
STRUCTURE OF CHEMICAL
COMPOUNDS. SPECTROSCOPY

Noncovalent Hydrogen Isotope Effects in Paramagnetic Molecules¹

A. L. Buchachenko^{a, b, c, d, *, **}, L. A. Wasserman^{a, e}, N. N. Breslavskaya^f, and I. I. Barashkova^a

^a*Institute of Chemical Physics, Russian Academy of Sciences, Moscow, 119991 Russia*

^b*Institute of Problems of Chemical Physics, Russian Academy of Sciences, Chernogolovka, 142432 Russia*

^c*Scientific Center in Chernogolovka, Chernogolovka, 142432 Russia*

^d*Moscow University, Moscow, 119992 Russia*

^e*Institute of Biochemical Physics, Russian Academy of Sciences, Moscow, 119991 Russia*

^f*Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Moscow, 119991 Russia*

**e-mail: abuchach@chph.ras.ru*

***e-mail: alb9397128@yandex.ru*

Received February 5, 2018

Abstract—Zero-point energies (ZPE) of intermolecular, non-bonded vibrations and isotope effects, induced by noncovalent interactions, are computed for paramagnetic molecules. They appear to be not significant for complexation of HO₂ and oxygen with C–H bonds and results to isotope effect, which deviates from unit by 5–10%. However, ZPE and isotope effects in complexes of HO₂ and nitroxyl radicals with water are larger and reach 50–70%. The largest effect, about 12, is found for complexation of hydrogen atom with water. Complexation of nitroxyl and peroxy radicals by hydrogen bonds is accompanied by transfer of spin density of unpaired electron from radical to the ligand molecules and induces high field paramagnetic shifts of the ligand NMR lines. It evidences that the spin transfer via intermolecular bonds occurs by mechanism of spin polarization.

Keywords: isotope effect, noncovalent interactions, hydrogen atom, nitroxyl radical, peroxy radical

DOI: 10.1134/S1990793118030053

INTRODUCTION

Zero-point energy (ZPE) of covalent atomic vibrations is an irrefutable evidence of the quantum nature of the molecular world: atoms never can be stopped. The difference in ZPE of isotopic molecules (with H and D atoms, for instance) produces the main contribution into the covalent isotope effects. It is a commonplace that these effects are powerful means to elucidate reaction mechanisms. However, there are many observations of the anomalous, intriguing and even magic properties of the effects, which evidently are incompatible with their fundamental properties. Thus, the magnitudes of experimentally measured isotope effects IE in the hydrogen/deuterium atom abstraction reactions were shown to depend on the solvent and presence of the third substances, besides of the pair of reactants. At last, in many cases enormously large isotope effects were observed at the mild conditions (room temperature, liquids); it is tempting to prescribe these effects to the tunneling but there is no trust to such an interpretation. These unexpected and having no explanations anomalies were detected both in common reactions and in enzymatic processes [1–3].

Analysing these discouraging isotope anomalies it is worthy to keep in mind that there exist noncovalent isotope effects, which are controlled by ZPEs of the intermolecular, noncovalent vibrations in weakly bound complexes of reactants with solvent or with other, foreign molecules [3]. They exhibit themselves in the ability to fractionate H/D isotopic molecules by chromatography [4–8]. Remarkably, that the efficiency of the fractionation linearly depends on the number of hydrogen atoms substituted by deuterium [3]. The linear dependence for various aromatic and aliphatic molecules unambiguously demonstrates that the major contribution into the noncovalent isotope effects stems from the local atom-atom interactions (such as hydrogen bonds), rather than from macroscopic properties (dielectric constant, optical polarizability, etc.).

The goal of the paper is to compute ZPEs of the non-covalent bonds for the paramagnetic complexes, to evaluate noncovalent isotope effects on the equilibrium constants for the complex formation and, finally, to estimate their contribution into the experimentally measured isotope effects.

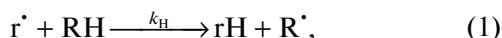
¹ The article is published in the original.

COMPUTATIONAL METHODS

Calculations of the energy and structural characteristics with full optimization of geometry for the complexes of hydrogen atom, nitroxyl and peroxy radicals, and O₂ were performed with the Gaussian-09 program package [9] using density functional theory (DFT) with M06-2X functional and Dunning's correlation-consistent aug-cc-pVDZ and aug-cc-pVTZ basis sets augmented by the diffuse functions [10] as well as coupled-cluster singles-doubles correction (CCSD) with the use of routine split valence basis sets 6-31+G(d,p) and 6-311+G(2d,2p). The M06-2X functional developed for calculating the non-covalent interactions was earlier effectively used in studies of different complexes [11–13]. The results of vibration frequency calculations of all complexes characterize the optimized structures as the energy minima. Neither ZPE of noncovalent bonds, nor isotope effects were shown to noticeably depend on the computational techniques used for calculations.

NONCOVALENT INTERACTIONS AND REACTION KINETICS

In the hydrogen (deuterium) atom abstraction reactions by radical r[•] from the molecules RH and RD



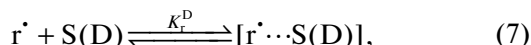
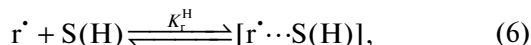
both molecules may be complexed with solvent molecules S:



By assuming that the complexation prevents reactions of [RH⋯S] and [RD⋯S], i.e. only free, not solvated molecules RH and RD are supposed to be able to react, one can derive the equation for the total, experimentally measured isotope effect IE:

$$IE = (k_H/k_D)(K^D/K^H). \quad (5)$$

The equation (5) may be generalized for the cases, when solvent molecules are protiated or deuterated (particularly, if the reaction is carried out in protiated and deuterated water). In these cases radical r[•] may also be solvated:



where S(H) and S(D) are protiated and deuterated solvents. Then the total isotope effect is expressed by equation (8):

$$IE = (k_H/k_D)(K^D/K^H)(K_r^D/K_r^H). \quad (8)$$

If only radicals are solvated then the equation (8) is reduced to equation (9):

$$IE = (k_H/k_D)(K_r^D/K_r^H). \quad (9)$$

Further we will consider particular case presented by equation (9) and calculate the ratios K_r^D/K_r^H for the complexation of paramagnetic molecules or radicals r[•]. Further we will omit index r and denote isotope effect K_r^D/K_r^H as K^D/K^H .

NONCOVALENT ISOTOPE EFFECTS

In general, the isotope effect, i.e. the ratio K^D/K^H , is determined as

$$K^D/K^H = \exp(\Delta H_H - \Delta H_D), \quad (10)$$

where ΔH_H and ΔH_D are the enthalpies for equilibrium (6) and (7). Note, that

$$(\Delta H_H - \Delta H_D) = \varepsilon(H) - \varepsilon(D),$$

where $\varepsilon(H)$ and $\varepsilon(D)$ are the differences of ZPEs of reactants:

$$\varepsilon(H) = \text{ZPE}[r^{\bullet} \cdots S(H)] - \text{ZPE}(r^{\bullet}) - \text{ZPE}[S(H)], \quad (11)$$

$$\varepsilon(D) = \text{ZPE}[r^{\bullet} \cdots S(D)] - \text{ZPE}(r^{\bullet}) - \text{ZPE}[S(D)]. \quad (12)$$

These values, $\varepsilon(H)$ and $\varepsilon(D)$, determine intermolecular, noncovalent ZPEs for the $[r^{\bullet} \cdots S(H)]$ and $[r^{\bullet} \cdots S(D)]$ complexes; they are ZPEs of non-covalent bonds and characterize intermolecular potential of the atom-atom contact in complex or compound molecule. The contribution of the noncovalent ZPEs into the isotope effect is determined by equation

$$K^D/K^H = \exp(\Delta\varepsilon_0), \quad (13)$$

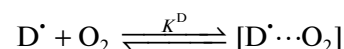
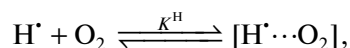
where

$$\Delta\varepsilon_0 = \varepsilon(H) - \varepsilon(D). \quad (14)$$

Since $\Delta\varepsilon_0 > 0$, the ratios $K^D/K^H > 1$, that is paramagnetic molecules are more tightly bound with deuterated solvating molecules S(D), than with protiated molecules S(H). These values, $\varepsilon(H)$ and $\varepsilon(D)$, denoted further as simply ε , as well as $\Delta\varepsilon_0$ and K^D/K^H will be presented below in the Tables for the different paramagnetic complexes.

Hydrogen Atom

Intermolecular structural parameters of complexes with oxygen molecules are shown in Fig. 1; computed energy characteristics are presented in Table 1. Intermolecular distance is rather large (see Fig. 1), i.e. the partners in these complexes are weakly bound. For this reason isotope effect K^D/K^H which refer to the equilibrium of complex formation



is small and does not exceed 7%.

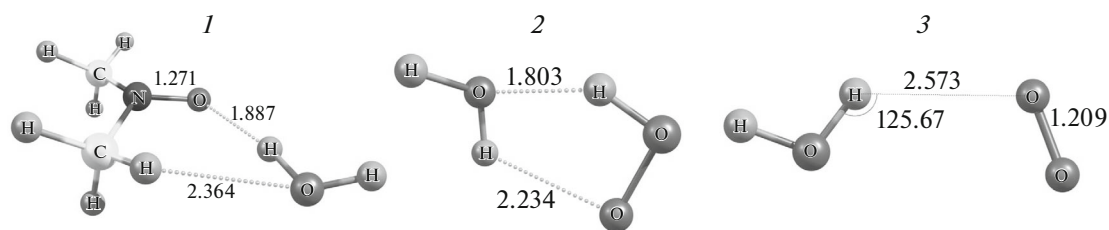


Fig. 1. Computed structures of selected paramagnetic complexes: $(\text{CH}_3)_2\text{NO}\cdots\text{HOH}$ (1); $\text{H}_2\text{O}\cdots\text{HO}_2$ (2); $\text{H}_2\text{O}\cdots\text{O}_2$ (3).

In contrast to oxygen complexes hydrogen atom strongly adheres to water molecule; both intermolecular distance (Fig. 1) and energy parameters (Table 1) clearly exhibit this property. The large difference of ZPE for hydrogen and deuterium atom complexes results to unexpectedly large isotope effect $K^{\text{D}}/K^{\text{H}}$; it hardly can be considered as noncovalent one, perhaps it occupies an intermediate position between covalent and noncovalent effect.

Nitroxyl Radicals

These radicals are very popular and widely used as spin probes and labels in molecular biology. They are known to be highly susceptible to complexation with water, alcohols, amines, and even with hydrocarbons [14–18]. Their non-covalent interactions reliably exhibit themselves in the NMR spectra by paramagnetic shifts and paramagnetic broadening of the NMR lines, which are induced by transfer of unpaired electron spin density from radical to the ligand molecules via intermolecular bonds (mostly hydrogen ones) as a bridge between partners. Figure 1 demonstrates computed structures of radical complexes with hydrogen and water molecules; in Table 2 their energy parameters are summarized.

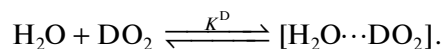
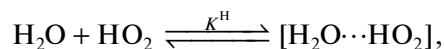
The ZPE differences in these complexes determined by equations (1)–(14) are not small and result to the isotope effects $K^{\text{D}}/K^{\text{H}}$ of 1.5–1.7 at 300 K.

Peroxy Radicals

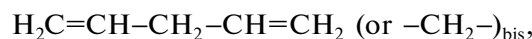
They are extremely important as the main radicals in the chain oxidation reactions. They provide chain propagation by hydrogen atom transfer reaction $\text{RO}_2 + \text{RH} \rightarrow \text{RO}_2\text{H} + \text{R}$ which is known to be solvent depen-

dent due to the complex formation between radical and solvent molecules. Moreover, the chain oxidation reactions exhibit enormously large hydrogen-deuterium isotope and magnetic field effects [3, 19].

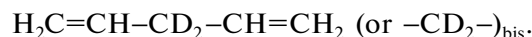
In order to estimate contribution of noncovalent interactions into isotope effect we have computed structure and energy of complexation of the HO_2 radical modelling peroxy radical RO_2 . The existence and properties of the HO_2 complexes were discussed in many papers [20–23]; the structure of complex is shown in Fig. 1. Table 3 collects energy parameters of complexes and isotope effects $K^{\text{H}}/K^{\text{D}}$; the latter refer to the equilibrium



The contribution of non-covalent interactions into the chain oxidation of arachidonic acids was computed for their complexes with HO_2 radicals. The structures of arachidonic acids were approximated as



and



In these molecules bis-allyl $-\text{CH}_2-$ and $-\text{CD}_2-$ groups are mostly vulnerable to oxidation and subjected to attack by peroxy radicals. We have computed parameters of non-covalent interactions and isotope effect in complexes $(-\text{CH}_2-)_{\text{bis}}\cdots\text{HO}_2$ and $(-\text{CD}_2-)_{\text{bis}}\cdots\text{HO}_2$ with HO_2 radical; they are presented in Table 3. For comparison the energy parameters and isotope effects were computed for non-allyl structures $(-\text{CH}_2-)_{\text{non}}\cdots\text{HO}_2$ and $(-\text{CD}_2-)_{\text{non}}\cdots\text{HO}_2$; they refer to molecules

Table 1. Hydrogen atom complexes

Complex	ZPE, kcal/mol	ϵ , kcal/mol	$\Delta\epsilon_0$, cal/mol	$K^{\text{D}}/K^{\text{H}}$ (300 K)
$\text{H}^{\bullet}\cdots\text{O}_2$	2.28	0.20	–	–
$\text{D}^{\bullet}\cdots\text{O}_2$	2.24	0.16	40	1.07
$\text{H}^{\bullet}\cdots\text{OH}_2$	16.83	3.29	–	–
$\text{D}^{\bullet}\cdots\text{OH}_2$	15.35	1.81	1480	11.8

Table 2. Nitroxyl radical complexes

Complex	ZPE, kcal/mol	ϵ , kcal/mol	$\Delta\epsilon_0$, cal/mol	K^D/K^H (300 K)
$(\text{CH}_3)_2\text{NO}\cdots\text{HH}$	61.00	1.49	–	–
$(\text{CH}_3)_2\text{NO}\cdots\text{DH}$	59.90	1.25	240	1.49
$(\text{CH}_3)_2\text{NO}\cdots\text{HOH}$	68.47	1.95	–	–
$(\text{CH}_3)_2\text{NO}\cdots\text{DOH}$	66.35	1.63	320	1.70

Table 3. Peroxy radical complexes

Complex	ZPE, kcal/mol	ϵ , kcal/mol	$\Delta\epsilon_0$, cal/mol	K^D/K^H (300 K)
$\text{H}_2\text{O}\cdots\text{HO}_2$	25.14	2.71	–	–
$\text{H}_2\text{O}\cdots\text{DO}_2$	23.25	2.52	180	1.34
$(-\text{CH}_2-)_{\text{bis}}\cdots\text{HO}_2$	81.98	1.82	–	–
$(-\text{CD}_2-)_{\text{bis}}\cdots\text{HO}_2$	77.82	1.79	30	1.05
$(-\text{CH}_2-)_{\text{non}}\cdots\text{HO}_2$	75.39	1.06	–	–
$(-\text{CD}_2-)_{\text{non}}\cdots\text{HO}_2$	71.17	1.01	50	1.09

Table 4. Oxygen complexes

Complex	ZPE, kcal/mol	ϵ , kcal/mol	$\Delta\epsilon_0$, cal/mol	K^D/K^H (300 K)
$(-\text{CH}_2-)_{\text{bis}}\cdots\text{O}_2$	74.52	0.81	–	–
$(-\text{CD}_2-)_{\text{bis}}\cdots\text{O}_2$	70.34	0.79	20	1.03
$\text{H}_2\text{O}\cdots\text{O}_2$	16.48	0.96	–	–
$\text{HOD}\cdots\text{O}_2$	14.60	0.89	70	1.12
$\text{D}_2\text{O}\cdots\text{O}_2$	12.70	0.84	120	1.22

$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_3$ and $\text{H}_3\text{C}-\text{CD}_2-\text{CH}_3$ and also are shown in Table 3.

It is worthy noting that the structure of $\text{H}_2\text{O}\cdots\text{HO}_2$ complex shown in Fig. 1 (a nearly planar five-membered ring) is identical to that computed earlier by Suma et al, and confirmed by analysis of microwave spectra in a supersonic jet [24]. Non-covalent isotope effects for $\text{H}_2\text{O}\cdots\text{HO}_2$ complexation is rather large and exceeds 30% in contrast to that for the bis-allyl and non-allyl structures $-\text{CH}_2-$ and $-\text{CD}_2-$ hydrocarbon groups; the latter do not exceed 5–9% and seems to be not significant in oxidation.

Oxygen

We have computed parameters of the noncovalent interactions and isotope effects in oxygen complexes $(-\text{CH}_2-)_{\text{bis}}\cdots\text{O}_2$ and $(-\text{CD}_2-)_{\text{bis}}\cdots\text{O}_2$ of the vulnerable to oxidation bis-allyl groups $-\text{CH}_2-$ and $-\text{CD}_2-$; the results are presented in Table 4.

Isotope effect on the complexation of bis-allyl $-\text{CH}_2-$ and $-\text{CD}_2-$ groups with oxygen is small and does not exceed 3%, similarly to that with HO_2 radicals. Both

are hardly contribute markedly into the experimentally observed isotope effects on the oxidation of polyunsaturated fatty acids [25]. Isotope effect on the complexation of water molecule with oxygen, which seems to be important in the Earth's atmosphere [26], is slightly larger but does not exceed 10–20%.

CONCLUSIONS

Zero-point energies (ZPE) of intermolecular, non-bonded vibrations and isotope effects, induced by noncovalent interactions, are computed for paramagnetic molecules. They appear to be not significant for complexation of HO_2 and oxygen with C–H bonds and results to isotope effects, which deviate from unit not more than by 5%. However, ZPE and isotope effects in complexes of HO_2 and nitroxyl radicals with water are larger and reach 50–70%. The largest effect, about 12, is found for the complex of hydrogen atom with water, which seems to be in equilibrium $\text{H}\cdots\text{OH}_2 \rightleftharpoons \text{H} + \text{H}_2\text{O}$. Perhaps, for this reason hyperfine coupling constant of hydrogen atom in the ESR spectra markedly depends on the presence of water in solutions [27, 28].

Complexation of nitroxyl and, undoubtedly, of peroxy radicals by hydrogen bonds is accompanied by transfer of negative spin density of unpaired electron from radical to the ligand molecules. This spin density induces high field paramagnetic shifts of the ligand NMR lines; it evidences that the spin transfer via intermolecular bonds occurs by mechanism of spin polarization [16, 17].

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research (project no. 17-03-00166) and the Russian Academy of Sciences under Program no. 38. The financial support within the frameworks of the state task for ICP RAS 082-2014-0018 (registration code AAAA-A17-117040610311-3) is also gratefully acknowledged.

REFERENCES

1. D. Wade, *Chem.-Biol. Interact.* **117**, 191 (1999).
2. L. Sobczyk, M. Obrzud, and A. Filarowski, *Molecules* **18**, 4467 (2013).
3. A. L. Buchachenko and E. M. Pliss, *Russ. Chem. Rev.* **85**, 557 (2016).
4. M. Turowski, N. Yamakawa, J. Meller, J. Kimata, K. Ikegami, T. Hosoya, N. Tanaka, and E. Thornton, *J. Am. Chem. Soc.* **125**, 13836 (2003).
5. D. Rechavi, A. Scarso, and J. Rebek, Jr., *J. Am. Chem. Soc.* **126**, 7738 (2004).
6. T. Haino, K. Fukuta, H. Iwamoto, and S. Iwata, *Chem. Eur. J.* **15**, 13286 (2009).
7. C. N. Filler and J. Label, *Compound Radiopharm.* **42**, 169 (1999).
8. A. Valleix, S. Carrat, C. Caussignac, E. Leonce, and A. Tchaplal, *J. Chromatogr., A* **1116**, 109 (2006).
9. M. J. Frisch et al., *Gaussian 09* (Gaussian Inc., Pittsburgh PA, 2009).
10. R. A. Kendall, T. H. Dunning, Jr., and R. J. Harrison, *J. Chem. Phys.* **96**, 6796 (1992).
11. Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A* **109**, 5656 (2005).
12. E. R. Kevin, M. Pitonak, P. Jurecka, and P. Hobza, *Chem. Rev.* **110**, 5023 (2010).
13. J. Ceponkus, P. Uvdal, and B. Nelander, *J. Chem. Phys.* **129**, 194306 (2008).
14. N. A. Sysoeva, A. Y. Karmilov, and A. L. Buchachenko, *Chem. Phys.* **7**, 123 (1975).
15. N. A. Sysoeva, A. Y. Karmilov, and A. L. Buchachenko, *Chem. Phys.* **15**, 313 (1976).
16. N. A. Sysoeva, A. Y. Karmilov, and A. L. Buchachenko, *Chem. Phys.* **15**, 321 (1976).
17. A. L. Buchachenko, *Russ. Chem. Rev.* **54**, 117 (1985).
18. A. L. Buchachenko, *Complexes of Radicals and Molecular Oxygen with Organic Molecules* (Nauka, Moscow, 1984) [in Russian].
19. E. M. Pliss, A. M. Grobov, K. Kuzaev, and A. L. Buchachenko, *Mendeleev Commun.* **27**, 246 (2017).
20. S. Aloisio and J. S. Francisco, *J. Phys. Chem. A* **102**, 1899 (1998).
21. N. Kanno, K. Tonokura, A. Tezaki, and M. Koshi, *J. Phys. Chem. A* **109**, 3153 (2005).
22. R. Joshi, T. K. Ghanty, S. Naumov, and T. Mukherjee, *J. Phys. Chem. A* **111**, 13590 (2007).
23. H. Tachikawa, *J. Phys. Chem. A* **114**, 4951 (2010).
24. K. Suma, Y. Sumiyoshi, and Y. Endo, *Science (Washington, DC, U. S.)* **311**, 1278 (2006).
25. C. R. Lamberson, L. Xu, H. Muchalski, J. R. Montenegro-Burke, V. V. Shmanai, A. V. Bekish, J. A. McLean, C. F. Clarke, M. S. Shchepinov, and N. A. Porter, *J. Am. Chem. Soc.* **136**, 838 (2014).
26. Y. Kasai, E. Dupuy, R. Saito, K. Hashimoto, A. Sabu, S. Kondo, Y. Sumiyoshi, and Y. Endo, *Atmos. Chem. Phys.* **11**, 8607 (2011).
27. E. Roduner, P. W. Louwrier, G. A. Brinkman, D. M. Garner, I. D. Reid, D. J. Arseneau, M. Senba, and D. G. Fleming, *Ber. Bunsenges. Phys. Chem.* **94**, 1224 (1990).
28. A. M. Lossack, E. Roduner, and D. M. Bartels, *Phys. Chem. Chem. Phys.* **3**, 2031 (2001).