Theoretical Study of the Solvent Effect on the properties of Indole-Cation-Anion Complexes

Jorge A. Carrazana-Garcia[1], **Enrique M. Cabaleiro-Lago**[1], **Jesus Rodriguez-Otero**[2]

[1] *Departamento de Química Física, Facultade de Ciencias, Universidade de Santiago de Compostela. Campus de Lugo. Avenida Alfonso X El Sabio s/n, Lugo 27002, SPAIN.*

[2] *Centro Singular de Investigación en Química Biológica e Materiais Moleculares (CIQUS), Universidade de Santiago de Compostela, Rúa Jenaro de la Fuente s/n, Santiago de Compostela 15782, SPAIN.*

Abstract

The properties of ternary indole-cation-anion (IMX) complexes are theoretically studied as simplified models of real systems in which some of the fragments used are parts of bigger and complicated structures, like proteins. The electro-neutrality of real systems and the presence of ions of both charges interacting simultaneously with aromatic residues in the proteins modeled justify the move from cation-π or anion-π (non-bonding interactions analyzed by our group in previous studies) to cation-π-anion complexes. With the intention of approaching more the model to reality, the solvent was also included in the study: aqueous solvent was represented by a combination of PCM + explicit addition of one water molecule to some IMX complexes. As model systems for this study the complexes with indole and the following cations and anions were selected: M = Na^+, NH_4^+; X = $HCOO^-$, NO_3^- or Cl^-. The effect of the solvent was studied not only on the energy but as well on some structural parameters like the proton transfer from the ammonium cation to the basic anion and the cation-anion separation. The results indicate that the PCM method alone properly reproduces the main energetic and geometrical changes, even at quantitative level, but the explicit hydration allows refining the solvent effect and detecting cases that do not follow the general trend.

Keywords: solvent effect, cation-π-anion interaction, PCM

Introduction

The interaction between a cation and an aromatic moiety is a common motif in biological systems, usually involving side chains of aromatic and cationic amino acids. [1-3] As a consequence of its importance, a lot of experimental and theoretical work has been done in order to understand the cation-π interactions, its physical origin and action mechanism. In this effort, Computational Chemistry takes an important part, for example elucidating that the nature of this interaction is more than electrostatic, as believed in the early studies.[4-6] Taking into account that in real systems cation-π interactions usually occur in conjunction with other non-bonding interactions, it is important to consider model structures in which multiple interactions occur together.[7-9] The electro-neutrality of real systems and the presence of ions of both charges interacting simultaneously with aromatic residues in the proteins modeled justify the move from cation-π to cation-π-anion complexes.[10, 11]

The present study is oriented to the equilibrium properties of ternary indole-ammonium-anion complexes in water, as simplified models of real systems in which some of the fragments used are parts of bigger and complicated structures, like proteins. The complexes studied include the ammonium cation (model of the cationic end of lysine) and the formate anion (present in the side chain of glutamic and aspartic acids) as well as Na^+, NO_3^- and Cl^- (ions with biological interest also). Indole, present in the aromatic side chain of tryptophan, is employed as a model of a π-system. This molecule includes in its structure the benzene ring (present in phenylalanine and tyrosine) and has additionally a pentagonal aromatic ring containing a N-H group, similar to that found in the imidazole ring of histidine. The presence of the two conjugated rings and the N-H group gives indole the possibility for interacting as donor or acceptor.[12, 13] Therefore, it can interact with ions of both charges, working as a good ion-pair receptor[14] and it has been recognized as the most frequent fragment in the cation-π interactions observed in protein systems.[15] In the present investigation it is assumed that the model complexes studied are formed from their isolated fragments. The main hypothesis is that the trends and conclusions reached can be extrapolated to the real systems in which one or two of the fragments (for example, indole and one of the ions) could be bound to a protein backbone.

It is presumable that the most common situation in real systems is given when the cation-π-anion complex is surrounded by an aqueous media. Therefore, with the intention of approaching the model to reality the solvent has been included in the study. The work done in this field applies one of the two main methods available: the micro-solvation approach[3, 16-25] or the use of a continuum model.[26-28] Both approximations to the solvation problem have its own benefits and drawbacks so, if the size of the system allows it, the combination of both methods is also employed with the aim of model simultaneously the specific and the non-specific solute-solvent interactions with a reasonable calculation effort.[29, 30] The solvent effect on the properties of the cation-π-anion complexes was performed in this work by applying the Polarizable Continuum Model combined with the explicit addition of one water molecule to some indole-ammonium-anion model complexes.

Computational Details

The geometries of the indole-cation-anion complexes and those of its monohydrates were optimized first in gas phase using the M06-2X/6-31+G* level of calculation and the stationary points found were characterized as minima by means of frequency calculations. It has been confirmed that this model Chemistry describes the energetic and geometric features of the systems studied with trends and numerical results close of that achieved with the MP2(full)/aug-cc-pVDZ//MP2/6-31+G* level of calculation.[31]

At the beginning of the geometry optimizations of the monohydrates, the H_2O molecule was added to each indole-cation-anion complex in several starting positions, covering the orientations suggested by the chemical intuition. Between the monohydrates minima reached in the geometry optimization, only those that are well differentiated structurally were selected for the study. The geometries of the ternary complexes and those of its monohydrates were then re-optimized at the same level of calculation but using the polarizable conductor-like model (C-PCM) for representing the aqueous solvent. Additional frequency calculations (M06-2X/6-31+G* + C-PCM) confirmed that the final structures (see Fig. 1 and Fig. 2) are minima in their respective potential energy surface. The structures are labeled as IMX and IMXw#, where the acronyms have the following meaning: π-system: I = indole; Cation (M): N = Na^+, A = NH_4^+; Anion (X): C = Cl^-, F = $HCOO^-$, N = NO_3^-; the “w” indicates the presence of a water molecule in the structure and the number “#” is used to arbitrarily distinguish between different monohydrates of the same complex.

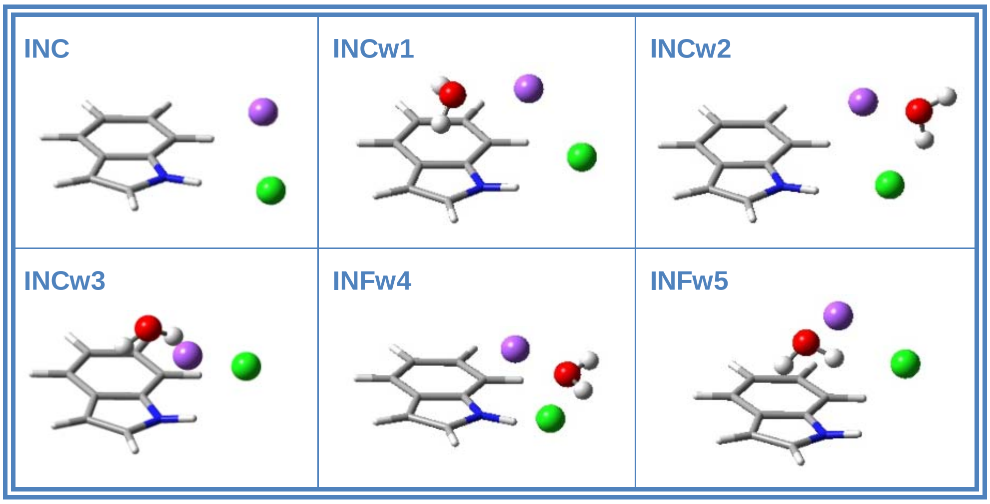


Figure 1. Structures of the indole-sodium-chloride complexes included in the present study. The solvent was modelled using a combination of PCM=water and the addition of one H_2O molecule. All the structures were optimized at the M06-2X/6-31+G* level of calculation with PCM=water and are minima in their respective PES.

The supermolecule approach was used for the calculation of E_{int}, the BSSE-free interaction energies,[32, 33] and the corresponding deformation energies (E_{def}) were also included. The combination of both is reported as binding energy: $E_{bind} = E_{int} + E_{def}$. As previously advised,[34-36] the BSSE computed at the same level of calculation in the gas phase with the geometries re-optimized in water is added to the interaction energies obtained with PCM using for each fragment its own basis.

Indole has two main ways for interacting with the anions: N-H···X and C-H···X. The complexes of indole with the same cation and anion are more stable when the anion is in the first of these orientations because of the extra stabilization conferred by the interaction between the anion and the N-H group of indole, more acidic than the C-H groups.[31] All the structures of the indole-cation-anion complexes included in the present study have the anion by the side of the N-H group of indole.

In the calculations of E_{int} for the IMXw complexes, the additional water molecule was considered as being part of the cation (hydrated cation) fragment. This approach was chosen because, considering isolated indole, anion and cation, the H_2O molecule establishes the strongest interaction with the last, and because in all but one of the hydrated complexes found exist a direct cation-H_2O interaction. All the calculations were performed with the Gaussian09 suite of programs.[37]

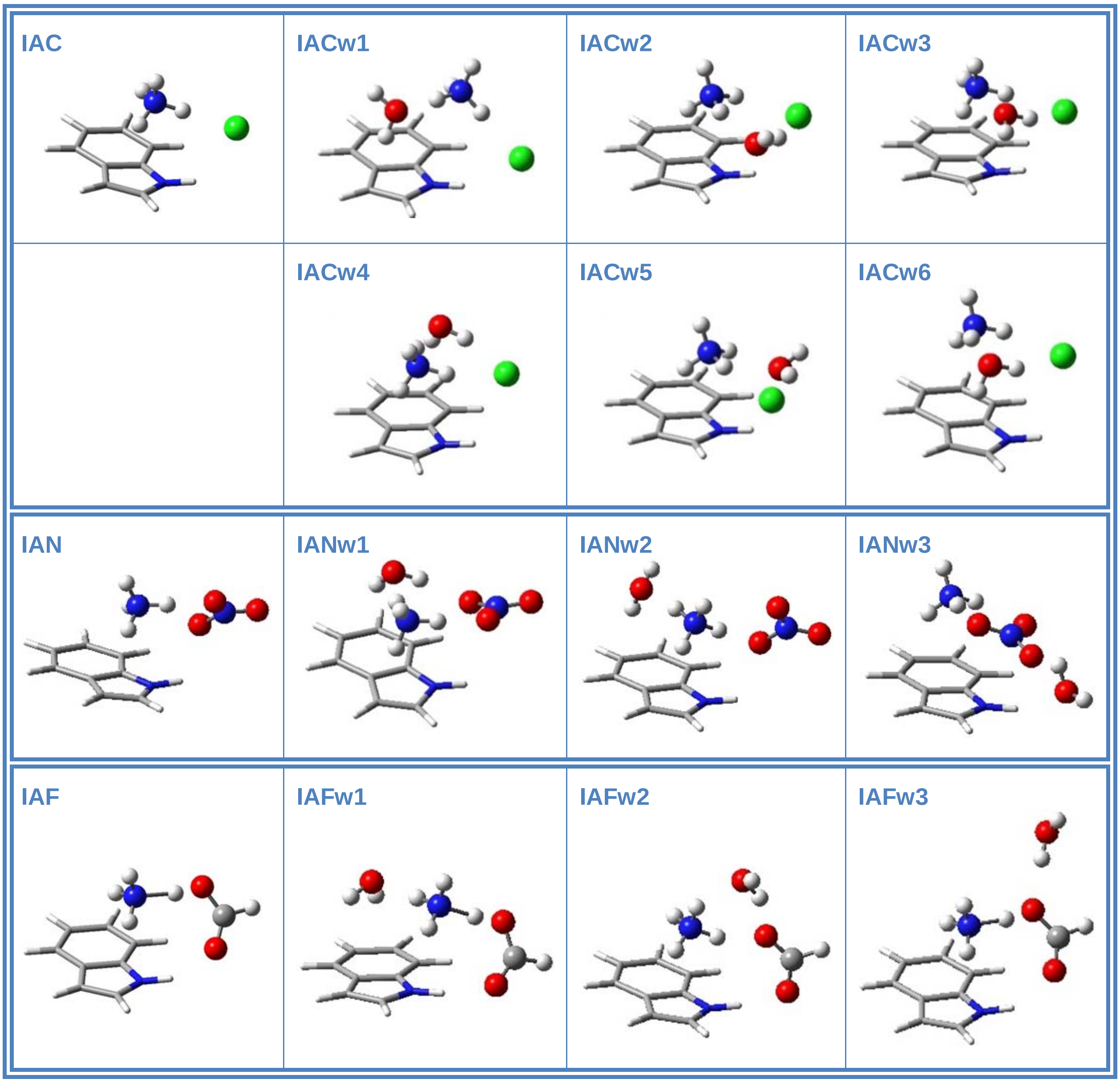
Table 1. Influence of the solvent on the geometry and binding energy of indole-sodium-chloride complexes. The structures were optimized at the M06-2X/6-31+G* level of calculation in gas phase or PCM=water, as indicated in the second column, and are minima in their respective PES. The complexes with a “w” in its label contain one water molecule. r (Na-Cl) is the length, in Å, between the cation and the anion. E_{bind} is the binding energy, in kcal/mol, for:

$$\text{Indole + (sodium·n water) + chloride} \rightarrow \text{complex·n water} \quad (n = 0, 1)$$

complex		r (Na-Cl)	relative change	E_{bind}	relative change
INC	Gas	2.454	--	-150.83	--
	PCM	2.658	8.3%	-2.28	-98.5%
INCw1	PCM	2.694	9.8%	-9.18	-93.9%
INCw2	PCM	2.772	13.0%	-5.48	-96.4%
INCw3	PCM	2.748	12.0%	-12.21	-91.9%
INCw4	PCM	2.753	12.2%	-5.61	-96.3%
INCw5	PCM	2.764	12.6%	-8.66	-94.3%

Results and Discussion

Solvent effect on the structure of indole-cation-anion complexes. As in all cation-π-anion complexes studied previously,[11,31] in the systems examined in the present investigation the anion and the cation are in the same side of the indole molecule (see their structures in Figures 1 and 2). This geometrical distribution is consequence of the cation-anion electrostatic attraction, which is the strongest interaction between the fragments of the ternary cation-π-anion complexes. This interaction is the most affected when the solute is surrounded by a medium with high dielectric constant and therefore the cation-anion separation can be used as geometrical indicator of the solvent effect on the structure of the cation-π-anion complexes.



IAC, IACw1, IACw2, IACw3

IACw4, IACw5, IACw6

IAN, IANw1, IANw2, IANw3

IAF, IAFw1, IAFw2, IAFw3

Figure 2. Structures of the indole-ammonium-anion complexes included in the present study. The solvent was modelled using a combination of PCM=water and the addition of one H_2O molecule. All the structures were optimized at the M06-2G/6-31+G* level of calculation with PCM=water and are minima in their respective PES.

Table 1 shows the cation-anion distance in the indole-sodium-chloride complex and its monohydrates. When the INC complex is in water (PCM) the expected increase in the cation-anion distance is observed. The addition of one H_2O molecule to the structure leads to five new structures in which water molecule occupies different positions and establishes interactions with the cation ($O \cdots Na^+$) that in some cases are accompanied by water-indole interactions ($O\text{-}H \cdots \pi$), in others by water-chloride interactions ($O\text{-}H \cdots Cl^-$) and in some hydrates the H_2O molecule interacts directly with the other three fragments of the complex. Despite the diversity of situations those specific interactions established by the explicit water molecule modify the cation-anion separation less than the non-specific effect of the water represented by the continuous, which capture the main part of the solvent effect on this parameter. Nevertheless, the ions that are part of the INC complex are monatomic and is convenient to extend the study to more complex ternary complexes. Indole-cation-anion complexes that include polyatomic ions, best related to the structure of the proteins that we try to model, are analyzed below.

In the configuration showed by the complexes studied, with both ions facing each other directly, the ammonium cation shows a particular behavior when paired with basic anions. In complexes with formate as well as with nitrate the N-H bond of NH_4^+, pointing towards the anion is stretched about 45% to 63% (in gas phase) with respect to the values observed in the isolated cation, indicating that a proton transfer is taking place. In complexes with chloride anion the mentioned N-H bond of NH_4^+ is stretched too, but to a smaller extent: 12% in IAC. The ammonium-basic anion proton transfer is also observed when the complexes are in water and the elongation of the N-H bond is modified because of the influence of the medium. In the indole-ammonium-anion complexes, this bond length constitutes an indication of the solvent effect on the structure, which has showed to be better than the cation-anion separation.

Table 2 shows the values of r (N-H), the length of the ammonium's N-H bond directed to the anion in the studied complexes and its relative change, calculated using as reference the length of this bond computed in the gas phase optimization of the non-hydrated (IAX) complexes. It can be observed that when the complexes are in water (PCM) this bond is shortened, reducing the proton (and therefore the charge) transfer. This is the expected result because a solvent with a high dielectric constant favor the charge separation and the complexes are stable even conserving the cation and anion charges without big changes. The effect is not large (a reduction of 5.9% in the N-H length) when the anion is formate (the strongest base) but the shortening is 8.2% when the anion is chloride and 28.7% when the anion is nitrate, even when both are very weak bases. This reveals the importance of specific interactions in the systems analyzed and a continuous method, like PCM, is not able of model them. The addition of one H_2O molecule to the complexes is the first step in the exploration of how important are these specific interactions compared with the solvent effect already expressed by the implicit method.

Table 2. Influence of the solvent on the geometry and binding energy of indole-ammonium-anion complexes. The structures were optimized at the M06-2X/6-31+G* level of calculation in gas phase or PCM=water, as indicated in the second column, and are minima in their respective PES. The complexes with a “w” in its label contain one water molecule. r (N-H) is the length, in Å, of the ammonium’s N-H bond directed to the anion. E_{bind} is the binding energy, in kcal/mol, for:

Indole + (ammonium·n water) + anion → complex·n water (n = 0, 1)

complex		r (N-H)	relative change	E_{bind}	relative change
IAC	Gas	1.149	--	-143.78	--
	PCM	1.055	-8.2%	-15.54	-89.2%
IACw1	PCM	1.046	-9.0%	-16.64	-88.4%
IACw2	PCM	1.037	-9.7%	-15.39	-89.3%
IACw3	PCM	1.045	-9.1%	-14.35	-90.0%
IACw4	PCM	1.040	-9.5%	-16.62	-88.4%
IACw5	PCM	1.042	-9.3%	-15.23	-89.4%
IACw6	PCM	1.038	-9.7%	-16.84	-88.3%
IAN	Gas	1.479	--	-139.42	--
	PCM	1.054	-28.7%	-16.93	-87.9%
IANw1	PCM	1.047	-29.2%	-18.61	-86.7%
IANw2	PCM	1.046	-29.3%	-17.69	-87.3%
IANw3	PCM	1.048	-29.1%	-17.44	-87.5%
IAF	Gas	1.664	--	-161.07	--
	PCM	1.547	-5.9%	-16.10	-90.0%
IAFw1	PCM	1.450	-11.8%	-20.94	-87.0%
IAFw2	PCM	1.052	-36.0%	-23.59	-85.4%
IAFw3	PCM	1.442	-12.3%	-18.38	-88.6%

The structures of the hydrated indole-ammonium-anion complexes optimized with PCM (IAXw#) are showed in Fig. 2. With a monoatomic anion (chloride) there is a major number of possible orientations and six monohydrated IACw were found. On the other hand, the trigonal structure of the anions $HCOO^-$ and NO_3^- limits the number of possible orientations and three isomers were found for the monohydrates with each one of these anions. A wide variety of mutual orientations between the fragments is observed and in all of the hydrates the length of the ammonium’s N-H bond directed to the anion is reduced additionally, in comparison with the values observed in the complexes without H_2O. The effect of the water molecule on the parameter r (N-H) is proportionally very small in the IAC and IAN systems: about 1% of additional shortening is observed comparing with the effect obtained modeling the solvent only with PCM. In these cases it can be concluded that the solvent effect on the structure of the studied complexes is well represented by the continuous solvation method, even at a quantitative level. In the monohydrates of the IAF set the effect of the additional water molecule is bigger and irregular. The IAFw2 complex clearly not follows the previous rule, and this result seems to suggest that when a basic anion is included, the explicit hydration approach is important in the study of the solvent effect on the structural properties of cation-π-anion complexes.

Solvent effect on the binding energy of indole-cation-anion complexes. The effect of the aqueous solvent in the binding energy of cation-π-anion complexes is drastic, as observed in Tables 1 and 2. When the complexes are in water (PCM) E_{bind} is reduced to the 10% or less of the values calculated in gas phase. Nevertheless, these results show that the main effect on the binding energy is caused by the continuum and the addition of a water molecule accounts for, proportionally, minor variations in E_{bind}. The solvent effect on the binding energy is less specific than on the geometric parameter analyzed in the previous section, and the explicit addition of one H_2O molecule change E_{bind} in a further 1% - 3% for the studied complexes.

Some cases deviate from this general rule, for example, in the INC set the greatest contribution of the water molecule to the change in E_{bind} is observed in the complex INCw3, in which the H_2O establishes simultaneously $O\cdots Na^+$; $O\text{-}H\cdots\pi$ and $O\text{-}H\cdots Cl^-$ interactions. In the IAX complexes it is observed again that the system IAFw2, in which the water molecule behaves simultaneously as proton acceptor (from ammonium) and donor (to formate), is out of the tendency shown by the other complexes that include polyatomic ions. These results indicate that the PCM method properly reproduces the main trends showed by E_{bind}, even at quantitative level, though the explicit hydration could allow detecting cases that do not follow the general behavior. A detailed microhydration + PCM study is out of the scope of this work, but seems to be the best combination in order to improve our understanding of the cation-π-anion interactions in aqueous solution, mainly when a basic anion in involved.

Conclusions

The solvent effect on the properties of indole-cation-anion complexes has been studied theoretically at the M06-2X/6-31+G* level of calculation. The presence of a polar solvent modelled by a continuous method (PCM) drastically weakens the interaction in the ternary complexes and modifies the cation-anion separation as well as the extension of the proton transfer from the ammonium cation to basic anions. Specific solvent effects tested by including one explicit water molecule into the model lead to a similar global picture, though it allows identifying cases that may be out of the general rule obtained with the continuum model alone. The combination of PCM with the addition of one H_2O molecule is recommended mainly when the cation-π-anion complex includes an acidic cation (like ammonium) combined with a very basic anion (like formate).

References

1. L. M. Salonen, M. Ellermann and F. Diederich, *Angew. Chem. Int. Ed.*, 2011, **50**, 4808-4842.
2. D. A. Dougherty, *Acc. Chem. Res.*, 2012, **46**, 885-893.
3. A. S. Mahadevi and G. N. Sastry, *Chem. Rev.*, 2012, **113**, 2100-2138.
4. T. J. Shepodd, M. A. Petti and D. A. Dougherty, *J. Am. Chem. Soc.*, 1988, **110**, 1983-1985.
5. M. Albertí, A. Aguilar, J. M. Lucas and F. Pirani, *J. Phys. Chem. A*, 2010, **114**, 11964-11970.
6. J. A. Carrazana-García, J. Rodríguez-Otero and E. M. Cabaleiro-Lago, *J. Phys. Chem. B*, 2011, **115**, 2774-2782.
7. D. Vijay and G. N. Sastry, *Chem. Phys. Lett.*, 2010, **485**, 235-242.
8. I. Alkorta, F. Blanco, P. Deyà, J. Elguero, C. Estarellas, A. Frontera and D. Quiñonero, *Theor. Chem. Acc.*, 2010, **126**, 1-14.
9. A. Ebrahimi, S. M. Habibi Khorassani, R. Behazin, S. Rezazadeh, A. Azizi and P. Karimi, *Mol. Phys.*, 2013, **112**, 41-48.
10. D. Kim, E. C. Lee, K. S. Kim and P. Tarakeshwar, *J. Phys. Chem. A*, 2007, **111**, 7980-7986.
11. J. A. Carrazana-Garcia, J. Rodriguez-Otero and E. M. Cabaleiro-Lago, *J. Phys. Chem. B*, 2012, **116**, 5860-5871.
12. E. M. Cabaleiro-Lago, J. Rodriguez-Otero and A. Pena-Gallego, *J. Chem. Phys.*, 2011, **135**, 134310/134311-134310/134318.
13. T. v. Mourik, S. L. Price and D. C. Clary, *Chem. Phys. Lett.*, 2000, **331**, 253-261.
14. K. N. Skala, K. G. Perkins, A. Ali, R. Kutlik, A. M. Summitt, S. Swamy-Mruthinti, F. A. Khan and M. Fujita, *Tetrahedron Lett.*, 2010, **51**, 6516-6520.
15. J. P. Gallivan and D. A. Dougherty, *Proceedings of the National Academy of Sciences*, 1999, **96**, 9459-9464.
16. A. S. Reddy, H. Zipse and G. N. Sastry, *J. Phys. Chem. B*, 2007, **111**, 11546-11553.
17. N. J. Singh, S. K. Min, D. Y. Kim and K. S. Kim, *J. Chem. Theory Comput.*, 2009, **5**, 515-529.
18. H. M. Lee, P. Tarakeshwar, J. Park, M. R. Kołaski, Y. J. Yoon, H.-B. Yi, W. Y. Kim and K. S. Kim, *J. Phys. Chem. A*, 2004, **108**, 2949-2958.
19. E. M. Cabaleiro-Lago, J. Rodríguez-Otero and Á. Peña-Gallego, *J. Chem. Phys.*, 2011, **135**, 214301-214309.
20. A. Campo-Cacharron, E. M. Cabaleiro-Lago and J. Rodriguez-Otero, *ChemPhysChem*, 2012, **13**, 570-577.
21. A. Campo-Cacharrón, E. M. Cabaleiro-Lago and J. Rodríguez-Otero, *Theor. Chem. Acc.*, 2012, **131**, 1290-1213.
22. A. Rodríguez-Sanz, E. Cabaleiro-Lago and J. Rodríguez-Otero, *J. Mol. Model.*, 2014, **20**, 1-10.
23. A. A. Rodríguez-Sanz, E. M. Cabaleiro-Lago and J. Rodríguez-Otero, *Org. Biomol. Chem.*, 2014, 2938-2949.
24. A. A. Rodriguez-Sanz, J. Carrazana-Garcia, E. M. Cabaleiro-Lago and J. Rodriguez-Otero, *J. Mol. Model.*, 2013, **19**, 1985-1994.
25. J. S. Rao, H. Zipse and G. N. Sastry, *J. Phys. Chem. B*, 2009, **113**, 7225-7236.
26. J. Tomasi and M. Persico, *Chem. Rev.*, 1994, **94**, 2027-2094.
27. C. J. Cramer and D. G. Truhlar, *Chem. Rev.*, 1999, **99**, 2161-2200.
28. J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999-3094.
29. C. Adamo, G. Berthier and R. Savinelli, *Theor. Chem. Acc.*, 2004, **111**, 176-181.
30. S. Thicoipe, P. Carbonniere and C. Pouchan, *Phys. Chem. Chem. Phys.*, 2013, **15**, 11646-11652.
31. J. A. Carrazana-Garcia, E. M. Cabaleiro-Lago, A. Campo-Cacharron and J. Rodriguez-Otero, *Organic & Biomolecular Chemistry*, 2014. DOI: 10.1039/C4OB01879F.
32. S. F. Boys and F. Bernardi, *Mol. Phys.*, 1970, **18**, 553.
33. G. Chałasiński and M. M. Szczęśniak, *Chem. Rev.*, 2000, **100**, 4227-4252.
34. Y. Masuda, Y. Mori and K. Sakurai, *J. Phys. Chem. A*, 2013, **117**, 10576-10587.
35. S. Grimme and M. Steinmetz, *Phys. Chem. Chem. Phys.*, 2013, **15**, 16031-16042.
36. A. Zawada, R. W. Góra, M. M. Mikołajczyk and W. Bartkowiak, *J. Phys. Chem. A*, 2012, **116**, 4409-4416.
37. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09*, 2009.