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Aliphatic-aromatic stacking interactions in cyclohexane–benzene are stronger than aromatic-aromatic interaction in benzene dimer

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Stacking interactions between cyclohexane and benzene were studied in crystal structures from the Cambridge Structural Database and by *ab initio* calculations. Calculated at the very accurate CCSD(T)/CBS level of theory, the cyclohexane-benzene interaction energy is –3.27 kcal/mol, which is significantly stronger than the interaction in the benzene dimer (–2.84 kcal/mol) indicating the importance of aliphatic-aromatic interactions.

Noncovalent interactions of aromatic molecules and other π–systems, including π–stacking[1–4] and CH/π interactions,[5–7] are recognized as very important in various molecular systems, from biomolecules to molecular crystals. Interactions between aromatic molecules were extensively studied on benzene dimer.[4] The energy of the stacking benzene-benzene interaction is -2.73 kcal/mol, while the most stable geometry is the tilted T-shape, with the interaction energy of -2.84 kcal/mol.[4a]

Although stacking interactions involving aromatic molecules have been extensively studied, the importance of these interactions at large horizontal displacements have only been reported recently.[8] Specifically, statistical analysis of the data from the Cambridge Structural Database (CSD) showed that in crystal structures the preferred stacking (parallel) benzene–benzene interactions are at large horizontal displacements (3.5 – 5.0 Å), and not at 1.5 Å, where the energy minimum is. By *ab initio* calculations on the parallel benzene dimer, substantial interaction energies of around –2.0 kcal/mol were obtained for large offsets of 3.5 – 5.0 Å.[8a] A more recent study[9] has confirmed our results on interactions at large horizontal displacements.

Stacking interactions are usually thought of as occurring between organic aromatic molecules or fragments; however, other molecules and fragments can also be involved in stacking interactions.[2,10-15] Moreover, recent results show that these alternative stacking arrangements can sometimes be stronger than stacking between benzene molecules.[10-18] For example, stacking interactions of chelate rings and stacking interactions of hydrogen bridged rings are stronger than stacking in the benzene dimer.[10f,16,17]

Considering stacking interactions between aliphatic and aromatic molecules, it is interesting that interaction between benzene and cyclohexane (–3.01 kcal/mol)[18] is somewhat stronger than interactions in stacking benzene dimer (–2.73 kcal/mol),[4a] or cyclohexane dimer (–2.62 kcal/mol).[19]

To study further aliphatic–aromatic interactions, herein we present the detailed results on the stacking interactions of cyclohexane–benzene dimers including interactions at large horizontal displacement. To the best of our knowledge this is the first study that includes both statistical analysis of crystallographic data from Cambridge Structural Database (CSD) and calculations on the potential energy surface of cyclohexane–benzene stacking interactions. In these interactions mean planes of phenyl and cyclohexyl are parallel with possibilities for CH/π interactions between two moieties (Fig. 1).
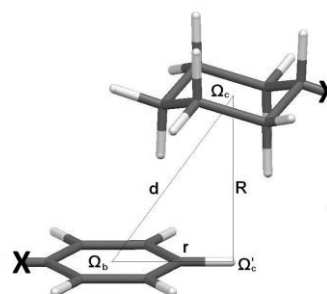

Fig. 1. Geometrical parameters used for describing the interactions between cyclohexyl and phenyl fragments with mutual parallel orientation. X can be any atom. Parameter **d** is the intermolecular distance between the centroids of phenyl and cyclohexyl rings. The normal distance between the average planes of the interacting rings is **R**. The distance between the center of phenyl ring (Ω_b) and the projection of the center of the cyclohexyl ring onto the plane of the phenyl ring (Ω'_c) is the horizontal displacement (offset) **r**.

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† Electronic Supplementary Information (ESI) available.

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Statistical analyses were done on structures obtained from the CSD (version 5.34 update May 2013).[20] A CSD search was performed using the ConQuest 1.15 program[21] to extract all structures containing phenyl and cyclohexyl fragments with parallel orientation between average planes of the fragments (those with inter–plane angle less than 10°). Center–center distance was screened to be less than 7.0 Å, and the normal distance between the average planes of the fragment were less than 5.0 Å. The structures also satisfied the following criteria: a) a crystallographic R factor below 10%, b) error–free coordinates, c) normalized H–atom positions, and d) no polymer structures. The geometrical parameters used for CSD search and analysis of the interactions between cyclohexyl and phenyl fragments, are presented in Fig. 1.
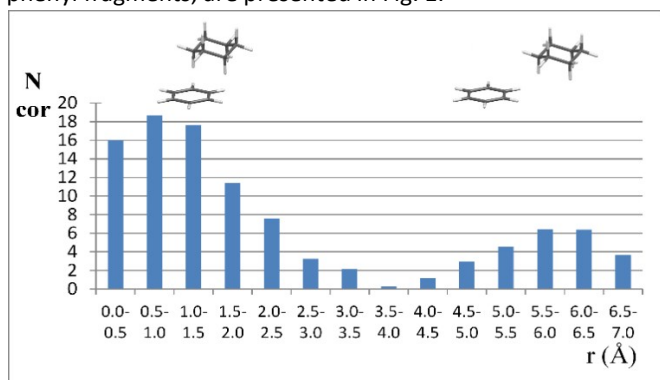

Fig. 2 The corrected distribution of the offset values r for cyclohexyl–phenyl interactions. N is number of the cyclohexyl–phenyl interactions.

We have applied an area correction[22] (ESI, I) on the distribution of the offset values r for cyclohexyl–phenyl stacking interactions, since the area covered by an interval r_1–r_2 is smaller for smaller r values. The non–corrected distribution of the offset values r for cyclohexyl–phenyl interactions is shown in Fig. S1 (ESI). The area corrected distribution of the offset values shows two maxima; the first is at the offset value of 0.5 – 1.5 Å and the second is at 5.0 – 6.5 Å (Fig. 2). The first maximum corresponds to geometries where the cyclohexyl ring overlaps the phenyl ring, forming one or two CH/π interactions (Fig. 3). The second of the maxima, smaller than the first, corresponds to geometries without any overlap of the rings, where only hydrogen atoms of two fragments are in proximity. The maxima in area-corrected histogram indicate that interactions at offsets near 1.5 Å are significantly more frequent than those at offset near 6.0 Å. More frequent interactions in the corrected distribution means that these interactions are stronger. That said, the second maximum indicates that the interaction energy at large offset is not negligible.

All energy calculations have been done in the Gaussian09 (version D.01) program.[23] The geometries of isolated cyclohexane and benzene molecules were optimized using B2PLYP–D2[24] method and def2–TZVP basis set.[25] The optimized geometries of cyclohexane and benzene molecules (ESI, II) were used to calculate the interaction energies for different parallel orientations of cyclohexane–benzene system. The MP2[26] method, with the def2–TZVP basis set, was used to
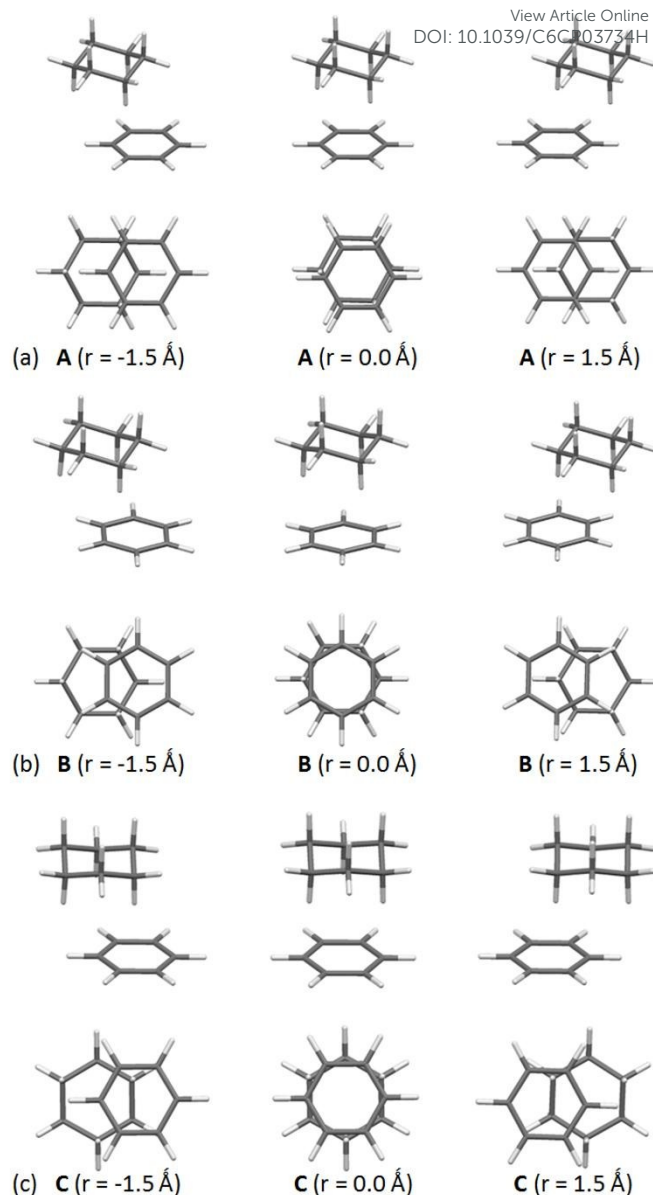
Fig. 3 Two views of the three cyclohexane–benzene orientations, (a) **A**, (b) **B** and (c) **C**, used for calculations. Geometries with offset values r of –1.5 Å, 0.0 Å and +1.5 Å are presented.

calculate potential surface. The MP2/def2–TZVP method, with correction for basis–set superposition error, gives results that are in good agreement with the accurate CCSD(T) data.[27] Namely, calculated energies for cyclohexane–benzene interactions at CCSD(T)/CBS[28] level for offset values r 0.0, 1.5, and 4.0 Å, are –3.05, –3.27 and –1.19 kcal/mol respectively, while MP2/def2–TZVP energies for the same geometries are –3.17, –3.34 and –1.19 kcal/mol, respectively (ESI, III, Table S1).

The interaction energies as a function of the horizontal displacements (*offsets r*) were examined for three different parallel orientations, **A**, **B** and **C** (Fig. 3) by varying the normal distance (*R*) between two molecules in a series of single point calculations for a cyclohexane–benzene system, while the geometries of the monomers were kept rigid.

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The calculated interaction energies at different horizontal displacements *(r)* for the cyclohexane–benzene dimer are presented in Fig. 4 and Table 1. The corresponding normal distances (R) at different horizontal displacements *(r)* are presented in Fig. S2 (ESI, IV).
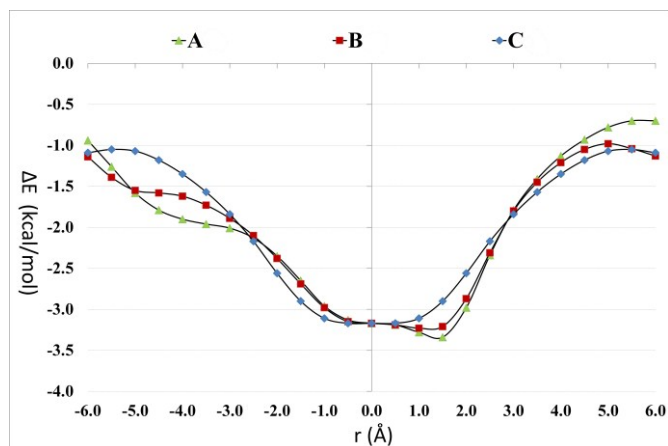

Fig. 4 Calculated interaction energies (ΔE), at MP2/def2–TZVP level, for three different orientations of cyclohexane–benzene dimer plotted as a function of the offset value r. The interactions energies for each offset value r were calculated by varying the normal distance (*R*) between two molecules in a series of single point calculations. The strongest calculated energy for each offset value is presented. The A, B, and C orientations are presented in Fig. 3.

Table 1. The calculated MP2/def2–TZVP interaction energies at different offset values *(r)* for cyclohexane–benzene dimer (Fig. 3)

orientation	r = -5.0 Å ΔE[a]	r = -4.0 Å ΔE[a]	r = -1.5 Å ΔE[a]	r = 0.0 Å ΔE[a]	r = 1.5 Å ΔE[a]	r = 4.0 Å ΔE[a]	r = 5.0 Å ΔE[a]
A	−1.58	−1.90	−2.65	−3.17	−3.34	−1.13	−0.78
B	−1.55	−1.62	−2.69	−3.17	−3.21	−1.21	−0.98
C	−1.07	−1.35	−2.90	−3.17	−2.90	−1.35	−1.07

[a] Interaction energies in kcal/mol

The interactions energies at offset r = 0.0 Å have coincidentally the same value for all three orientations (Table 1, Fig. 4, Table S2), although the geometry at r = 0.0 Å for orientation **A** is different than geometry for orientations **B** and **C** (Fig. 3).

The interaction energy curves for negative and positive offsets for orientations **A** and **B** (Fig. 4) are asymmetric, because of differences in the interaction of hydrogen atoms for positive and negative offsets (Fig. 3), while that for orientation **C** is symmetric due to symmetry of the geometries (Fig. 3).

The minima on the potential curves for **A** and **B** orientations occur at offset values, 1.5 and 1.0 Å, with similar interaction energies (Table 1). The geometries of **A** and **B** at minima are also similar; in both an axial hydrogen atom of cyclohexane is above the center of the benzene ring, forming CH/π interaction, while the two others are between benzene's hydrogen atoms in **A**, and above benzene's C-H bonds in **B** (Fig. 3a and 3b). The minimum on the potential curve for

orientation **C** is at offset 0.0 Å (Table 1). In the minimum geometry for orientation **C**, all three axial hydrogen atoms of cyclohexane are oriented above the C-C bond mid-points of the benzene, which could be considered as weak CH/π interactions. The offset motion for this orientation does not bring a cyclohexane hydrogen to the center of the benzene ring (Fig. 3c).

The most stable interaction energy of -3.27 kcal/mol (at CCSD(T)/CBS level), at the minima of potential curve A, is not very different to previously reported cyclohexane-benzene interaction of -3.01 kcal/mol[19] at CCSD(T)/aug-CC-PVTZ level.

To compare calculated cyclohexane-benzene stacking interaction energies at minima with energies of cyclohexane-benzene CH/π interactions, we calculated CH/π interactions of axial and equatorial cyclohexane H atoms with benzene (ESI, V). The geometry with the most stable CH/π interaction of an axial H atoms (the distance between the center and the H is 2.6 Å, and C-H…center of ring angle of 90° Fig. S3a, ESI) is very similar to the minimum at potential curve for A orientation and has the interaction energy of -3.26 kcal/mol. On the other hand, calculated the most stable CH/π interaction with one equatorial H atom (the distance between the center and the H is 2.5 Å, and C-H…center of ring angle of 90° Fig. S3b, ESI)); has energy of -2.55 kcal/mol. This geometry can be considered as T-shaped cyclohexane-benzene geometry with one CH/π interaction. We also calculated optimized tilted T-shape geometry (Fig. S3c, ESI); the interaction energy is -3.11 kcal/mol. The calculated energies shows that stacking interaction (-3.34 kcal/mol) is stronger than T-shaped cyclohexane-benzene interactions (-2.55 kcal/mol and -3.11 kcal/mol). The stronger stacking interaction is a consequence of three cyclohexane axial hydrogen atoms interacting with negative potential of benzene (Fig. 3).

At large offset values, both positive and negative (above 3.0 Å), the calculated interaction energies are quite weak (Table 1) and without CH/π interactions. At positive offset values larger than 5.0 Å some stabilization is achieved by interaction of equatorial hydrogen of cyclohexane and π-electrons of benzene in orientations **B** and **C**. For negative offset values orientations of both axial and equatorial hydrogens of cyclohexane in orientations **A** and **B** do not form favourable interactions, while curve for orientation **C** is symmetrical, as was mentioned above.

The calculated potential curves are in agreement with the data observed in crystal structures (Fig. 2). The large maximum at shorter offset values corresponds to the strongest calculated interactions; the minima on potential curves are calculated at offset values 0.0 – 1.5 Å (Fig. 4, Table 1). In agreement with the higher stability calculated for offsets greater than 0.5 Å for orientations **A** and **B**, the experimental frequency distribution is skewed in this direction (Fig. 2).

It is very interesting that the calculated interaction between cyclohexane and benzene of −3.27 kcal/mol, (at CCSD(T) level), is significantly stronger than stacking interaction in benzene dimer (−2.73 kcal/mol), stronger than the most stable, tilted T-shape, benzene dimer (-2.84 kcal/mol, calculated also at CCSD(T)/CBS level),[4a] and stronger than

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interaction in cyclohexane dimer, -2.62 kcal/mol, (at CCSD(T)/CBS). [19]

The strong interaction between cyclohexane and benzene can be explained by electrostatic potential maps (ESI, VI). The strong interaction is a consequence of simultaneous interactions of positive potentials of three cyclohexane hydrogens with benzene negative potential. One of these interactions is close to optimal CH-π interaction, while the other two positive hydrogens interact with the edge of the benzene negative potential (Fig. S4, ESI). As was shown above, optimal CH-π interaction between cyclohexane and benzene is quite strong, -2.55 kcal/mol, hence it is not surprising that interaction between benzene and cyclohexane is stronger than stacking between two benzene molecules. Since two molecules are in close contact one has also recognize significance of dispersion component in the cyclohexane-benzene interaction.

In conclusion, our analysis of the crystal-structure data and corresponding calculations of the interaction energies indicate that aliphatic-aromatic interactions can be stronger than aromatic-aromatic interactions. Such strong and often overlooked interactions can be particularly important in all molecular systems with aromatic and aliphatic groups, such as co-polymers, proteins, and engineered crystals.

Notes and references

1   a) K. N. M. Daeffler, H. A. Lester and D. A. Dougherty, *J. Am. Chem. Soc.*, 2012, **134**, 14890–14896; b) N. B. Shustova, T. C. Ong, A. F. Cozzolino, V. K. Michaelis, R. G. Griffin and M. Dincǎ, *J. Am. Chem. Soc.*, 2012, **134**, 15061–15070; c) H–J. Schneider, *Angew. Chem. Int. Ed.* 2009, **48**, 3924–3977; d) C. Janiak, *J. Chem. Soc., Dalton Trans.*, 2000, 3885 –3896.

2   a) J. W. G. Bloom and S. E. Wheeler, *Angew.Chem. Int. Ed.* 2011, **50**, 7847 H. J. Schneider, *Angew. Chem. Int. Ed.* 2009, 487849; b) S. Grimme, *Angew. Chem. Int. Ed.* 2008, **47**, 3430 –3434.

3   a) S. E. Wheeler, *J. Am. Chem. Soc.* 2011, **133**, 10262 –10274; b) S. E. Wheeler and K. N. Houk, *J. Chem. Theory Comput.* 2009, **5**, 2301–2312; c) L. M. Salonen, M. Ellermann and F. Diederich, *Angew. Chem. Int. Ed.* 2011, **50**, 4808–4842; d) M. Watt, L. K. E. Hardebeck, C. C. Kirkpatrick and M. Lewis, *J. Am. Chem. Soc.* 2011, **133**, 3854–3862; e) H. Cybulski and J. Sadlej, *J. Chem. Theory Comput.*, 2008, **4**, 892–897; f) A. I. Anzellotti, C. A. Bayse and N. P. Farrell, *Inorg. Chem.* 2008, **47**, 10425–10431; g) J. Šponer, K. E. Riley and P. Hobza, *Phys. Chem. Chem. Phys.*, 2008, **10**, 2595–2610; h) J. Moellmann and S. Grimme, *Phys. Chem. Chem. Phys.*, 2010, **12**, 8500–8504.

4   a) E. C. Lee, D. Kim, P. Jurecka, P. Tarakeshwar, P. Hobza and K. S. Kim, *J. Phys. Chem. A*, 2007, **111**, 3446–3457; b) M. Pitonak, P. Neogrady, J. Rezac, P. Jurecka, M. Urban and P. Hobza, *J. Chem. Theory Comput.* 2008, **4**, 1829–1834; c) O. Bludský, M. Rubeš, P. Soldán and P. Nachtigall, *J. Chem. Phys.* 2008, **128**, 114102/1–14102/8; d) T. Janowski and P. Pulay, *Chem. Phys. Lett.* 2007, **447**, 27–32; e) H. F. Bettinger, T. Kar and E. Sanchez–Garcia, *J. Phys. Chem. A*, 2009, **113**, 3353–3359.

5   a) M. Nishio, Y. Umezawa, K. Honda, S. Tsuboyama and H. Suezawa, *CrystEngComm*, 2009, **11**, 1757–1788; b) M. Nishio, *Phys. Chem. Chem. Phys.* 2011, **13**,13873–13900; c) M. Nishio, Y. Umezawa, J. Fantini, M. S. Weiss and P.

Chakrabarti, *Phys. Chem. Chem. Phys.* 2014, **16**, 12648–12683.

6   C. I. Yeo, S. N. A. Halim, S. W. Ng, S. L. Tan, J. Zukerman-Schpector, M. A. B. Ferreira and E. R. T. Tiekink, *Chem. Commun.*, 2014, **50**, 5984.

7   a) V. B. Medaković, M. K. Milčić, G. A. Bogdanović and S. D. Zarić, *J. Inorg. Biochem.* 2004, **98**, 1867–1873; b) V. B. Medaković, G. A. Bogdanović, M. K. Milčić, G. V. Janjić and S. D. Zarić, *J. Inorg. Biochem.* 2012, **117**, 157–163.

8   a) D. B. Ninković, G. V. Janjić, D. Ž. Veljković, D. N. Sredojević and S. D. Zarić, *ChemPhysChem*, 2011, **12**, 1–4; b) D. B. Ninković, J. M. Andrić and S. D. Zarić, *ChemPhysChem*, 2013, **14**, 237–243; c) D. B. Ninković, J. M. Andrić, S. N. Malkov and S. D. Zarić, *Phys. Chem. Chem. Phys.*, 2014, **16**, 11173–11177.

9   R. Kruszynski and T. Sierański, *Cryst. Growth Des .,* 2016, 16, 587-595.

10 a) E. R. T. Tiekink, *Chem. Commun.*, 2014, **50**, 11079‑11082; b) T. S. Basu, Baul, S. Kundu, S. Mitra, H. Höpfl, E. R. T. Tiekink and A. Linden, *Dalton Trans.*, 2013, **42**, 1905‑1920.

11 a) D. P. Malenov, D. B. Ninković, D. N. Sredojević and S. D. Zarić, *ChemPhysChem*, 2014, **15**, 2458‑2461

12 Z. D. Tomić, V. M. Leovac, S. V. Pokorni, D. Zobel and S. D. Zarić, *Eur. J. Inorg. Chem.*, 2003, 1222‑1226; e) D. N. Sredojević, Z. D. Tomić and S. D. Zarić, *Cryst. Growth Des.*, 2010, **10**, 3901‑3908;

13 H. R. Khavasi and B. Mir Mohammad Sadegh, *Dalton Trans.*, 2015, **44**, 5488‑5502;

14 a) A. Castineiras, A. G. Sicilia–Zafra, J. M. Gonzales–Perez, D. Choquesillo–Lazarte and J. Niclos–Gutierrez, *Inorg. Chem.* 2002, **41**, 6956–6958; b) E. Craven, C. Zhang, C. Janiak, G. Rheinwald and H. Lang, *Z. Anorg. Allg. Chem.* 2003, **629**, 2282–2290; c) S. Chowdhury, M. G. B. Drew and D. Datta, *Inorg. Chem. Commun.* 2003, **6**, 1014–1016; d) K. Helios, R. Wysokinski, W. Zierkiewicz, L. M. Proniewicz and D. Michalska, *J. Phys. Chem. B* 2009, **113**, 8158–8169.

15 K. F. Konidaris, C. N. Morrison, J. G. Servetas, M. Haukka, Y. Lan, A. K. Powell, J. C. Plakatouras and G. E. Kostakis, *CrystEngComm*, 2012, **14**, 1842–1849.

16 H. H. Monfared, M. Vahedpour, M. M. Yeganeh, M. Ghorbanloo, P. Mayer and C. Janiak, *Dalton Trans.* 2011, **40**, 1286–1294

17 J. P. Blagojević and S. D. Zarić, *Chem. Commun.* 2015, **51**, 12989–1299.

18 J. Ran and M. W. Wong, *J. Phys. Chem. A* 2006, **110**, 9702–9709.

19 K. S. Kim, S. Karthikeyan and N. J. Singh, *J. Chem. Theory Comput.* 2011, **7**, 3471–3477

20 F. H. Allen, Acta Crystallogr., B *2002*, **58**, 380‑388.

21 I. J. Bruno, J. C. Cole, P. R. Edgington, M. Kessler, C. F. Macrae, P. Mc Cabe, J. Pearson and R. Taylor, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2002, **58**, 389‑397.

22 Z. Ciunik and G. R. Desiraju, *Chem. Commun.*, 2001, 703–704.

23 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. A. Montgomery, Jr., 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.

Journal Name

Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

24 a) S. Grimme, *J. Chem. Phys.*, 2006, **124**, 034108/1–034108/16. b) S. Grimme, *J. Comput. Chem.*, 2006, **27**, 1787–1799.

25 a) F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305; b) A. Schaefer, H. Horn and R. Ahlrichs, *J. Chem. Phys.*, 1992, **97**, 2571–2577.

26 a) C. Møller and M. S. Plesset, *Phys. Rev.* 1934, **46**, 618–622. b) M. Head–Gordon, J. A. Pople and M. J. Frish, *Chem. Phys. Lett.* 1988, **153**, 503–506.

27 J. A. Pople, M. Head–Gordon, K. Raghavachari, *J. Chem. Phys.* 1987, **87**, 5968–5975.

28 I. D. Mackie, G. A. DiLabio, *J. Chem. Phys.* 2011, **135**, 134318.