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Solvent impact on the aromaticity of benzene analogues: implicit versus explicit solvent approach

Piotr Cysewski · Beata Szefler · Katarzyna Kozłowska

Abstract Solvent impact on the structural index of aromaticity was modelled by polarised continuum field approximation (IEFPCM) and hybrid quantum chemistry (QM/MM) method. Significant solvent related relaxation of the solutes geometries were noticed especially for highly polar species. The significant reduction of the aromaticity was observed for some aromatic compounds in water solution compared to gas phase. The rationale of this fact was provided based on dipole moment changes, energy penalty for polarisation of solute and the distribution of frontier orbital densities. The incoherent predictions of explicit and implicit solvation models are noticed since in some cases the PCM approach artificially exaggerate the geometry relaxation in solution which is not observed if explicit solvent molecules are taken into account.

Keywords Aromaticity · Benzene analogues · HOMA · PCM · QM/MM · Solvent effect

Introduction

Aromaticity is an important and widely used concept characterising properties and structure of many organic and inorganic chemical compounds [1–3]. In the last few decades it has been generally accepted that aromaticity is a multidimensional phenomenon [4] related to greater stability of cyclic aromatic compounds if compared with their

chain analogues [5], to bond lengths between those typical of the single and double ones [6, 7] and to the existence of π-electron ring current responsible for magnetic field susceptibility [8–11]. The principal component analysis clearly identified the multidimensional nature of the aromatic behaviour [12, 13]. Thus, different quantitative criterions of aromaticiy were proposed in the last few decades [1–3] as for example the harmonic oscillator model of aromaticity (HOMA) [1, 2], the NICS, NICSzz and NICSπzz tensors [3, 14, 15], electron localisation function (ELF) [16], aromatic fluctuation index (FLU) [17], para-delocalisation index (PDI) [18], integrated induced currents as aromaticity index [19, 20] and others. Despite the fact that solvent effects may in many cases affect dramatically the chemical and physicochemical properties of molecules [21], the gas phase conditions are often found to be in acceptable agreement with experimental data and with chemical intuition [22]. Thus, the majority of studies devoted to aromaticity/anti-aromaticiy ignore the influence of the environment [4–13]. However, the structure of aromatic compounds may be profoundly affected by its molecular neighbourhood [23–25], electrostatic field of solvent [21, 26], complex formation with ions [6, 27] and direct intermolecular interactions with organic or inorganic molecules [28–31]. For example Katritzky et al. [26] has shown that aromaticity of many heterocycles and some carbocycles increases with an increase of polarity of the medium. Aromaticity of azulene and some heteroaromatic systems (such as imidazole, pyrrole or pyrazole) depends on the environment because of the changes in electric dipole moment. Geometry-based aromaticity index HOMA was used for description of micro-hydrated sodium and magnesium para-nitroso phenolates [6, 27] and dramatic change of the ring aromaticity was noticed in these complexes. However, the micro-hydration not always

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imposes significant alteration of aromatic character as for example in the case of complexation of pyrylium cation interacting with 1-3 water molecules [28]. In recent study [29] the changes in aromaticity upon complexation were studied for different ions and usually a decrease of aromaticity was observed [30, 31]. The hydrogen bond formation may also affect aromatic properties. For example in case of p-nitrophenol and phenol complexes with fluoride aromaticity of the ring correlates with the strength of the H-bond [32]. Furthermore, the significant change of the cyclic π-electron delocalisation of the DNA bases was reported after Watson–Crick hydrogen bonding [33, 34]. Besides, the chemical reactants approaching aromatic compound are important factors determining aromatic character. For example during electrophilic aromatic nitration of benzene, phenol and benzonitrile the loss of aromaticity and π -electron delocalisation is observed in the first step [35]. The above examples demonstrate how complex phenomena may occur between aromatic compound and the surrounding environment. Concentrating only on the solvent effects, the problem arises of the method selection for quantitative description of solvent imposed geometry relaxation and aromaticity alteration. Several excellent reviews have been published describing different theoretical foundations and applicability of modern approaches to solute–solvent interactions [36–38]. In general, there are three alternative choices for simulations of solute properties in bulk solution, namely implicit, explicit and mixed solvent models. The first one simplifies the solvent as continuum and homogeneous medium, which is characterised exclusively by scalar and static dielectric constant of solvent. Many alternative polarisable continuum models (PCM) were proposed differing in detailed description of solute immersion into solvent. On the contrary the explicit models directly take into account the solvent molecules *via* super-molecule approach. The hybrid quantum mechanics and molecular mechanics (QM/MM) approach belongs to this group and was successfully used to predict solvent polarisation effects at the quantitative level for such properties as reaction barriers, equilibrium constants and solvation free energies [39–41]. These distinct approaches are characterised by so many different assumptions and simplifications that it is not clear if they are able to predict molecular properties in a consistent way. In this study only one property is analysed in detail based on these two approaches, namely aromatic character described by harmonic oscillator model of aromaticity (HOMA). Thus, the aim of this work is the analysis of the solvent imposed alteration of geometries of selected benzene analogues. To our best knowledge this is the first study comparing quantitatively the influence of the explicit and implicit solvent molecules on the aromatic character of mono- and para-substituted benzene derivatives.

Methods

The aromatic character of 132 mono or para-substituted benzene analogues was analysed based on geometric criterion [1–2]. The harmonic oscillator model of aromaticity (HOMA) is widely used [6, 7] by many authors due to its simplicity and straightforward correlation to other measures of aromaticity [4]. This geometry-based index is defined as follows:

$$HOMA = 1 - \frac{\alpha}{n} \sum \left(R_{opt} - R_i \right)^2$$

where n is the number of bonds in the aromatic skeleton and α is an empirical constant chosen to give HOMA = 0 for the hypothetical Kekule structures of the aromatic systems with the CC bonds lengths equivalent to 1,3-butadiene and HOMA = 1 for system with all bonds equal to the optimal value R_{opt}. In the case of benzene moiety $\alpha =$ 257.7 and R_{opt}=1.388 [7]. The R_i values come from actual geometry obtained either from experiments or from quantum chemistry calculations. In this paper the source of structural parameters are full gradient optimisations on B3LYP/6-311 + G(d,p) level in the gas phase or in the presence of the solvent. The structures of all analysed compounds are schematically presented in Fig. 1. In the first part the simple continuum approach was used for mimicking solvent environment. Among many available models of solvation the IEFPCM [42, 43] was chosen with Merz-Kollman (Pauling) atomic radii [44] and explicit hydrogen atoms. Since inherent feature of any PCM model is the lack of explicit water molecules the solvent imposed changes in molecular properties of solutes are mainly electrostatic in nature. Thus, additional calculations were performed within explicit solvent framework. The hybrid quantum chemistry method offers an intuitive model for supermolecule systems since solute, hydration shells and the bulk solvent may be treated by different levels of theory. This approach enables taking into account explicit water molecules, is well suited for description of a system in which the direct interactions between solute and solvent molecules take place. The quenching molecular dynamics runs were followed by hybrid QM/MM geometry optimi-
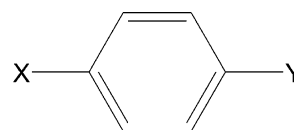
{X,Y} = {-H, -NH₂, -NO, -NO₂, -CN, -CHO, -CH₃, -OCH₃, -OH, -F, -Cl, -Br}

Fig. 1 Structure of studied benzene analogues. All possible combinations of X and Y substituents were considered which makes 132 different compounds

sation. Thus, in our model one solute molecule was immersed in a $60 \times 60 \times 60$ Å cube filled with 5332 water molecules of TIP3P type [45]. Such an explicit solvent model corresponds to infinite dilution. The periodic boundary conditions were applied at room temperature and after initial equilibration, the 500 ps long MD runs were performed. All systems readily underwent equilibration usually just after 20 ps, what was observed by stable fluctuations of root mean square deviation, total, potential and kinetic energies. Starting from 100 ps collection of snapshots was performed every 5 ps for each run and minimised using AMBER force field. Ten low energy conformations were used for further QM/MM calculations. Before the ONIOM [46–48] hybrid calculations were performed each system was divided into two layers. The HIGH layer was treated by quantum chemistry method (B3LYP/6-311 + G**) and the LOW one was treated by molecular mechanics (AMBER force field). Three alternative definitions were used for HIGH layer, namely (i) only one solute molecule, (ii) solute with nine closest water molecules and (iii) benzene analogue along with 15 water molecules in nearest proximity to the solute. The definition of QM/MM system was schematically presented in Fig. 2. The rest of the water molecules were defined as LOW layer. All hybrid calculations were performed based on Gaussian03 [49], whereas molecular dynamics simulations were done using Amber 8.0 software [50]. The atomic charges indispensible for MM and MD simulations were obtained according to Merz-Kollmann scheme [44].
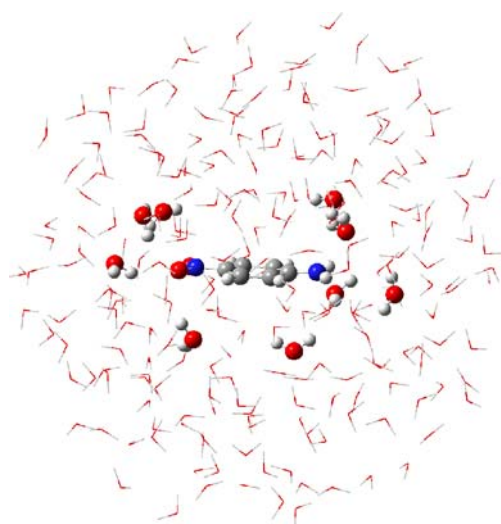

Fig. 2 The schematic representation of layers used in the hybrid QM/MM calculations. The LOW layer comprises all water molecules not included in the HIGH shell. Three alternative definitions of HIGH layer were considered, namely (i) only solute molecule, (ii) solute with adjacent nine water molecules and (iii) solute along with 15 water molecules in nearest proximity to solute

Results and discussion

PCM solvent imposed alteration of HOMA

Initially the solvent-imposed changes of solute structural properties were analysed based on continuum approach. In Fig. 3 there is presented a correlation between the structural aromaticity index (HOMA) estimated for geometries coming from optimisation either in the gas phase or in the presence of the solvent. Interestingly, the non-linear relationships are noticed. Both water and tetrahydrofurane (THF) affects the geometry relaxation as a result of the presence of the solvent field. In both cases the reduction of the aromaticity is observed in solutions at infinite dilutions with respect to the gas phase. The higher polarity of water imposes higher geometry alterations of the analysed compounds. Although for many compounds there is observed rather small decline of the HOMA values, there are species for which significant changes are noticed. Among all studied compounds, p-NO-aniline was found as the most sensitive molecule to the character of the environment. In water solutions the PCM model predicts about 25% reduction of aromatic character of this compounds since HOMA values changed from 0.922 (vapour) to 0.735 (water solution). The corresponding value for THF solution is equal to 0.803. For more detailed analysis of the solvent impact on the HOMA index, eight selected compounds were re-optimised in the presence of a series of solvent differing by dielectric constant. As it may be inferred from Fig. 4 in all analysed cases solvent imposed reduction of aromatic character. Even such non-polar medium as benzene (with dielectric constant $\varepsilon = 2.25$) imposes geometry changes on most analysed compounds. However, in the case of this organic solvent the decrease in HOMA values is the smallest among all analysed mediums. As it may be inferred from Fig. 4 there are smooth and non-linear relationships between HOMA values and solvent dielectric constants. The increase of solvent polarity from non-polar to semi-polar leads to the most significant changes of HOMA values. The further increase of environment polarity up to highly polar solvents does not affect so dramatically the solutes structures and presented curves tend to stable solute-related values. However, the geometries of some of analysed compounds are almost insensitive to the presence of the solvent field. It is interesting to see what is the origin of solvent imposed geometry relaxation. The first obvious source of HOMA alterations is polarity of the solute. The values of dipole moments (μ) presented in Fig. 4 allow concluding that only polar solutes with $\mu^{gas} > 5.0 D$ are very sensitive to the presence of the solvent field. However, this obvious statement does not fully describe complexity of the observed phenomena, since values of dipole moments estimated in water solution are affected on
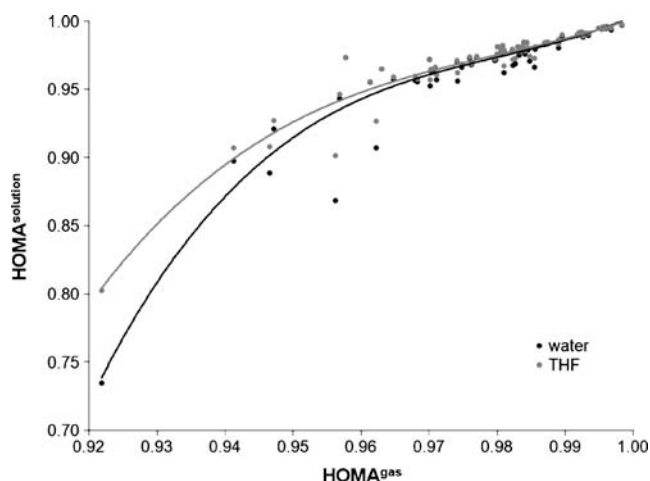
Fig. 3 The values of HOMA index estimated for broad range of benzene analogues in the gas phase and water or THF solutions. The structural criterion of aromaticity was applied to geometries fully optimised by means of B3LYP/6-311 + G(d,p) method. The IEFPCM model of solvation was applied with Merz-Kollman (Pauling) atomic radii and explicit hydrogen atoms

different ways for different solutes. Although the aim of this paper is not the detailed analysis of the correlation between HOMA and molecular descriptors, typical quantitative relationships analysis was performed. Usually molecular descriptors are estimated *via* semiprirical procedures [51–53]. Here, more than 1500 molecular descriptors were generated and used for standard regression analysis according to common QSAR methodology [53]. Unfortunately no satisfactory linear relationships were obtained bases on such approach. This suggests that the geometry relaxation imposed by solvent environment of analysed compounds is a complex and non-linear phenom-
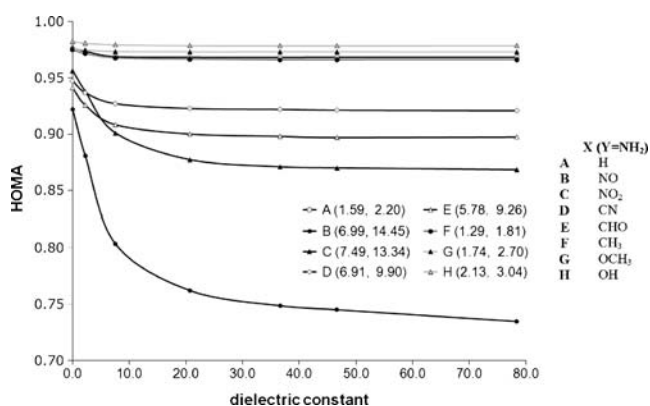
enon. Despite such dissatisfactory results other functions were tested. Among many considered equations the highest correlation was obtained using the following empirical formula:

$$\lambda^{est}[\%] = \left(\frac{HOMA^{\,gas}}{HOMA^{\,water}} - 1 \right)$$

$$= 2.023 \cdot \mu^{water} - 2.771 \cdot \mu^{gas} + 0.0456 \cdot \exp\left(0.5 \cdot G^{pol}\right)$$

where μ^{gas}, μ^{water} stand for the values of dipole moments (in Debays) estimated in gas phase and water environment. The G^{pol} is the component of solvation Gibbs free energy (in kcal mol^{-1}) corresponding only to solute polarisation. The left hand side of this equation has simple meaning of the relative changes of HOMA values if solute is transferred from gas phase to water solution. The higher value of λ^{est} the stronger impact of the environment on the aromaticity. The right hand side of above equation defines molecular properties that are crucial for description of geometry relaxation. Apart from the values of dipole moments the third parameter quantifies the polarisation of solute in water solution. Interestingly, only this component seems to be important since other solvation terms as total solvation Gibbs free energy, total electrostatic or total non-electrostatic, as well as cavitation, dispersion or repulsion are not directly correlated to λ factor. In Fig. 5 correlation is presented between λ^{est} (estimated based on above empirical formula) and λ^{DFT} (directly calculated from optimised geometry at B3LYP/6-311 + G** level). The correlation is quite satisfactory since R^2>0.95. Many other molecular properties were also considered as for example HOMO or
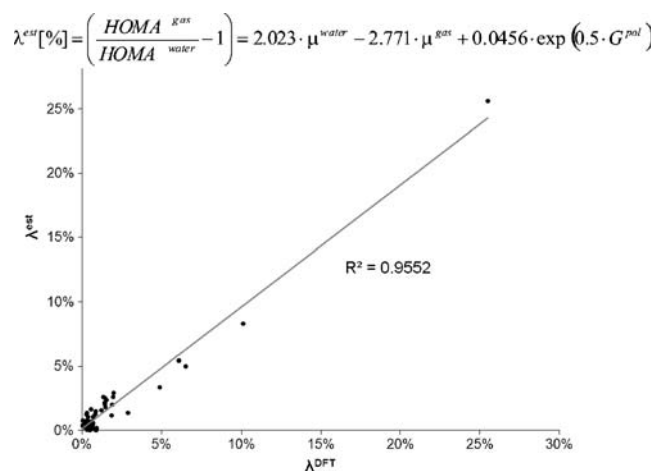

Fig. 4 The values of HOMA index estimated for selected compounds in different solutions. The following solvents were used in IEFPCM model: water (ε=78.39), DMSO (ε=46.70), acetonitrile (ε=36.64), acetone (ε=20.70), THF (ε=7.58), benzene (ε=2.25), where ε stands for dielectric constants. In figure legend there are supplied values of solute dipole moments (in Debays) corresponding to the gas phase (first value) and water solution (second value)

Fig. 5 The relationship between values of λ factor (in %) estimated based on B3LYP/6-311 + G** optimised geometries (λ^{DFT}) and obtained according to provided empirical formula (λ^{est}), where μ^{gas}, μ^{water} stand for the values of dipole moments (in Debays) estimated in gas phase and water environment but G^{pol} is the component of solvation Gibbs free energy (in kcal mol^{-1}) corresponding only to solute polarisation

LUMO energy, their difference, IP values, electron affinity, quadrupole and octapole moments, exact polarisabilities, diagonal vibrational polarisabilities, electronic spatial extent and polarised surface area, but no direct relations was observed to alteration of HOMA values. In the proposed empirical formulae the coefficients scaling values of dipole moments (μ^{gas}, μ^{water}) are rather close to each other, which suggests that the change of dipole moments is more important than the absolute values. Thus, aromaticity alteration has their origin mainly in the increase of dipole moments after immersing in polar environment. Besides, the energetic penalty on solute polarisation (G^{pol} is always positive) associated with this process of solvation is also important as a factor affecting the aromatic character of analysed compounds. Since 132 different compounds were used in above analysis one may believe that conclusions provide some general insight into the origin of the aromaticity changes.

Additional interesting observation may be documented if HOMO and LUMO densities are considered. In Fig. 6 the distributions of these frontier orbitals are presented for two selected compounds. The most significant solvent imposed changes of HOMA values were observed for p-NO-aniline. Interestingly, this compound is characterised by significant dislocation of densities coming from HOMO and LUMO distributions. Thus, considerable asymmetric interactions may occur in polar environments. These parts of the p-NO-aniline molecule, which are rich in electron densities (high HOMO densities) will interact with positive edges of
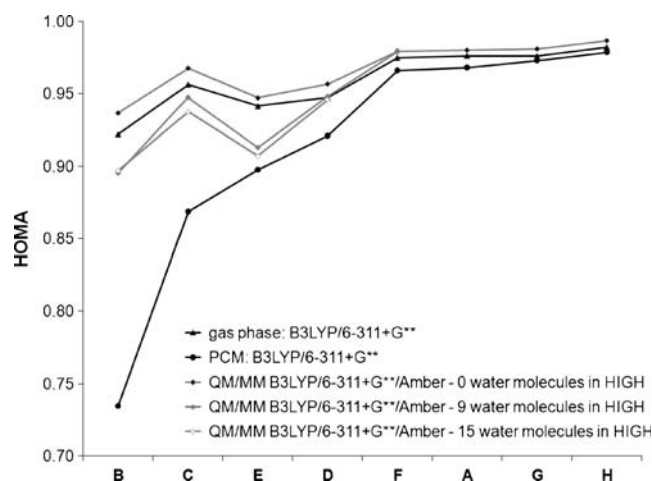

Fig. 7 The values of structural index of aromaticity (HOMA) estimated by different methods. Notation of compounds is the same as in Fig. 4. Analysed species were sorted by decreasing values of HOMA

solvent dipoles (i.e. hydrogen atoms in case of water solutions). On the other hand those regions with high LUMO densities are prone to interactions with negative parts of solvent dipoles (lone pairs of oxygen in the case of water). The observed significant solvent imposed changes of HOMA values originates then from stretching of the p-NO-aniline molecule especially in water solution. The other compounds do not posses this feature. For example in Fig. 6 the distribution of the frontier orbitals characterising p-CH₃-aniline were also presented. In this case (and also for

Fig. 6 The distributions of HOMO and LUMO densities corresponding to p-NO-aniline and p-methylaniline estimated in the gas phases on B3LYP/6-311 + G** level
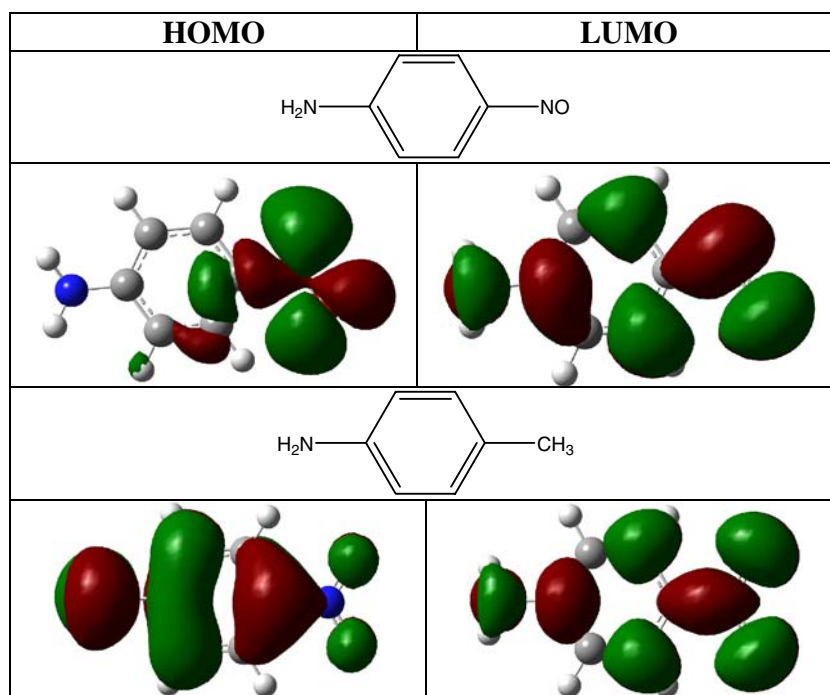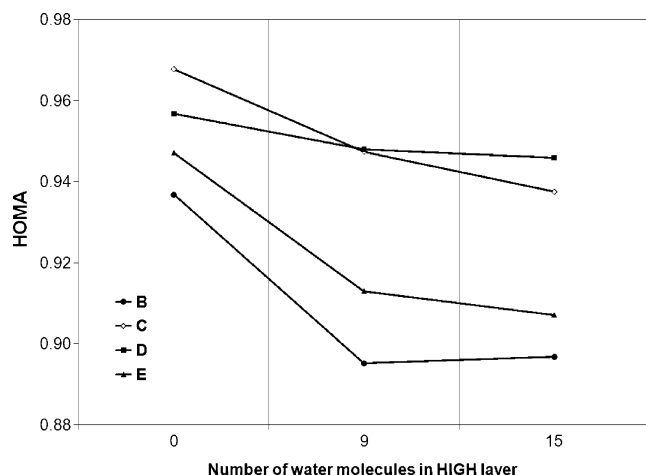
Fig. 8 The correlation between HOMA values and the definition of the HIGH layer in QM/MM calculations. Notation of compounds is the same as in Fig. 4

other analysed compounds) there is no visible dislocation of frontier orbitals. Thus, much smaller geometry relaxations are expected even in highly polar solvents.

MD quenching and QM/MM method

The most interesting observation documented above is the extremely significant impact of the solvents on the aromatic character of some compounds if PCM model is applied. However, it is well known that continuum models do not take into account all effects of solute-solvent interactions [36]. This is related both to inherent simplification of PCM methods and to the lack of explicit solvent molecules interacting with solute. Thus, in this part the QM/MM computations were performed as a complementary characteristics of solvent imposed changes of solute geometry. Due to computational expenses that are needed in quenching MD simulations combined with QM/MM approach only four compounds were analyse, namely p-NO-aniline (B), p-NO$_2$-aniline (C), p-CN-aniline (D) and p-CHO-aniline (E). The aromaticities of these compounds were

found as the most susceptible to solvent environment. It is important to notice that an inherent feature of any explicit model are the fluctuations of the position of solvent molecules in the solvation layers. These conformation changes, especially in the closest proximity to the solute, obviously affect its geometry. Hence, the explicit solvent model is more realistic although more computationally expensive since several conformations of solvent molecules must be taken into account. The quenching MD method provides rationale source of meaningful solute-solvent structure. As was mentioned in the methodology part several conformations were generated from MD snapshots and only the lowest energy ones were taken into account. The predicted values of HOMA index presented in Fig. 7 were obtained as an averaged value of ten QM/MM optimisations. Three alternative definitions were used for specification of the HIGH layer differing in number of solvent molecules treated by quantum chemistry approach. This provides some interesting methodological clues. The crudest model comprised no water molecules in the HIGH layer, which was formed only by one solute molecule. As it is presented in Fig. 7 this is a rudimentary assumption leading to wrong description of the solvent imposed geometry relaxation of solute molecule. The values of HOMA index increased in this case if compared to gas phase values. Since all other models predict opposite trend, it is clear that the quantum effects are important for solute-solvent interactions and must be taken into account. The extension of HIGH layer and including nine water molecules in the first solvation layer leads to decrease of aromaticity with respect to the gas phase. The first solvation layer was defined as the region comprising all water molecules within 3.0Å from any heavy atom of the solute. The observed reduction of the HOMA values is much smaller in this case if compared to PCM predictions. There is still question about the size of the solvation shell defined as HIGH layer. Additional calculations were performed with extension of the size of the HIGH layer up to 4.0Å from any heavy atom of the solute. This leads to inclusion of 15 water molecules in the nearest proximity to the solute

Table 1 The HOMA values estimated based on geometries optimised in the gas phase and in water solutions modelled by QM/MM and IEFPCM approaches

	B	C	D	E
QM/MM(0)	0.937(*0.005*)	0.968(*0.005*)	0.957(*0.004*)	0.947(*0.005*)
QM/MM(9)	0.895(*0.031*)	0.947(*0.023*)	0.948(*0.005*)	0.913(*0.013*)
QM/MM(15)	0.897(*0.039*)	0.937(*0.017*)	0.946(*0.010*)	0.907(*0.020*)
PCM	0.735	0.868	0.921	0.897
gas phase	0.922	0.956	0.947	0.941

In parenthesis the values of standard deviations were provided. For QM/MM method the number of water molecules treated in the HIGH layer were provided

molecule. As it is presented in Fig. 7 only small reduction of HOMA values were observed in this case. Alternative presentation of this aspect is demonstrated in Fig. 8. As it may be inferred from presented plots, the saturation effect is observed and clear trends of HOMA values may be guessed. Thus, the 3.0Å radius seem to be sufficient for proper description of water solute interactions. This is a fortunate circumstance increasing efficiency of the applied method to the description of the solvent impact on the aromatic character enumerated by geometry index. The detailed values of HOMA index characterising selected compounds were presented in Table 1. Interestingly, standard deviations are the smallest in the simplest case of QM/MM method and increase with extension of the HIGH layer. However, there are statistically significant differences between HOMA values estimated based on QM/MM and PCM methods.

Conclusions

The geometry relaxation imposed by presence of the solvent depends on many factors related not only to physical properties of system components but also to the applied methodology. The HOMA index widely used as a measure of alteration of bond length in aromatic systems seems to be adequate for quantifying of solvent imposed geometry changes on solute molecules. According to presented results the PCM approach reduces the aromaticity of analysed benzene analogues in the presence of the solvent with respect to the gas phase. The most significant changes of HOMA values were observed for highly polar compounds characterised by dipole moment greater than 5.0 Debays in the gas phase. The empirical formula proposed for quantitative prediction of the reduction of water imposed HOMA values (λ factor) uses two criterions, which must be taken into account, namely water imposed changes of solute dipole moments with respect of the gas phase and energetic penalty of the solute polarisation.

On the other hand the explicit solvent model predicts much smaller impact of the water molecules on the reduction of the HOMA values of those solutes, which are susceptible to solvent imposed geometry relaxation. This suggest that continuum approach overestimates the influence of the solvent molecules on the solute geometry alteration. One of the sources of the observed discrepancies is the manifestation of direct intermolecular interactions between water molecules in the first hydration shell. The formation of the net of very strong hydrogen bonds between water molecules around much less polar solutes is commonly known as hydrophobic effect (forces). It reduces the direct impact of water molecules on the solute geometry. The self-association of explicit water molecules

that is not taken into account in any PCM model is expected to be the main source of observed model-related alterations of HOMA values. In our opinion the explicit model is more realistic and explains aromaticity with higher precision than PCM approach. Thus, the quenching MD simulations accomplished with QM/MM geometry optimisations and rational definition of the quantum chemistry layer provide a promising way for the dynamic and structural description of bulk systems and last but not least, it is in good accord with chemical intuition.

References

1. Krygowski TM, Cyrański MK (2001) Chem Rev 101:1385–1419
2. Krygowski TM, Cyrański MK, Czarnocki Z, Häfelinger G, Katritzky AR (2000) Tetrahedron 56:1783–1796
3. Chen Z, Wannere CS, Corminboeuf C, Puchta R, Schleyer PvR (2005) Chem Rev 105:3842–3888
4. Cyrański MK, Krygowski TM, Katritzky AR, Schleyer PvR (2002) J Org Chem 67:1333–1338
5. Cyrański MK (2005) Chem Rev 105:3773–3811
6. Krygowski TM (1993) J Chem Inf Comput Sci 33:70–78
7. Krygowski TM, Cyrański MK (1996) Tetrahedron 52:1713–1722
8. Heine T, Corminboeuf C, Seifert G (2005) Chem Rev 105:3889–3910
9. Schleyer PvR, Puehlhofer F (2004) Org Lett 4:2873–2876
10. Gomes JANF, Mallion RB (2001) Chem Rev 101:1349–1383
11. Balaban AT, Schleyer PR, Rzepa HS (2005) Chem Rev 105:3436–3447
12. Katritzky AR, Barczyński P, Musumarra G, Pisnao D, Szafran M (1989) J Am Chem Soc 111:7–15
13. Caruso L, Musumarra G, Katritzky AR (1993) Quant Struct Act Relat 12:146–151
14. Corminboeuf C, Heine T, Weber (2003) J Phys Chem Chem Phys 5:246–251
15. Heine T, Schleyer PvR, Corminboeuf C, Seifert G, Reviakine R, Weber J (2003) J Phys Chem A 107:6470–6475
16. Santos JC, Tiznado W, Contreras R, Fuentealba P (2004) J Chem Phys 120:1670. doi:10.1063/1.1635799
17. Matito E, Duran M, Sola M (2005) J Chem Phys 122:014109. doi:10.1063/1.1824895
18. Poater J, Fradera X, Duran M, Sola M (2003) Chem Eur J 9:400–410
19. Juselius J, Sundholm D, Gauss J (2004) J Chem Phys 121:3952. doi:10.1063/1.1773136
20. Johansson MP, Juselius J, Sundholm D (2005) Angew Chem Int Ed 44:1843–1846
21. Reichardt C (2003) Solvent effects in organic chemistry, Third, updated and enlarged edition. Wiley, Weinheim
22. Bachrach SM (2007) Computational Organic Chemistry, Wiley, New York
23. Krygowski TM, Cyrański MK (2003) Phys Chem Chem Phys 6:249–255
24. Schleyer PvR, Jiao H (1996) Pure Appl Chem 68:209–218
25. Krygowski TM, Ciesielski A, Bird CW, Kotschy A (1995) J Chem Inf Comput Sci 35:203–210
26. Katritzky AR, Karelson M, Wells AP (1996) J Org Chem 61:1619–1623
27. Talberg H (1997) J Acta Chem Scand A31:37–40
28. Parreira RLT, Galembeck SE (2006) J Mol Struct (THEOCHEM) 760:59–73

29. Rodríguez-Otero J, Cabaleiro-Lago EM, Peña-Gallego A (2008) Chem Phys Lett 452:49–53
30. Garau C, Frontera A, Quiñonero D, Ballester P, Costa A, Deya PM (2004) J Phys Chem A 108:9423–9427
31. Guell M, Poater J, Luis JM, Mo O, Yañez M, Sola M (2005) Chem Phys Chem 6:2552–2561
32. Krygowski TM, Zachara JE, Szatylowicz H (2004) J Org Chem 69:7038–7043
33. Box VGS, Jean-Mary F (2001) J Mol Model 7:334–342
34. Cyrański MK, Gilski M, Jaskólski M, Krygowski TM (2003) J Org Chem 68:8607–8613
35. Arrieta A, Cossio FP (2007) J Mol Struct (THEOCHEM) 811:19–26
36. Van Gunsteren WF, Weiner PK, Wilkinson AJ (1997) Eds Computer simulation of biomolecular systems. Theoretical and experimental applications, Kluwer, Dordrecht, vol. 3
37. Orozco M, Luque FJ (2000) Chem Rev 100:4187–4226
38. Tomasi J, Mennucci B, Cammi R (2005) Chem Rev 105:2999–3094
39. Gao J, in: Lipkowitz KB, Boyd DB (Eds) (1996) Reviews in Computational Chemistry, vol. 7, VCH, New York
40. Gao J, Xia X (1992) Science 258:631–635
41. Gao J, Xia X (1993) J Am Chem Soc 115:9667–9675
42. Tomasi J, Mennucci B, Cancès E (1999) J Mol Struct (THEOCHEM) 464:211–226
43. Mennucci B, Cancès E, Tomasi J (1997) J Phys Chem B 101:10506–10517
44. Besler BH, Merz KM Jr, Kollman PA (1990) J Comp Chem 11:431–439
45. Jorgensen WL, Chandrasekhar J, Madura J, Klein ML (1983) J Chem Phys 79:926–935
46. Maseras F, Morokuma K (1995) J Comp Chem 16:1170–1179
47. Humbel S, Sieber S, Morokuma K (1996) J Chem Phys 105:1959–1969
48. Svensson M, Humbel S, Morokuma K (1996) J Chem Phys 105:3654–3661
49. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery Jr JA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2004) Gaussian 03, revision C.02. Gaussian, Inc, Wallingford CT
50. Case DA, Darden TA, Cheatham TE III, Simmerling CL, Wang J, Duke RE, Luo R, Merz KM, Wang B, Pearlman DA, Crowley M, Brozell S, Tsui V, Gohlke H, Mongan J, Hornak V, Cui G, Beroza P, Schafmeister C, Caldwell JW, Ross WS, Kollman PA (2004) AMBER 8. University of California, San Francisco
51. Tetko IV, Gasteiger J, Todeschini R, Mauri A, Livingstone D, Ertl P, Palyulin VA, Radchenko EV, Zefirov NS, Makarenko AS, Tanchuk VY, Prokopenko VV (2005) J Comput Aid Mol Des 19:453–463
52. Todeschini R, Consonni C (2000) Handbook of Molecular Descriptors, WILEY-VCH
53. Selassie CD (2003) In: Burger's medicinal chemistry and drug discovery, sixth edn, volume 1: Drug discovery, Abraham DJ ed., Wiley, New York, p4-48