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Theoretical studies of electron and hydrogen transfer reactions between semiquinone radicals and oxygen

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Abstract. To explore the interactions between ubiquinones and oxygen in living organisms, the thermodynamics of a series of electron and hydrogen transfer reactions between semiquinone radicals, as well as their corresponding protonated forms, and oxygen, singlet or triplet, were studied using the hybrid Hartree–Fock–density functional theory method Becke's three parameter hybrid method with the Lee, Yang, and Parr correlation functional. Effects of the solvent and of the isoprenyl tail on the electron and hydrogen transfer reactions were also investigated. It is found that semiquinone radicals (semiquinone anion radicals or protonated semiquinone radicals) cannot react with triplet oxygen to form the superoxide anion radical $O_2^{-\bullet}$. In contrast, neutral quinones can scavenge $O_2^{-\bullet}$ efficiently. In the gas phase, only protonated semiquinone radicals can react spontaneously with singlet oxygen to produce peroxyl radical ($HO_2^{\bullet}$). However, both semiquinone anion radicals and protonated semiquinone radicals can react with singlet oxygen to produce harmful oxygen radicals ($O_2^{-\bullet}$ and $HO_2^{\bullet}$, respectively) in aqueous and protein environments. The free-energy changes of the corresponding reactions obtained for different ubiquinone systems are very similar. It clearly shows that the isoprenyl tail does not influence the electron and hydrogen transfer reactions between semiquinone radicals and oxygen significantly. Results of electron affinities, vertical ionization potentials, and proton affinities also show that the isoprenyl tail has no substantial effect on the electronic properties of ubiquinones.

Key words: Semiquinone radicals – Electron transfer – Proton transfer – Hydrogen transfer – Solvent effect

1 Introduction

Ubiquinones are important ubiquitous coenzymes in biology. Their properties have attracted increased research interest, and several experimental and theoretical studies related to the properties of quinones have been carried out during the past decades. However, the roles of ubiquinones in biological systems, especially the interactions between ubiquinones and oxygen, are still far from clear owing to the complexity of living organisms and the limitation of experimental techniques.

In addition to acting as the well-known electron and proton mediators in respiration, ubiquinones are often considered as a source of the superoxide anion radicals, $O_2^{-\bullet}$ [1–3], which are very harmful to living organisms either through direct damage to cells or via proton leakage to decrease the production of ATP. Although there is not enough direct experimental evidence, some researchers believe that semiquinone anion radicals can react with oxygen via a direct electron transfer reaction to produce superoxide anion radicals [4, 5]:

$$Q^{-\bullet} + O_2 \rightarrow Q + O_2^{-\bullet}$$

It is also suggested that the electron transfer reactions between semiquinone anion radicals and oxygen require the availability of protons [2, 6]:

$$Q^{-\bullet} + H^+ + O_2 \rightarrow Q + HO_2^{\bullet}$$

However, contradictory to the above, there are also studies showing that ubiquinones can act as antioxidants by scavenging superoxide anion radicals [6]:

$$Q + O_2^{-\bullet} \rightarrow Q^{-\bullet} + O_2$$

The roles of ubiquinones in living systems are complex, and as seen the previously mentioned results do not provide a clear picture. Additional studies are hence necessary, and the aim of the present study is to use modern electronic structure methods to help resolve some of the ambiguities regarding the reactions between ubiquinones and molecular oxygen.

Since electron correlation is incorporated in their basic formalism, density functional methods (DFT)

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[7–13] have been shown to be able to provide accurate molecular structures, electronic energies, and vibration frequencies with moderate computational cost. Several theoretical studies on quinone systems [14–19] have been carried out during the past decades; however, most of the theoretical work has focused on the electronic properties and electron transport roles of quinones, and very little has been performed on the interactions between ubiquinones and oxygen. To investigate the roles of ubiquinones in living organisms, especially the interactions between quinones and oxygen, it is necessary to study the mechanisms of the electron transfer and proton transfer reactions between ubiquinones and oxygen.

In another study, we extensively studied the thermodynamics of the electron transfer reactions between semibenzoquinone radicals and oxygen, using the hybrid density functional method Becke's three parameter hybrid method with the Lee, Yang, and Parr correlation functional (B3LYP) [11–13, 20] with different basis sets. It has been found that combined B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) method can provide good thermodynamic properties for the reactions compared with experimental results. To investigate the roles of ubiquinones and the interactions between ubiquinones and oxygen in biological organisms, the reactions between different ubiquinones and oxygen were studied further with the B3LYP method in the present work. Solvent effect and the effect of the isoprenyl tail on the electronic properties of quinones and the interactions between quinones and oxygen were also investigated.

2 Theoretical method and model

The gradient-corrected DFT functional method B3LYP was employed throughout the present study. The structure optimization and frequency analysis were carried out with the 6-31G(d) basis set, followed by single-point energy calculations with the 6-311G(2d,p) basis set. The polarized continuum model (PCM) [21–30] was used to incorporate the effects of solvents.

The standard free-energy change, ΔG^0, of a reaction can be expressed by

$$\Delta G^0 = \Delta E_{\mathrm{electron}} + \Delta \mathrm{ZPE} + \Delta(H_{\mathrm{T}} - H_0) - T\Delta S \ ,$$

where ZPE and S are the zero-point vibration energy and the entropy, respectively, and $(H_{\mathrm{T}} - H_0)$ is the heat content, the difference in enthalpy at 0 K and T K, where T is the temperature. In our previous work, it was shown that ΔG^0 of the reactions mainly results from the corresponding electronic energy change, $\Delta E_{\mathrm{electron}}$, and that the entropy change, ΔS, the ZPE correction, ΔZPE, and the heat content $\Delta(H_{\mathrm{T}} - H_0)$ are usually very small. To reduce the computational cost, only electronic energy changes were considered in the present work. The Gaussian 98 [31] program was used throughout the present work.

Schematic structures of the quinones studied are shown in Fig. 1.

3 Results and discussion

3.1 Electron transfer and hydrogen transfer reactions between semiquinone anion radicals and oxygen in the gas phase

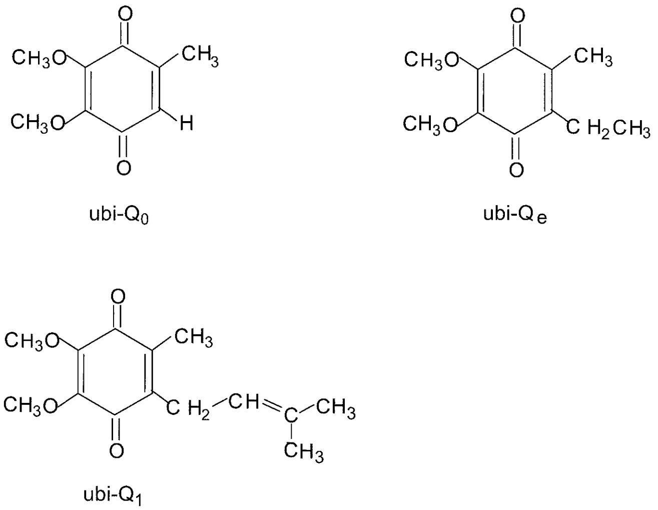
ubi-Q0
ubi-Qe
ubi-Q1

Fig. 1. Schematic structure of ubiquinone systems

The following electron transfer and hydrogen transfer reactions between semiquinone anion radicals or protonated semiquinone radicals and oxygen, triplet or singlet state, were first studied in the gas phase.

$$Q^{-\bullet} + {}^3O_2 \rightarrow Q + O_2^{-\bullet} \tag{1}$$

$$QH^{\bullet} + {}^3O_2 \rightarrow QH^{+} + O_2^{-\bullet} \tag{2}$$

$$QH^{\bullet} + {}^3O_2 \rightarrow Q + HO_2^{\bullet} \tag{3}$$

$$Q^{-\bullet} + {}^1O_2 \rightarrow Q + O_2^{-\bullet} \tag{4}$$

$$QH^{\bullet} + {}^1O_2 \rightarrow QH^{+} + O_2^{-\bullet} \tag{5}$$

$$QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet} \tag{6}$$

The free energy changes of the reactions in Eqs. (1), (2), (3), (4), (5), and (6) for different quinones calculated in the gas phase are shown in Table 1. The results show that neither semiquinone anion radicals nor protonated semiquinone radicals can react with oxygen, singlet state or triplet state, to form a superoxide anion radical $O_2^{-\bullet}$ spontaneously in the gas phase with positive free-energy change. In addition the reactions between protonated semiquinone radicals and oxygen (Eqs. 2, 5) are much more difficult than the corresponding reactions between semiquinone anion radicals and oxygen (Eqs. 1, 4). However, protonated semiquinone radicals ($QH^{\bullet}$) can react with singlet oxygen to form a peroxyl radical $HO_2^{\bullet}$ via hydrogen transfer (Eq. 6), with negative free-energy

Table 1. ΔG^0 of the reactions calculated with Becke's three parameter hybrid method with the Lee, Yang, and Parr correlation functional (*B3LYP*)/6-311G(2d,p)//B3LYP/6-31G(d) in the gas phase (kcal/mol)

	Q_0	Q_1	Q_e
$Q^{-\bullet} + {}^3O_2 \rightarrow Q + O_2^{-\bullet}$	47.6	48.9	47.2
$QH^{\bullet} + {}^3O_2 \rightarrow QH^{+} + O_2^{-\bullet}$	164.0	159.0	160.2
$QH^{\bullet} + {}^3O_2 \rightarrow Q + HO_2^{\bullet}$	14.4	13.3	12.8
$Q^{-\bullet} + {}^1O_2 \rightarrow Q + O_2^{-\bullet}$	8.5	9.9	8.2
$QH^{\bullet} + {}^1O_2 \rightarrow QH^{+} + O_2^{-\bullet}$	125.0	120.0	121.2
$QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet}$	−24.6	−25.8	−26.2

change, −24.6, −25.8, and −26.2 kcal/mol for ubi-Q_0, ubi-Q_1, and ubi-Q_e systems. respectively. The corresponding reactions (Eq. 3) between protonated semiquinone radicals and triplet oxygen cannot proceed spontaneously owing to the positive free-energy changes. These results agree with our previous theoretical results calculated for *p*-benzoquinone systems.

It is well known that the long isoprenyl tail of ubiquinone plays an important role in the interactions between ubiquinones and their environment. Whether this long tail influences the electronic properties and biological roles of ubiquinones has been under debate. By comparing the results obtained for different quinones (Table 1), we found that the energy changes of the corresponding reactions are very similar. The biggest difference in the free-energy changes of the reactions between ubi-Q_0 and ubi-Q_1 systems is about 5 kcal/mol for reactions $QH^{\bullet} + {}^3O_2 \rightarrow QH^+ + O_2^{-\bullet}$ and $QH^{\bullet} + {}^1O_2 \rightarrow QH^+ + O_2^{-\bullet}$, and the smallest difference is only about 1 kcal/mol (for hydrogen transfer reactions $QH^{\bullet} + {}^3O_2 \rightarrow Q + HO_2^{\bullet}$ and $QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet}$).

The differences in energy changes of the corresponding reactions related to ubi-Q_1 and ubi-Q_e systems are even less, between 0.5 and 1.7 kcal/mol. It therefore seems that the isoprenyl tail has no substantial effect on the electron transfer, proton transfer, and hydrogen transfer reactions between different ubiquinones and oxygen.

The electronic properties of *p*-benzoquinone has been extensivly studied using different methods with different basis sets [16, 17]. It has been shown that the hybrid Hatree–Fock (HF)–DFT method B3LYP with polarized basis sets 6-311G(d,p), 6-311G(3d,p) can give accurate electron affinity (1.85 eV) compared to experimental data (1.91 ± 0.06 eV) [32, 33], but results in large deviation with diffuse function basis sets 6-311 + + G(d,p) and 6-311 + + G(3d,p) (2.17 and 2.13 eV, respectively). We also found that the B3LYP method with the polarized basis set 6-311G(2d,p) gives good results for the thermodynamic properties of reactions between semibenzoquinone radicals and oxygen, but gives contradictory result with the diffuse function basis set 6-311 + G(2d,p) compared to experimental results. The electron affinities, vertical ionization potentials of neutral ubiquinones, and the proton affinities of the ubiquinone radical anions calculated with B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) are shown in Table 2. The electron affinities of the different quinones are found to be very close. The difference between ubi-Q_0 and ubi-Q_1 calculated with B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) is 0.06 eV and is only 0.01 eV between ubi-Q_0 and ubi-Q_e. The proton affinities of the corresponding ubiquinone radicals are also very close, with 0.1 eV deviation between $Q_0^{-\bullet}$ and $Q_1^{-\bullet}$ and 0.05 eV deviation between $Q_1^{-\bullet}$ and $Q_e^{-\bullet}$. The vertical ionization potentials of ubi-Q_0, ubi-Q_1, and ubi-Q_e show a larger spread (within 0.6 eV for the three systems). The electron affinities, the vertical ionization potentials, and the proton affinities again show that the isoprenyl tail has no distinctive effect on the electron transfer and proton transfer properties of ubiquinones.

Table 2. Electronic properties of ubiquinones calculated with B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) (eV, without zero-point energy correction)

	$Q_0(Q_0^{-\bullet})$	$Q_1(Q_1^{-\bullet})$	$Q_e(Q_e^{-\bullet})$
Electron affinity	1.71	1.77	1.70
Ionization potential	6.56	5.95	6.47
Protein affinity	14.86	14.76	14.81

3.2 Solvent effect on the electron transfer and hydrogen transfer reactions between semiubiquinone radicals and oxygen

The environments of ubiquinones in biological organisms are complex, ranging from aqueous solution to proteins and phospholipid membranes, which probably influence the electronic properties of quinones and interactions between semiquinone anion radicals and oxygen significantly. To estimate the effect of the environment on the electron transfer and hydrogen transfer reactions between semiubiquinone radicals and oxygen, the reactions discussed previously were also studied using a dielectric model to simulate aqueous and protein environments. The corresponding results are listed in Tables 3 and 4, respectively.

Table 3 shows that neither semiquinone radicals nor protonated semiquinone radicals can react spontaneously in a protein environment with triplet oxygen to form harmful oxygen radicals ($O_2^{-\bullet}$ and $HO_2^{\bullet}$, respectively), owing to the positive free-energy change. The direct electron transfer reactions between $QH^{\bullet}$ and ${}^1O_2$ to form $O_2^{-\bullet}$ ($QH^{\bullet} + {}^1O_2 \rightarrow QH^+ + O_2^{-\bullet}$) are also very difficult to proceed. However, both semiquinone anion radicals and protonated semiquinone radicals can react

Table 3. ΔG^0 (kcal/mol) of the reactions calculated with the polarizable continuum model (*PCM*)/B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) in a protein environment ($\varepsilon = 4$)

	Q_0	Q_1	Q_e
$Q^{-\bullet} + {}^3O_2 \rightarrow Q + O_2^{-\bullet}$	23.0	22.6	21.0
$QH^{\bullet} + {}^3O_2 \rightarrow QH^+ + O_2^{-\bullet}$	74.9	74.2	71.2
$QH^{\bullet} + {}^3O_2 \rightarrow Q + HO_2^{\bullet}$	9.4	9.2	8.0
$Q^{-\bullet} + {}^1O_2 \rightarrow Q + O_2^{-\bullet}$	−15.8	−16.1	−17.7
$QH^{\bullet} + {}^1O_2 \rightarrow QH^+ + O_2^{-\bullet}$	36.1	35.4	32.4
$QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet}$	−29.4	−29.5	−30.8

Table 4. ΔG^0 (kcal/mol) of the reactions calculated with the PCM/B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) in aqueous solution ($\varepsilon = 79$)

	Q_0	Q_1	Q_e
$Q^{-\bullet} + {}^3O_2 \rightarrow Q + O_2^{-\bullet}$	16.0	16.1	14.1
$QH^{\bullet} + {}^3O_2 \rightarrow QH^+ + O_2^{-\bullet}$	39.2	44.4	39.5
$QH^{\bullet} + {}^3O_2 \rightarrow Q + HO_2^{\bullet}$	4.1	2.4	3.9
$Q^{-\bullet} + {}^1O_2 \rightarrow Q + O_2^{-\bullet}$	−22.5	−22.5	−24.4
$QH^{\bullet} + {}^1O_2 \rightarrow QH^+ + O_2^{-\bullet}$	0.6	5.9	1.0
$QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet}$	−34.4	−36.2	−34.7

with singlet oxygen to form $O_2^{-\bullet}$ and $HO_2^{\bullet}$, respectively($Q^{-\bullet} + {}^1O_2 \rightarrow Q + O_2^{-\bullet}$ and $QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet}$), but the former reaction cannot proceed spontaneously in the gas phase.

On comparing the results calculated for the gas phase (Table1) and those in a protein environment (Table 3), it is found that the free-energy changes of all the previous reactions calculated in a protein environment are much lower than corresponding results obtained for the gas phase, especially for the electron transfer reactions between protonated semiubiquinone radicals and triplet or singlet oxygen, $QH^{\bullet} + {}^3O_2 \rightarrow QH^{+} + O_2^{-\bullet}$ and $QH + {}^1O_2 \rightarrow QH^{+} + O_2^{-\bullet}$. This is due to the stabilizing effect of the protein environment of the charged species (product side) relative to the neutral species (reactant side).

Table 3 clearly shows that environment can influence the interactions between ubiquinones and oxygen considerably. The electron and hydrogen transfer reactions were studied further in aqueous solution, and the corresponding results are listed in Table 4. Similar results to those obtained in a protein environment were also obtained in water. Semiquinone anion radicals or protonated semiquinone radicals will not react with ground-state triplet oxygen to form the superoxide anion radical $O_2^{-\bullet}$ or the peroxyl radical $HO_2^{\bullet}$ (positive free-energy change). In contrast, neutral ubiquinones can scavenge harmful oxygen radicals $O_2^{-\bullet}$ and $HO_2^{\bullet}$ efficiently. However, both semiquinone anion radicals and protonated semiquinone radicals can react with singlet oxygen to form $O_2^{-\bullet\bullet}$ or $HO_2^{\bullet}$, respectively.

On comparing the results obtained in aqueous and protein environments, it is seen that the larger dielectric constant (larger polarity) of water makes all the reactions considerably more exothermic than a bulk protein environment does. The electron transfer reaction $Q^{-\bullet} + {}^1O_2 \rightarrow Q + O_2^{-\bullet}$ and the hydrogen transfer reaction $QH^{\bullet} + {}^1O_2 \rightarrow Q + HO_2^{\bullet}$ can proceed much more easily owing to the more negative free-energy change. It is interesting to note that the free-energy changes of the electron transfer reaction $QH^{\bullet} + {}^1O_2 \rightarrow QH^{+} + O_2^{-\bullet}$ are very small, about 0.6, 6, and 1 kcal/mol for the Q_0, Q_1, and Q_e systems, respectively, and may possibly occur through the perturbation or catalysis of the local environment. This also holds for the net hydrogen atom transfer reaction $QH^{\bullet} + {}^3O_2 \rightarrow Q + HO_2^{\bullet}$, with only 4.1, 2.4, and 3.9 kcal/mol free-energy change for Q_0, Q_1, and Q_e.

4 Conclusions

Electron and hydrogen transfer reactions between a series semiquinone anion radicals, as well as corresponding protonated semiquinone radicals, and triplet or singlet oxygen were systematically investigated in the present work. The effect of the solvent and the effect of isoprenyl tail on the properties of ubiquinones and the interactions with oxygen were also investigated. The theoretical results show that the solvent significantly influences the thermodynamics of the electron and hydrogen transfer reactions between semiquinone radicals and oxygen. In the gas phase, only hydrogen transfer reactions between protonated semiquinone radicals and singlet oxygen can proceed spontaneously to form peroxyl radical. No other electron or hydrogen transfer reactions will occur spontaneously, owing to the high positive free-energy change. However, not only the hydrogen transfer reactions, but also direct electron transfer reactions between semiquinone anion radicals and singlet oxygen can occur spontaneously in a protein environment and more readily so in aqueous solution. It can be concluded that in most cases neutral ubiquinones can act as antioxidants by scavenging superoxide anion radicals or peroxyl radicals to form semiquinone radicals and ground-state triplet oxygen. However, in the presence of singlet oxygen, semiquinone radicals will easily react to form harmful superoxide anion radicals or peroxyl radicals.

By comparing the results obtained from different ubiquinones, it is furthermore found that the isoprenyl tail has no significant effect on the free-energy changes of the electron and hydrogen transfer reactions, and the results obtained for the ubi-Q_0 and ubi-Q_1 systems may be extended to more complex ubiquinone systems in living organisms.

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References

1. Cadenas E, Boveris A, Ragan CI (1977) Arch Biochem Biophys 180: 248
2. Nohl H (1990) Free Radical Res Commun 8: 307
3. Nohl H, Stolze K (1992) Free Radical Res Commun 16: 409
4. Brunori M, Rotilio G (1984) Methods Enzymol 105: 22
5. Liu SH, Jiao X, Wang X, Zhang L (1996) Sci China Ser C 39: 168
6. Cadenas E, Packer L (eds) (1996) Handbook of antioxidants. Dekker, New York
7. Slater JC (1974) Quantum theory of molecules and solids. McGraw Hill, New York
8. Parr RG, Yang W (1989) Density functional theory of atoms and molecules. Oxford University Press, Oxford
9. Hohenberg P, Kohn W (1964) Phys Rev B 136: 864
10. Kohn W, Sham L (1965) J Phys Rev A 140: 1133
11. Lee C, Yang W, Parr RG (1988) Phys Rev B 37: 587
12. Devlin PJ, Chablowski CF, Frisch MJ (1994) J Phys Chem 98: 11623
13. Becke AD (1993) J Chem Phys 98: 1372
14. O'Malley PJ (1998) J Am Chem Soc 120: 5093
15. Colle R, Curioni A (1998) J Am Chem Soc 120: 4832
16. Boesch SE, Grafton AK, Wheeler RA (1996) J Phys Chem A 100: 10083
17. Eriksson LA, Himo F, Siegbahn PEM, Babcock GT (1997) J Phys Chem A 101: 9496
18. Himo F, Babcock GT, Eriksson LA (1999) J Phys Chem A 103: 3745
19. Nonella M (1998) J Phys Chem B 102: 4217
20. Becke AD (1998) Phys Rev A 38: 3098
21. Miertus S, Scrocco E, Tomasi J (1981) J Chem Phys 55: 117
22. Miertus S, Tomasi J (1982) J Chem Phys 65: 239
23. Mennucci B, Cammi R, Tomasi J (1998) J Chem Phys 109: 2798
24. Cossi M, Barone V, Cammi R, Tomasi J (1996) J Chem Phys Lett 255: 327
25. Cossi M, Barone V, Mennucci B, Tomasi J (1998) Chem Phys Lett 286: 253

26. Cances E, Mennucci B, Tomasi J (1998) J Chem Phys 109: 260
27. Cances MT, Mennucci V, Tomasi J (1997) J Chem Phys 107: 3032
28. Barone V, Cossi M (1998) J Phys Chem 102: 1995
29. Barone V, Cossi M, Tomasi J (1997) J Chem Phys 107: 3210
30. Barone V, Cossi M, Tomasi J (1998) J Comp Chem 19: 404
31. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ciosliowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith TA, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson BG, Chen W, Wong MW, Andres JL, Head-Gordon M, Replogle ES, Pople JA (1998) GAUSSIAN98. Gaussian, Pittsburgh, Pa
32. Chowdhury S, Grimsrud EP, Kebarle P (1986) J Phys Chem 90: 2747
33. Heinis T, Chowdhury S, Scott SL, Kebarle P (1988) J Am Chem Soc 110: 400