst (Fluka) were mixed together. A solid mixture containing 0.5 g of *L*-amino acid was placed in a 10 mL ampule. The ampule was evacuated and filled with gaseous tritium until a pressure of 100−500 Torr was achieved. The reaction was carried out at 100−180 °C for 20−90 min.[13] Amino acid was desorbed with 0.1 N hydrous ammonia containing 20% ethanol and then purified by ligand exchange chromatography on chiral sorbents.[20] Tritium incorporation in amino acids was measured by liquid scintillation counting. ^3H NMR accomplished tritium distribution in amino acids.

Acknowledgment. This study was supported by the International Scientific Foundation and the Russian Fund of Fundamental Research.

References and Notes

(1) Sermon, P. A.; Bond, D. C. *Catal. Rev.* **1973**, *8*, 211.

(2) Lamatrine, R.; Perrin, R. *Stud. Surf. Sci. Catal.* **1983**, *17*, 251.

(3) Zolotarev, Yu. A.; Kozic, V. S.; Dorokhova, E. M.; Zaitsev, D. A.; Myasoedov, N. F. *Dokl. Chem.* **1989**, *308*, 1146. Zolotarev, Yu. A.; Kozic, V. S.; Dorokhova, E. M.; Zaitsev, D. A.; Myasoedov, N. F. *J. Radioanal. Nucl. Chem.* **1992**, *162*, 3.

(4) Levy, R.; Boudart, M. *J. Catal.* **1974**, *32*, 304.

(5) Keren, E.; Soffer, A. *J. Catal.* **1977**, *50*, 43.

(6) Borisov, Yu. A.; Zolotarev, Yu. A.; Laskatelev, E. V.; Myasoedov, N. F. *Russ. Chem. Bull.* **1997**, *46*, 407.

(7) Iaroslavtcev, A. B. *Russ. Chem. Rev.* **1994**, *63*, 449.

(8) Stumbo, A. M.; Grande, P.; Delmon, B. *Stud. Surf. Sci. Catal.* **1997**, *112*, 211.

(9) Kosheleva, L. S. *Russ. Chem. Bull.* **1995**, *44*, 236.

(10) Marchese, L.; Wright, P. A.; Thomas, J. M. *J. Phys. Chem.* **1993**, *97*, 8109.

(11) Barrer, R. M.; Klinowskii, J. *J. Chem. Soc., Faraday Trans. 1* **1975**, *71*, 690.

(12) Evleth, E. M.; Kassab, E.; Sierra, L. R. *J. Phys. Chem.* **1994**, *98*, 1421.

(13) Zolotarev, Yu. A.; Dorokhova, E. M.; Nezavibatko, V. N.; Borisov, Yu. A.; Rosenberg, S. G.; Myasoedov, N. F. *Amino Acids* **1995**, *8*, 353.

(14) Borisov, Yu. A.; Zolotarev, Yu. A.; Laskatelev, E. V.; Myasoedov, N. F. *Russ. Chem. Bull.* **1996**, *45*, 1764−1766.

(15) Møller, C.; Plesset, S. *Phys. Rev.* **1934**, *49*, 618.

(16) Woon, D. E.; Dunning, T. H. *J. Chem. Phys.* **1993**, *98*, 1358.

(17) Schmidt, M. W.; Gordon, M. S.; Dupuis, M. *J. Am. Chem. Soc.* **1985**, *107*, 2585.

(18) Zolotarev, Yu. A.; Laskatelev, E. V.; Dorokhova, E. M.; Borisov, Yu. A.; Rosenberg, S. G.; Myasoedov, N. F. *Russ. Chem. Bull.* **1997**, *46*, 726.

(19) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Mtsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupius, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(20) Zolotarev, Yu. A.; Kozic, V. S.; Dorokhova, E. M.; Zaitsev,D. A.; Myasoedov, N. F. *J. Radioanal. Nucl. Chem.* **1988**, *121*, 469.