Interaction of adenine with synthetic receptors: a theoretical study †

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The interaction of adenine with synthetic macrocyclic receptors has been modelled using, as simplified molecular systems, the monoamide derivatives of pyridine and 1,8-naphthyridine. DFT methods (B3LYP/6-31+G**) have been used to characterise the complexes stabilised by multiple hydrogen bonds. The theoretical results indicate that while the synthetic receptors with pyridines can interact simultaneously forming pseudo-Watson–Crick and pseudo-Hoogsten complexes with adenine, in the case of the 1,8-naphthyridines only one of the complexes is possible. The energetic results that favour the pyridine receptors are in agreement with the experimental binding constants.

Introduction

A number of widely different designed receptors are possible with multiple binding modes, including macrocycles,[1] tweezers[2] and clefts.[3] Hamilton and co-workers[1] introduced a 1,2-bis(2-amino-6-pyridyl)ethane moiety into a macrocycle for adenine binding. Zimmerman *et al.*[2] reported a molecular tweezers in which a binding site is created by the convergence of two aromatic surfaces and a carboxylic acid. Conn *et al.*[3a] introduced a receptor to bind adenosine derivatives within a pocket formed through induced fit. The building block of this receptor consists of a 3,6-diaminocarbazole-based moiety functionalised with a pendant tail which can stack on top of an adenosine within the hydrogen-bonding cleft. This 'scorpion-like'[4] binding geometry provides a mechanism for sequestering the bound nucleoside from the bulk solvent. In contrast, Lonergan *et al.*[5] reported the use of a hydroximide scaffold to produce a cleft for adenine binding.

Wilcox and Adrian introduced another approach for adenine binding.[6] They used the Tröger's base spacer, which has a carboxylic acid moiety, in order to bind adenine in the Watson–Crick (WC) and Hoogsteen (H) modes simultaneously. In this paper we report the effect of a 1,8-naphthyridine system on the binding interaction with adenine. We have found that macrocycles containing 1,8-naphthyridinediamides are less effective in binding adenine compared to those with ethylene bipyridinediamides.

By using DFT methods we have studied the hydrogen-bonded complexes of adenine with amide derivatives of pyridine and 1,8-naphthyridine as model compounds of the corresponding macrocycles. The results help to account for the experimental binding constants of 9-butyladenine with several synthetic receptors. In addition, the WC and Hoogsteen configurations of the **A**–**U** dimer and two configurations of the **A**–**C** complex (Fig. 1) were calculated and compared with earlier results.

† Electronic supplementary information (ESI) available: Cartesian coordinates of all the complexes. See http://www.rsc.org/suppdata/p2/b2/b200915n/

Table 1 Binding constants of receptors **1**–**4** with 9-butyladenine[7]

Macrocycle	K_a/M^{-1}
1	73
2	3200
3	80
4	20

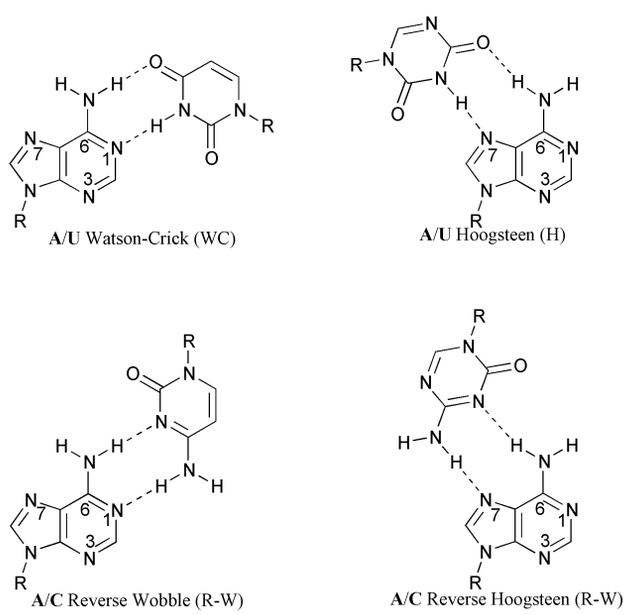

Fig. 1 Watson–Crick and Hoogsteen configurations of **A**–**U** and reverse Wobble and reverse Hoogsteen of **A**–**C**. The numbering of adenine is included.

Results and discussion

The binding affinities of 9-butyladenine towards several macrocyclic synthetic receptors (**1**–**4**, Fig. 2), which have separated pyridine[1] and naphthyridine[7] moieties, have been tested (Table 1). The results show that a system having two separated

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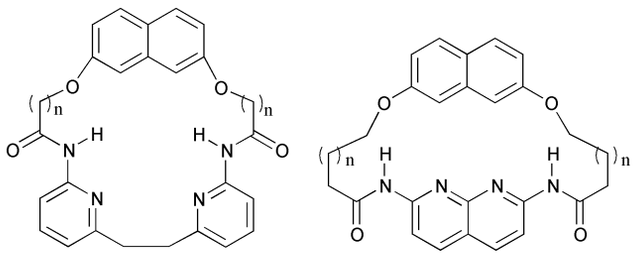


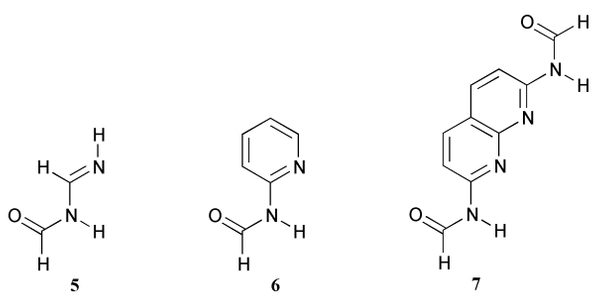
1 n = 2
2 n = 3

3 n = 1
4 n = 3

Fig. 2 Synthetic receptors whose binding constants towards adenine have been measured.

pyridine moieties, **2**, is much more efficient in the binding of adenine compared to one with two fused pyridines, *i.e.* the 1,8-naphthyridine system (macrocycles **3** and **4**). Although belonging to the first system, the macrocyclic receptor **1** is less efficient in binding 9-butyladenine, possibly because its cavity size is too small to accommodate 9-butyladenine. In the case of macrocycles having 1,8-naphthyridine moieties, receptors **3** and **4** show binding constants of the same magnitude, with that of **3** being slightly higher than that of **4**.

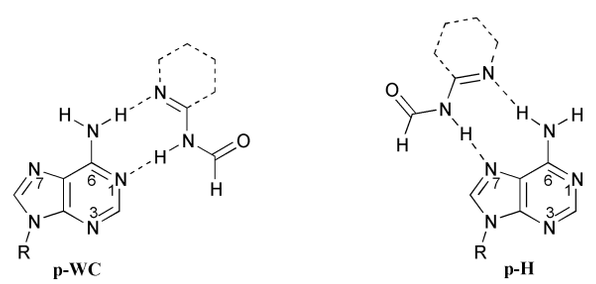
In order to rationalize the experimental results, a series of hydrogen-bonded complexes between adenine and model synthetic receptors were calculated at the B3LYP/6-31+G** level. In a first approach, a simplified model system **5** was used (Fig. 3), which contains the hydrogen bond donor and acceptor



5 **6** **7**

Fig. 3 Structure of the model compounds studied.

centres in a similar arrangement to the amide derivatives of pyridine and 1,8-naphthyridine, **6** and **7**, respectively. The geometry of the amide groups was assumed to be *trans*. The geometry obtained for the **A5** complex was used as the starting point for the **A**–**6** and **A**–**7** complexes. The two configurations studied have been defined as pseudo-WC (p-WC) and pseudo-H (p-H) by analogy with those of the dimers of natural nucleic acid bases (Fig. 4). In addition, several



p-WC **p-H**

Fig. 4 p-WC and p-H arrangements.

arrangements of the **A**–**U** and **A**–**C** complexes have been considered: the first one because it is the dimer found in nature and the second one since it better resembles the complexes studied here with two NH ··· H hydrogen bonds.

The energetic results are gathered in Table 2. The strengths of all the calculated hydrogen-bonded dimers range between −7.75 and −12.3 kcal mol^{-1}, which corresponds to an average

Table 2 Total energy (hartree), interaction and corrected interaction energy (kcal mol^{-1}) of the calculated complexes at the B3LYP/6-31+G** level

System	Configuration	E_T	E_I	$E_{I + BSSE + ZPE}$
A–**5**	p-WC	−730.73848	−12.91	−10.55
A–**5**	p-H	−730.73703	−12.00	−9.62
5–**A**–**5**	p-WC + p-H	−994.12049	−23.76	−19.44
A–**6**	p-WC	−884.38890	−10.65	−8.58
A–**6**	p-H	−884.38746	−9.75	−7.75
A–**7**	p-WC	−1222.79733	−12.45	−10.36
A–**7**	p-H	−1222.79560	−11.36	−9.26
A–**U**	WC	−882.221156	−12.94	−11.59
A–**U**	H	−882.222243	−13.62	−12.26
A–**C**	R-W	−862.33846	−13.87	−11.40
A–**C**	R-H	−862.33748	−13.26	−10.78

hydrogen bond strength of −5.0 kcal mol^{-1}. For comparative purposes, it should be mentioned that the hydrogen-bonding interaction in the water dimer accounts for its similar value (experimentally it is −5.3 kcal mol^{-1}).[8] The strongest hydrogen-bonded complexes correspond to the **A**–**U** dimer in the H configuration and the weakest are those of **A**–**6**.

Regarding the most favourable arrangement for each pair of molecules, in all cases the pseudo-WC disposition (reverse Wobble in the **A**–**C** dimer) is about 1 kcal mol^{-1} more favourable than the pseudo-H one (reverse Hoogsteen in the **A**–**C** dimer), except for the **A**–**U** dimer where the Hoogsteen complex is more stable. However, in the latter case the two hydrogen bonds correspond to one NH ··· N and one NH ··· O interaction, while the rest of the cases possess two NH ··· N contacts.

The results obtained with model compound **5** (Fig. 5) seem to be in reasonable agreement with those obtained for **6** and **7**. Thus, the trimer **5**–**A**–**5**, in which two molecules of **5** simultaneously interact with **A**, can be used as a model for the similar trimer **6**–**A**–**6**. In the former case, the stabilisation energy is approximately the sum of that for the two **A**–**5** complexes (p-WC and p-H), which indicates that for the **6**–**A**–**6** trimer the interaction energy should be around 19 kcal mol^{-1}.

From the theoretical results it can be seen that the **A**–**6** complex is less stable than the **A**–**7** complex, but the separated pyridine rings can bind adenine from both sides. In contrast, the 1,8-naphthyridine moiety is unable to bind from both sides. A comparison of the nitrogen distances in the **5**–**A**–**5** indicate that the amide nitrogens are at 8.0 Å and the aromatic ones at 5.0 Å, while in the case of the compound **7** they are at 6.9 and 2.3 Å. A model of **1** in which two pyridine moieties are linked by two methylene groups has been optimized and the results superimposed on those for **5** in the arrangement obtained for the **5**–**A**–**5** complex (Fig. 6). This superposition indicates that the **1**–**A** complex can accommodate the hydrogen bonds in a similar way to the **5**–**A**–**5** one.

Hence, the sum of two pyridine moieties shows greater binding, *i.e.* two **A**–**6** binding, than the 1,8-naphthyridine moiety, *i.e.* only one **A**–**7** binding, which also supports the experimental observations.

The hydrogen-bonding distances (Table 3) cover a very narrow range (between 1.93 and 2.08 Å) and in all cases the hydrogen-bonding angles are close to being perfectly linear. If we consider that a shorter hydrogen-bonding distance is an indication of stronger interaction, the strongest ones are those where one of the ring nitrogen atoms of **A** (N1 and N7) are involved as the hydrogen-bonding acceptor, while those from the NH_2 group of **A** as donors are the weakest. In addition, the hydrogen-bonding distances in the p-WC complexes are smaller

Table 3 Geometric parameters (Å and deg) of the hydrogen bonds formed (obtained at the B3LYP/6-31+G** level)

System	Configuration	N1 ··· H	N1 ··· HN	H(6′) ··· N	NH(6′) ··· N
A–5	p-WC	1.935	179.3	1.967	176.0
5–A–5	p-WC	1.944	179.7	2.012	178.5
A–6	p-WC	2.000	172.6	1.999	177.7
A–7	p-WC	1.972	173.3	1.997	174.4
A–U	WC	1.824	179.0	1.921[a]	173.9
A–C	R-W	1.953	179.1	1.953	175.5
		N7 ··· H	N7 ··· HN	H(6′) ··· N	NH(6′) ··· N
A–5	p-H	1.951	175.2	1.994	168.4
5–A–5	p-H	1.962	176.0	2.018	166.2
A–6	p-H	2.012	167.5	2.040	166.8
A–7	p-H	2.011	165.3	2.078	165.3
A–U	H	1.801	176.0	1.955[a]	170.5
A–C	R-H	1.981	176.2	1.980	167.6

[a] Oxygen as hydrogen bond acceptor.

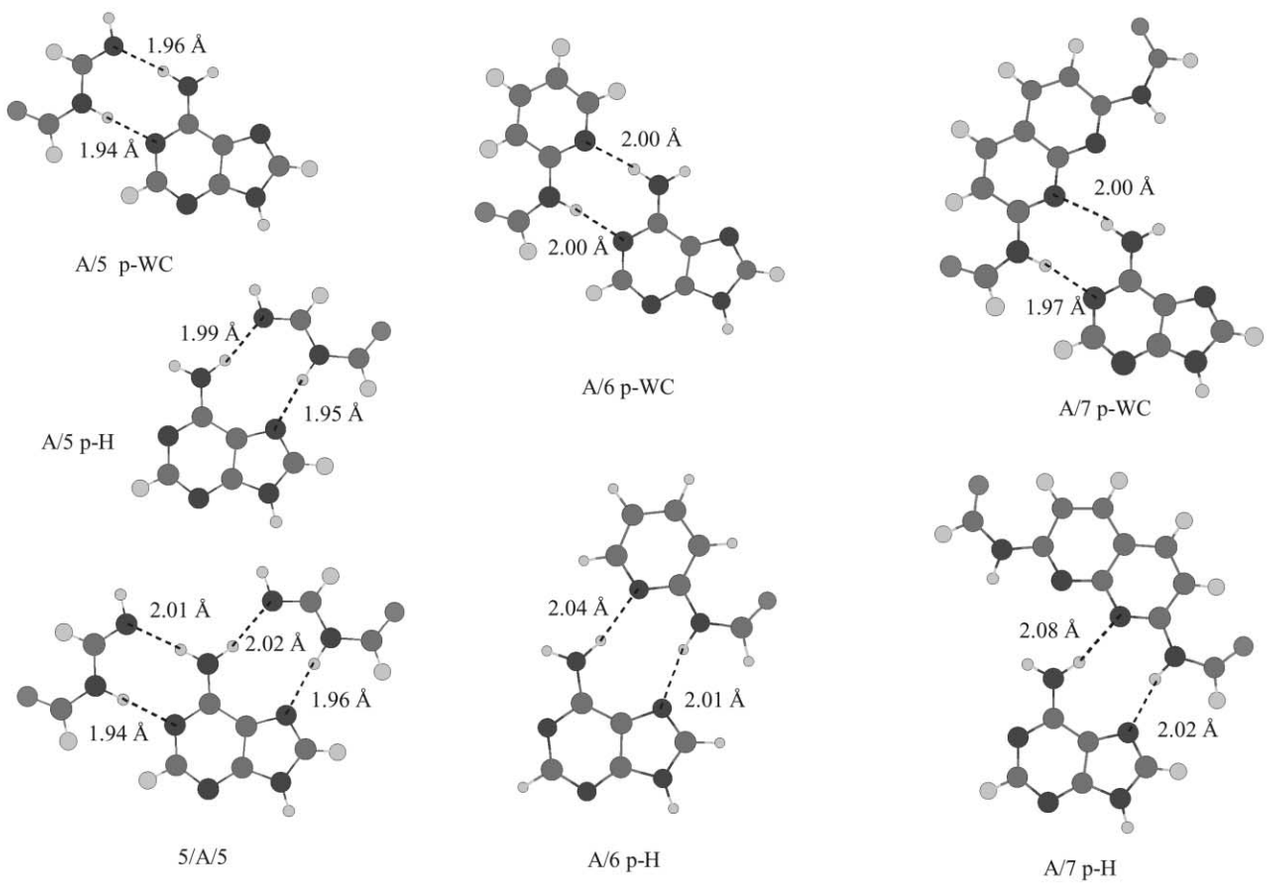


Fig. 5 Optimized geometry of the complexes studied.

than the p-H ones, except for the **A**–**U** dimer whose relative stability is opposite to those of the rest of the complexes studied here.

The "atoms in molecules" (AIM) analysis (Table 4) shows that the bond critical points in the hydrogen bonds formed have small values of the electron density and positive Laplacians, as is usual in this kind of interaction. A linear correlation is obtained between the hydrogen-bonding distance and the electron density or its Laplacian (Fig. 7). As has been shown previously, these relationships become logarithmic when the hydrogen-bonding distance considered is longer.[9–11]

Conclusions

The interaction of adenine with several synthetic receptors has been modelled using amide derivatives of pyridine and 1,8-naphthyridine. The complexes have been optimised using DFT (B3LYP/6-31+G**) computational methods. The different binding modes of pyridine and 1,8-naphthyridine with adenine have been compared to those of the latter with uracil and cytosine. The dispositions of the calculated complexes indicate that the synthetic receptors with two pyridine moieties are able to interact simultaneously with two different parts of the adenine molecule. In contrast, those receptors with a 1,8-naphthyridine moiety are able to interact at only one site. The experimental data confirm that the pyridine receptors bind adenine more tightly than the naphthyridine ones.

AIM methodology has been used to characterise the hydrogen bonds formed. Linear correlations, in the range of values

Table 4 Electron density ρ and its Laplacian $\nabla^2\rho$ (au) at the hydrogen-bonding critical points

System	Configuration	N1 ··· HN		NH(6′) ··· N	
		ρ	$\nabla^2\rho$	ρ	$\nabla^2\rho$
A–5	p-WC	0.032	0.073	0.029	0.071
5–A–5	p-WC	0.031	0.072	0.026	0.065
A–6	p-WC	0.028	0.065	0.027	0.066
A–7	p-WC	0.030	0.068	0.027	0.067
A–U	WC	0.040	0.090	0.027	0.076
A–C	R-W	0.030	0.071	0.030	0.073
		N7 ··· HN		NH(6′) ··· N	
		ρ	$\nabla^2\rho$	ρ	$\nabla^2\rho$
A–5	p-H	0.030	0.072	0.027	0.067
5–A–5	p-H	0.029	0.071	0.026	0.065
A–6	p-H	0.026	0.064	0.025	0.061
A–7	p-H	0.026	0.065	0.023	0.057
A–U	H	0.041	0.097	0.024	0.071
A–C	R-H	0.028	0.068	0.028	0.070

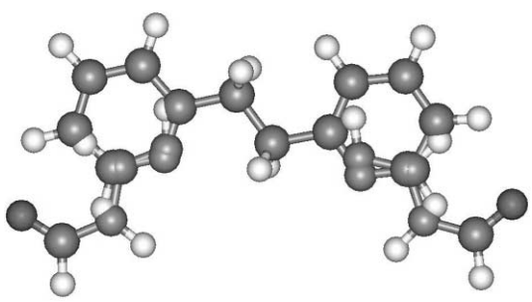


Fig. 6 Superposition of the Py–CH_2–CH_2–Py molecule on **5** as found in the arrangement of the **5**–**A**–**5** complex.

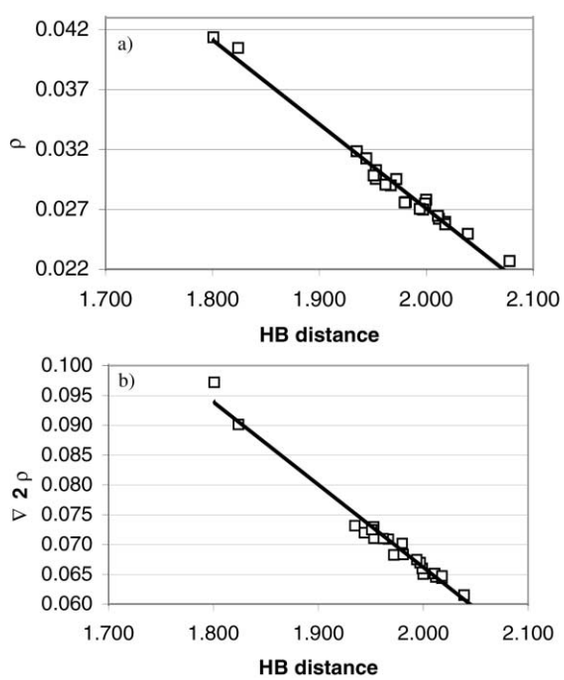


Fig. 7 a) Electron density at the bond critical point (au) *vs.* hydrogen-bonding distance (Å). The fitted equation is: ρ = 0.17 − 0.071(hydrogen-bonding distance), R^2 = 0.98. b) Laplacian of the electron density at the bond critical point (au) *vs.* hydrogen-bonding distance (Å). The fitted equation is: $\nabla^2\rho$ = 0.34 − 0.14(hydrogen-bonding distance), R^2 = 0.98.

found here, have been found between the electron density and its Laplacian for the hydrogen-bonding critical point *vs.* the hydrogen-bonding distance.

Computational details

All the calculations were carried out at the B3LYP/6-31+G** [12,13] computational level within the Gaussian 98 program package.[14] Initially, the geometry of the monomers and dimers was assumed to be planar. Frequency calculations were carried out for the optimized geometries in order to verify that they were minima. In only one complex (**A–6**, p-H), was one small imaginary frequency obtained, which did not disappear using the tight optimization option. The corresponding optimized complex without symmetry showed all real frequencies and was only 0.02 kcal mol^{-1} more stable than the one with C_s symmetry. The Cartesian coordinates of all the complexes are available as electronic supplementary information.

The interaction energy (E_I) was calculated as the difference between the total energy of the complexes and the sum of the isolated monomers. The inherent basis set superposition error (BSSE) was corrected using the full counterpoise method proposed by Boys and Bernardi.[15] In addition, corrections for zero point energy (ZPE) were also included.

$$E_I = E_{AB} - E^{A}{}_{A} - E^{B}{}_{B} \quad (1)$$

$$\mathrm{BSSE} = (E^{AB}{}_{A'} - E^{A}{}_{A'}) + (E^{AB}{}_{B'} - E^{A}{}_{B'}) \quad (2)$$

$$\mathrm{ZPE_{corr}} = \mathrm{ZPE^{AB}} - \mathrm{ZPE^{A}} - \mathrm{ZPE^{B}} \quad (3)$$

$$E_{I\,+\,\mathrm{BSSE}\,+\,\mathrm{ZPE}} = E_I + \mathrm{BSSE} + \mathrm{ZPE_{corr}} \quad (4)$$

$E^{A}{}_{A}$ represents the energy of the minimum geometry of the isolated molecule A calculated with its basis set and $E^{AB}{}_{A'}$ corresponds to the calculated energy of molecule A for its geometry in the AB complex using the basis function of the complex AB.

A study of the electron density of the complexes with the AIM methodology [16] allowed the characterisation of the hydrogen bonds formed.

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References

1 S. Goswami, A. D. Hamilton and D. Van Engen, *J. Am. Chem. Soc.*, 1989, **111**, 3425.
2 S. C. Zimmerman, W. Wu and Z. Zeng, *J. Am. Chem. Soc.*, 1991, **113**, 196.
3 (*a*) M. Morgan Conn, G. Deslongchamps, J. de Mendoza and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1993, **115**, 3548; (*b*) J. Rebek, Jr., *Science*, 1987, **235**, 1478; (*c*) J. Rebek, Jr., B. Askew, P. Ballester, C. Buhr, S. Jones, D. Nemeth and K. Williams, *J. Am. Chem. Soc.*, 1987, **109**, 5033; (*d*) B. Askew, P. Ballester, C. Buhr, K. S. Jeong, S. Jones, K. Parris, K. Williams and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1989, **111**, 1082; (*e*) K. Williams, B. Askew, P. Ballester, C. Buhr, K. S. Jeong, S. Jones and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1989, **111**, 1090.
4 First introduced by U. Olsher, F. Forlow, N. K. Dalley, J. Weiming, Z.-Y. Ye, J. M. Knobelo and R. A. Bartsch, *J. Am. Chem. Soc.*, 1991, **113**, 6570.
5 D. G. Lonergan, G. Deslongchamps and S. Tomàs, *Tetrahedron Lett.*, 1998, **39**, 7861.
6 J. C. Adrian and C. S. Wilcox, *J. Am. Chem. Soc.*, 1989, **111**, 8055.
7 S. P. Goswami and R. Mukherjee, manuscript in preparation.
8 L. A. Curtis and M. Blander, *Chem. Rev.*, 1988, **88**, 827.
9 I. Alkorta, I. Rozas and J. Elguero, *Struct. Chem.*, 1998, **9**, 243; I. Alkorta, L. Barrios, I. Rozas and J. Elguero, *THEOCHEM*, 2000, **496**, 131.

10 E. Espinosa, M. Souhassou, H. Lachekar and C. Lecomte, *Acta Crystallogr., Sect. B*, 1999, **55**, 563.
11 A. M. Pendas, A. Costales and V. Luaña, *J. Phys. Chem. B*, 1998, **102**, 6937.
12 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
13 P. A. Hariharan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213.
14 Gaussian 98, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1998.
15 S. B. Boys and F. Bernardi, *Mol. Phys.*, 1970, **19**, 553.
16 R. F. W. Bader, *Atoms in Molecules. A Quantum Theory*, Oxford University Press, New York, 1990.