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Density functional theory calculation of lipophilicity for organophosphate type pesticides

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Abstract: Density functional method with continuum solvation model is used for the calculation of the partition coefficient log K_{OW} and the determination of lipophilicity of 22 most frequently used organophosphate type pesticides. Excellent agreement with experimental data is obtained using three different density functional approximations (one local, one general gradient and one hybrid), and our results highlight DFT as a reliable and trustworthy method for the calculation of lipophilicity for this important class of molecules. Furthermore, the calculated lipophilicity results are associated with the experimentally determined LD_{50} and LC_{50} values, showing that the most toxic pesticides are those with transient characteristics (medium lipophilicity), although this conclusion must be taken with a caution, due to the many factors influencing the ingestion and action of a certain substance in the body besides lipophilicity.

Keywords: DFT; lipophilicity; organophosphate pesticides; toxicity; partition coefficient; log K_{OW}.

INTRODUCTION

Since the mid-1950s the use of pesticides has grown continuously every year so that the total amount of pesticide active ingredients in use is now around 1.1 million kg per year. Pesticides, together with fertilizers, play a central role in agriculture and contribute to the enhanced food production worldwide. The need for food is directly related to the population growth, and pesticides are used more and more to increase the crop yield. Pesticides are released into the natural environment and are frequently detected in water, soil and sediments, and are in

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most cases extremely toxic for wildlife, domestic animals and humans. Major pesticide families are organophosphates (OPs), dithiocarbamates, pyrethroids and neonicotinoids. OPs are known as highly effective and extensively used agricultural pesticides, and at the same time are one of the most regular pollutants found in the contaminated sites. This class of molecules recently came under increasing scrutiny due to the environmental health concerns, particularly its association with neurodevelopmental defects.[1,2] The major public health problem originating from wide OPs usage is the constantly increasing number of self--poisoning cases.[3–5] OPs insecticides, acting as acetylcholinesterase inhibitors, are responsible for more than 2/3 of deaths due to their high toxicity and widespread use. Medical treatment is difficult, with case fatality often over 20%.[6] Since the lipophilicity represents the affinity of a molecule or moiety to dissolve in fats, oils, lipids, and non-polar solvents, it affects the important biological processes that follow chemical intake such as absorption, distribution, passage through biological membranes, receptor interactions, toxicity and metabolism,[7] we have decided to put an emphasis on the computational determination of lipophilicity of a series of 22 OPs pesticides presented in this work (Fig. 1; see Table S-I and Fig. S-1 of the Supplementary material to this paper for systematic names). Although many different organophosphate pesticides exist, we decided to examine the selected 22, due to their frequent usage.[2,8] Logarithm of octanol–water partition coefficient (log K_{OW}) is a widely accepted measure of lipophilicity and can be determined for various compounds. According to the original "shake-flask" method based on liquid–liquid partitioning, K_{OW} is defined as a concentration ratio of compound distributed between n–octanol and aqueous phase,[9,10] but it can also be obtained by the methods based on the solid–liquid partitioning (retention on reversed-phase high-performance liquid chromatography (RP-HPLC)[11,12] or thin-layer chromatography (TLC)[13] system). Partition coefficient is a highly important physicochemical parameter in medicinal chemistry, and has special usefulness in pharmacology and toxicology, as confirmed by a large number of literature data.[14–17] Water is the most important solvent in the mammalian body and at the same time represents the environment in which all vital biochemical processes occur. Also, octanol, like phospholipids and proteins which are the building blocks of all biological membranes, posseses polar hydrophilic head and nonpolar hydrophobic tail, which is why it shows the amphiphilic characteristics. For these reasons, the octanol–water system is used as a rational model of the partition between the aqueous phase and biophase in the mammalian organism.[18] The modern theoretical methods in quantum chemistry, such as density functional theory (DFT), have great predictive power and can be used to obtain the partition coefficients (log P, *i.e.*, log K_{OW}), although log P values are often obtained by the quantitative structure–activity relationship (QSAR) models.[19] DFT in conjugation with continuum solvation models is an effective, *ab initio* tool for studying the solvent effects on molecular structure, spectra, and energetics[20–24] and

has been used with success for determination of partition coeficients,[9,25,26] pK_a values,[26–28] redox potentials,[29] and so on.

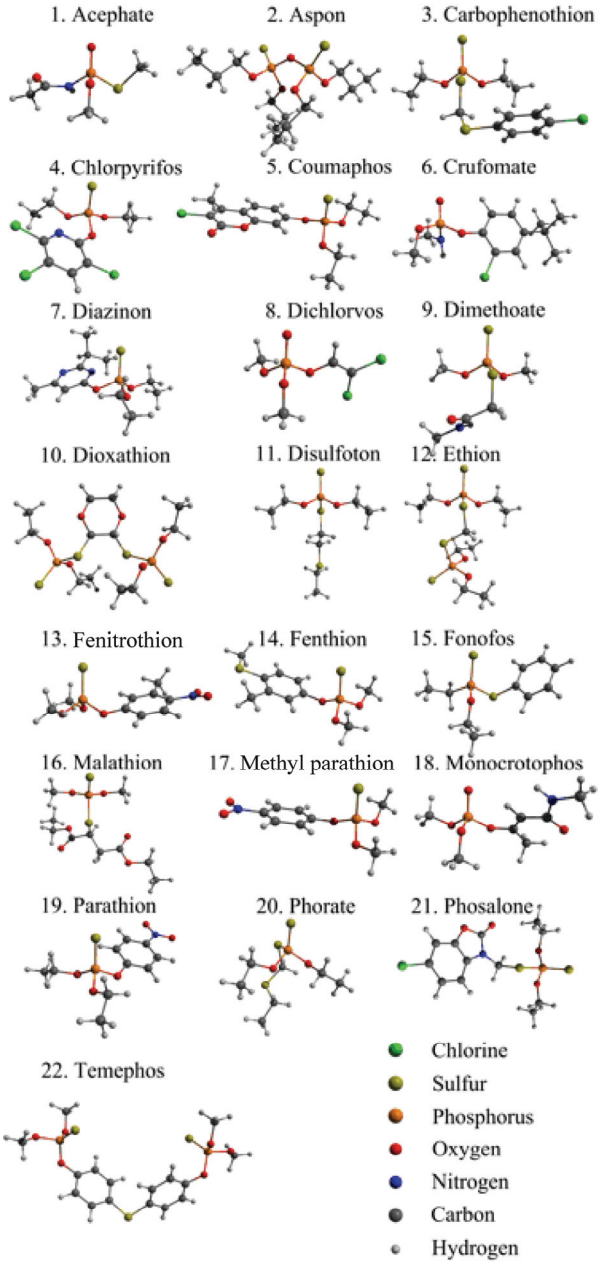

Fig. 1. Gas-phase optimized geometries of 22 OPs examined in present work, at M06L/6-31+G(d,p) level of theory.

From a great variety of solvent models,[30] the universal solvation model based on density (SMD),[22] proposed by Marenich *et al.*, is used in this work for the calculation of log K_{OW} for all investigated OPs, due to the proven accuracy for the first-principle calculation of solvation energies.[31] This way we aimed to determine the lipophilicity of different OPs, and to test the DFT approach in reproducing the experimentally obtained properties of pesticides under investigation. This study will pave a road toward the non-empirical methodology, capable to predict the lipophilicity of newly designed OPs pesticides.

COMPUTATIONAL DETAILS

All the DFT calculations have been carried out with the Gaussian 09, revision D.02 electronic structure program package.[32] For the gas phase geometry optimizations, as well as for the determination of log K_{OW}, two pure (PBE[33,34] and M06L[35,36]) and one hybrid (M062X[36]) density functional approximations (DFA) were used. For all three DFAs 6-31G+(d,p) basis set[37] was used for all atoms. Hessian analysis showed no presence of imaginary frequencies proving that all optimized structures are true minima. The free energies of solvation were calculated using the continuum solvation model based on density (SMD).[22] With SMD, the 298 K solvation free energy change is defined as the difference between the solvent and gas electronic energies,[38] necessitating the corresponding gas-phase calculation.

RESULTS AND DISCUSSION

Geometries of all 22 molecules were optimized using three different levels of theory (M06L, PBE and M062X). The geometry optimizations were carried out in gas phase, also using water and octanol as solvents, with SMD model for the overall solvation effect. The common logarithm of K_{OW} is calculated as:

$$\log K_{OW} = \frac{\Delta G_{solv(water)} - \Delta G_{solv(octanol)}}{2.303RT} \quad (1)$$

where ΔG_{solv} is the standard state solvation free energy change of a given complex in octanol or in water at T = 298 K. The standard-state solvation free energy is defined as the free energy of transfer from the gas phase to the condensed phase, under the standard state conditions. Because the gas-phase free energies are calculated with respect to a standard state of 1 atm, a correction factor of RTln 24.46 (that is 1.894 kcal* mol^{-1} at 298 K) needs to be added to convert it to the standard state of 1 mol dm^{-3}.

The calculated values for log K_{OW}, at all three levels of theory, are compared to the experimentally obtained log P values (Table I), and *MSE* (mean signed error) and *MAE* (mean absolute error),[43] RMSE (root-mean-square error),[43] *MAD* (mean absolute deviation), *RMSD* (root-mean-square deviation) and *LE*[43] (largest error in absolute value) are given in Table II.

The DFA showing the best agreement with experimental data is the M06L functional (*MAE* = 0.44). Calculated values of logK_{OW} at M06L/6-31+G(d,p)

* 1 kcal = 4184 J

level of theory differ from the experimentally obtained log *P* in less than 0.5 log units, except for the molecules 8, 10, 11 and 19. The results obtained with two popular, but different Minnesota functionals, whereas one is pure local (M06L) and the other hybrid functional (M062X), are very similar (Table S-II of the Supplementary material). It is interesting to note that M062X fluctuates more around the experimental result (*MSE* is only 0.08) and has a smaller *LE*, while M06L has a somewhat higher tendency to overestimate the partition coefficient (*MSE* = 0.21). Furthermore, although M06L has comparable errors as M062X, former has a smaller dispersion around a reference point. The next approximation functional that we chose for our calculations was the general gradient one, PBE, to complete the diversity of possible approximations and determine their influence on the obtained results. PBE also performed successfully (Table S-III). The linearity between the experimentally obtained log *P* and the theoretically determined partition coefficient log K_{OW} was obtained for all investigated OPs pesticides at all three levels of theory (Fig. 2).

TABLE I. Calculated solvation free energy change of transfer from the gas phase to water phase ($\Delta G_{solv(water)}$ / kcal mol^{-1}) and octanol phase ($\Delta G_{solv(octanol)}$) / kcal mol^{-1}) under standard state conditions, and corresponding log K_{OW} values of examined OPs pesticide set at M06L/6--31+G(d,p) level of theory, with experimentally determined log *P*

Organophosphate	$\Delta G_{solv(water)}$	$\Delta G_{solv(octanol)}$	log K_{OW}	log *P* (exp.)	Ref.
Acephate	–15.7	–15.5	–0.2	–0.8	39
Aspon	–9.1	–17.9	6.5	6.0	39
Carbophenothion	–8.4	–15.8	5.4	5.3	39
Chlorpyrifos	–4.4	–11.9	5.5	5.0	40
Coumaphos	–10.8	–16.3	4.0	4.5	41
Crufomate	–9.7	–13.7	2.9	3.4	39
Diazinon	–8.1	–12.8	3.4	3.8	39
Dichlorvos	–5.9	–9.0	2.2	1.4	39
Dimethoate	–16.8	–17.9	0.9	0.8	39
Dioxathion	–13.0	–20.1	5.2	4.3	39
Disulfoton	–8.1	–15.2	5.2	4.0	39
Ethion	–9.5	–17.0	5.5	5.1	39
Fenitrothion	–6.5	–10.5	2.9	3.3	39
Fenthion	–5.7	–11.5	4.2	4.1	42
Fonofos	–9.0	–14.4	3.9	3.9	39
Malathion	–12.4	–16.2	2.8	2.4	39
Methyl parathion	–6.6	–10.1	2.6	2.9	39
Monocrotophos	–14.7	–14.9	0.2	–0.2	39
Parathion	–7.2	–12.1	3.7	3.8	39
Phorate	–7.1	–13.2	4.5	3.6	39
Phosalone	–11.0	–16.5	4.1	4.4	39
Temephos	–7.9	–16.4	6.3	6.0	39

TABLE II. Summary of error analysis of calculated log K_{OW} values (compared to the reference experimentally determined log *P*) with different DFAs

DFA	*MSE*	*MAE*	*RMSE*	*MAD*	*RMSD*	*LE*
M06L	0.21	0.44	0.53	0.41	0.48	1.20
PBE	0.48	0.60	0.76	0.49	0.59	1.60
M062X	0.08	0.45	0.52	0.45	0.52	1.10

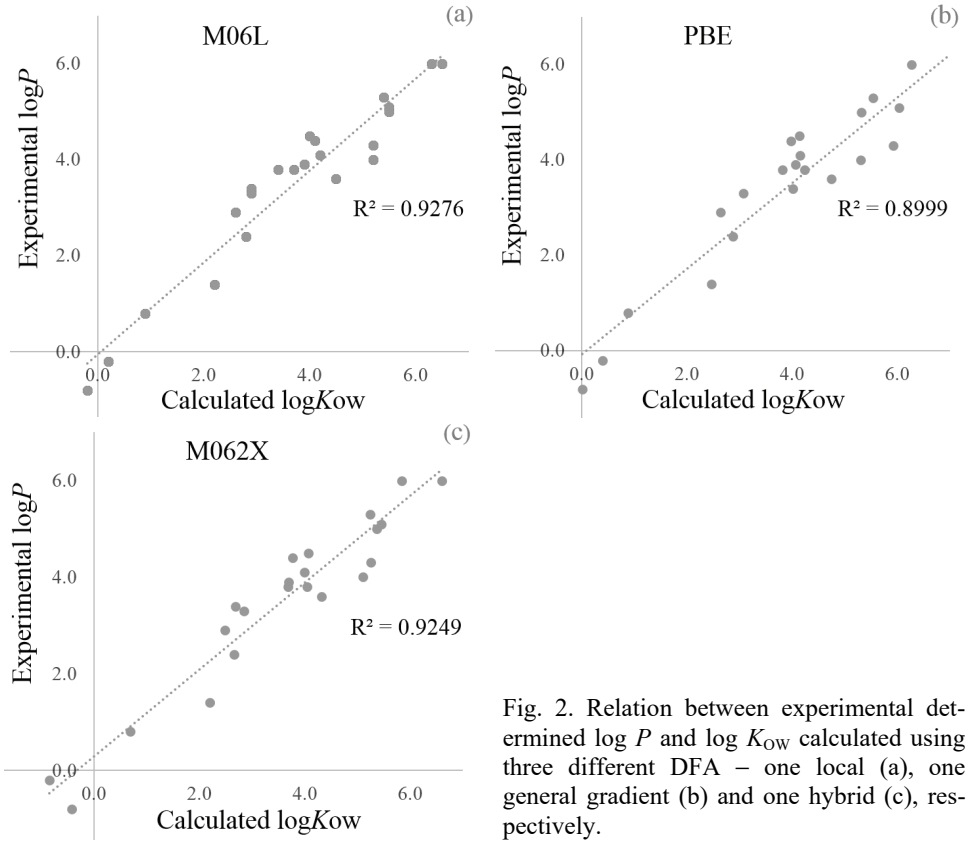

Fig. 2. Relation between experimental determined log *P* and log K_{OW} calculated using three different DFA – one local (a), one general gradient (b) and one hybrid (c), respectively.

The partition coefficient significantly influences the kinetics of drugs and poisons in the body, defining the concentration which reaches the place of action, and therefore the intensity of their effect (therapeutic or toxic effect). Furthermore, the partition coefficient is closely related to the retention time of these substances and the speed of their elimination from the human and animal body.[44] Hydrophobic substances (which have the high octanol–water partition coefficient) are mainly distributed in hydrophobic compartments, such as lipid bilayers of cells. In contrast, the low octanol–water partition coefficient characterize a certain substance as hydrophilic, and it can be primarily found in body-fluid compartments (intracellular fluid, transcellular fluid or blood plasma).[45,46]

For the efficient transcellular transport, the substance must be sufficiently hydrophobic in order to enter the lipid bilayer cell membranes, but not too hydrophobic in order to pass through the membrane. In most cases the drug or poison reaches the target site by the passive passing through the cell membrane (diffusion), and in this regard it is optimal for the molecule to possess transient characteristics (not to be too lipophilic or too hydrophilic). If we apply the previously stated concept in the context of our work, it is expected for the organophosphates with transient characteristics to have higher toxicity.

By comparing Tables I and III, it is clear that organophosphates that are extremely hydrophilic (low value for log *P*): acephate (–0.8), dimethoate (0.8), malathion (2.4), as well as organophosphates that are highly lipophilic (high value for log *P*): aspon (6.0), temephos (6.0), show high values of LD_{50} and LC_{50}; in other words, they are less toxic. On the contrary, the organophosphates with a log *P* value between highly hydrophilic and highly lipophilic (approximately between 3 and 5): phorate (3.6), parathion (3.8), methyl parathion (2.9), phonophos (3.9), disulfotone (4.0), dioxathion (4.3), coumaphos (4.5), carbophenothion (5.3), are many times more toxic than the previous ones (they have low values of LD_{50} and LC_{50}) and according to Globally Harmonized System of Classification and Labelling of Chemicals (GHS) belong to category 1 and 2 (acute toxicity estimates – ATE).

TABLE III. Values of acute median lethal doses (LD_{50}) of examined OPs for oral and dermal exposure and the median lethal concentration (LC_{50}) for inhalation exposure in male rats

Organophosphate	Oral LD_{50} mg kg^{-1}	Dermal LD_{50} mg kg^{-1}	Inhalation LC_{50} mg L^{-1}
Acephate	1000–1400	> 10000[a]	> 15
Aspon	> 2800	> 2000[a]	No data
Carbophenothion	10–30	27–54	0.002 (4 h)
Chlorpyrifos	95–270	> 2000	> 0.2 (4 h)
Coumaphos	13–41	860	1.1 (1 h)
Crufomate	770–950	> 2000	No data
Diazinon	300–466	200–900	3.5 (4 h)
Dichlorvos	25–80	70–250	0.2 (4 h)
Dimethoate	180–330	100–600	> 2 (4 h)
Dioxathion	23–43	63–235	No data
Disulfoton	2–12.5	3.6–16	0.09 (1 h)
Ethion	13–191	62	0.864 (4 h)
Fenitrothion	250–800	> 890	5.0 (4 h)
Fenthion	180–298	330–1000	2.4–3.0 (1 h)
Fonofos	3.2–18.5	147	0.9 (4 h)
Malathion	1000 – >10000	>4000	> 5 (4 h)
Methyl parathion	6–50	67	0.24 (1 h)
Monocrotophos	17–20	112–126	0.8 (4 h)
Parathion	2–30	6.8–50	0.084 (4 h)

TABLE III. Continued

Organophosphate	Oral LD_{50} mg kg^{-1}	Dermal LD_{50} mg kg^{-1}	Inhalation LC_{50} mg L^{-1}
Phorate	1.1–3.7	2.5–6.2	0.06 (1 h)
Phosalone	80–200	1500	No data
Temephos	2000–13000	1370	1.3 (4 h)

[a]In male rabbits

CONCLUSION

This computational study set out to calculate the partition coefficient log K_{OW}, and in this regard predict the lipophilicity of 22 organophosphate type pesticides. Regardless of the applied density functional approximations (local, general gradient or hybrid), using the solvation model based on density (SMD), the accurate reproduction of the experimentally determined log P has been achieved. In other words, our present work highlights DFT as an important tool for the lipophilicity calculation of existing pesticides, and this method that can be reliable for the predicting of the lipophilicity of pesticides that have not been synthesized yet. Besides the excellent agreement between theoretical and experimental data, our present work also reveals the connection between the lipophilicity and toxicity, whereas the pesticides with medium lipophilicity are extremely toxic in small doses, in contrast to OPs with significantly high or significantly low lipophilicity. This phenomenon occurs due to the specific requirements of transcellular transport, where the transported substance must be hydrophobic enough in order to enter the lipid bilayer cell membranes, but not too hydrophobic in order to pass through the membrane. In this, and similar studies, log K_{OW}/log P shouldn't be applied unilaterally, and should be considered with caution, as there are a number of other factors that influence the intensity of the action of a certain substance in the body. This relates primarily to: molecular weight and molecular size, a degree of binding to blood plasma proteins, some characteristics of specific barriers in the organism, *etc*.

SUPPLEMENTARY MATERIAL

IUPAC names of all 22 OPs pesticides and calculated solvation free energies are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ИЗРАЧУНАВАЊЕ ЛИПОФИЛНОСТИ ОРГАНОФОСФАТНИХ ПЕСТИЦИДА УПОТРЕБОМ ТЕОРИЈЕ ФУНКЦИОНАЛА ГУСТИНЕ

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Теорија функционала густине у комбинацији са SMD моделом солватације је употребљена за рачунање подеоног коефицијента log K_{OW} и одређивање липофилности 22 најчешће коришћена органофосфатна пестицида. Одлично слагање са експериментом је остварено применом три различите апроксимације функционала густине (једне локалне, једне генерализованог градијента и једне хибридне), а наши резултати истичу теорију функционала густине као поуздану и веродостојну методу за рачунање липофилности ове битне класе једињења. Добијени резултати липофилности доведени су у везу са експериментално одређеним вредностима токсичности LD_{50} и LC_{50}, указујући на то да су најтоксичнији пестициди они са прелазним карактеристикама (средњом липофилношћу), мада се овај закључак мора разматрати са опрезом, због многих фактора који утичу на уношење одређене супстанце у организам и активности у њему, поред саме липофилности.

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REFERENCES

1. B. Eskenazi, A. R. Marks, A. Bradman, K. Harley, D. B. Barr, C. Johnson, N. Morga, N. P. Jewell, *Environ. Health Perspect.* **115** (2007) 792
2. M. Balali-Mood, M. Abdollahi, *Basic and Clinical Toxicology of Organophosphorus Compounds*, Springer, London, 2013
3. World Health Report, World Health Organization, Geneva, 2004
4. M. Eddleston, M. R. Phillips, *Br. Med. J.* **328** (2004) 42
5. C. H. S. Rao, V. Venkateswarlu, T. Surender, M. Eddleston, N. A. Buckley, *Trop. Med. Int. Health* **10** (2005) 581
6. M. Eddleston, *QJM: Int. J. Med.* **93** (2000) 715
7. P. D. Leeson, B. Springthorpe, *Nat. Rev. Drug. Discov.* **6** (2007) 881
8. L. Karalliedde, S. Feldman, J. Henry, T. Marrs, *Organophosphates and Health*, Imperial College Press, London, 2001
9. R. F. Ribeiro, A. V. Marenich, C. J. Cramer, D. G. Truhlar, *Phys. Chem. Chem. Phys.* **13** (2011) 10908
10. A. Jalan, R. W. Ashcraft, R. H. West, W. H. Green, *Annu. Rep. Prog. Chem., Sect. C: Phys. Chem.* **106** (2010) 211
11. C. Giaginis, A. Tsantili-Kakoulidou, *J. Liq. Chromatogr. Relat. Technol.* **31** (2007) 79
12. K. Valkó, *J. Chromatogr., A* **1037** (2004) 299
13. A. Tsantili-Kakoulidou, *Encyclopedia of Chromatography*, 2nd ed., CRC Press, Boca Raton, FL, 2005, p. 993
14. S. Balaz, *Chem. Rev.* **109** (2009) 1793
15. J. Sangster, *Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry*, Wiley, New York, 1997
16. C. Giaginis, A. Tsantili-Kakoulidou, *J. Pharm. Sci.* **97** (2008) 2984

17. S. Aurijit, E. K. Glen, *Curr. Top. Med. Chem.* **10** (2010) 67
18. N. Bodor, P. Buchwald, *Adv. Drug Deliv. Rev.* **36** (1999) 229
19. M. Michalík, V. Lukeš, *Acta Chim. Slov.* **9** (2016) 89
20. C. J. Cramer, D. G. Truhlar, *Chem. Rev.* **99** (1999) 2161
21. J. Tomasi, M. Persico, *Chem. Rev.* **94** (1994) 2027
22. A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem., B* **113** (2009) 6378
23. J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **105** (2005) 2999
24. C. J. Cramer, D. G. Truhlar, *Acc. Chem. Res.* **41** (2008) 760
25. K. S. A. M. Shweshein, F. Andric, A. Radoicic, M. Zlatar, M. Gruden-Pavlovic, Z. Tesic, D. Milojkovic-Opsenica, *Sci. World J.* **2014** (2014) 10
26. M. Remko, M. Swart, F. M. Bickelhaupt, *Bioorg. Med. Chem.* **14** (2006) 1715
27. C. C. R. Sutton, G. V. Franks, G. da Silva, *J. Phys. Chem., B* **116** (2012) 11999
28. E. L. M. Miguel, P. L. Silva, J. R. Pliego, *J. Phys. Chem., B* **118** (2014) 5730
29. M.-H. Baik, R. A. Friesner, *J. Phys. Chem., A* **106** (2002) 7407
30. R. E. Skyner, J. L. McDonagh, C. R. Groom, T. van Mourik, J. B. O. Mitchell, *Phys. Chem. Chem. Phys.* **17** (2015) 6174
31. M. Kolář, J. Fanfrlík, M. Lepšík, F. Forti, F. J. Luque, P. Hobza, *J. Phys. Chem., B* **117** (2013) 5950
32. M. J. Frisch, G. W. Trucks, H. B. Schlegel, Gaussian 09, Revision D.02, 2016
33. J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **77** (1996) 3865
34. J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **78** (1997) 1396
35. Y. Zhao, D. G. Truhlar, *J. Chem. Phys.* **125** (2006) 194101
36. Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **120** (2008) 215
37. P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **28** (1973) 213
38. R. F. Ribeiro, A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem., B* **115** (2011) 14556
39. Y. C. Martin, *J. Med. Chem.* **39** (1996) 1189
40. J. Sangster, *J. Phys. Chem. Ref. Data* **18** (1989) 1111
41. C. T. Garten, J. R. Trabalka, *Environ. Sci. Technol.* **17** (1983) 590
42. B. T. Bowman, W. W. Sans, *J. Environ. Sci. Health, B* **18** (1983) 667
43. P. Pernot, B. Civalleri, D. Presti and A. Savin, *J. Phys. Chem., A* **119** (2015) 5288
44. N. Bodor, P. Buchwald, *Retrometabolic Drug Design and Targeting*, Wiley, New York, 2012
45. P. Keen, in *Concepts in Biochemical Pharmacology: Part 1*, B. B. Brodie, J. R. Gillette, H. S. Ackerman, Eds., Springer, Heidelberg, 1971, p. 213
46. L. Shargel, A. Yu, S. Wu-Pong, *Applied Biopharmaceutics & Pharmacokinetics*, 6th ed., McGraw-Hill Education, New York, 2012.