The molecular structure of acyclic aralkyl compounds studied by a crystallographic database survey. Relevance of the intramolecular CH/π hydrogen bond to conformation

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A database study was carried out, by the use of the Cambridge Structural Database, to investigate the conformation of aralkyl compounds $ArCH_2XCH_2Y$ **1** and $ArCHCH_3XCH$ **2** in crystals. The structure bearing R (R: any group) and Ar in the *syn* relationship has often been found in these compounds. The proportion of crystal structures bearing R and Ar in the *syn* relationship relative to the *anti* conformation ($r_{syn/anti}$) varied from 0.55 for **1** to 3.68 for **2**. The logarithm of $r_{syn/anti}$ was plotted against the difference in Gibbs energy $\Delta G_{syn-anti}$ obtained by MO calculations of model compounds at the MP2/6-311G(d,p)//MP2/6-31G(d) level: $C_6H_5CH_2XCH_3$ and $C_6H_5CHCH_3XCH_3$. A linear correlation has been shown between $\ln r_{syn/anti}$ and $\Delta G_{syn-anti}$. The CH/π interaction is suggested to operate in controlling the R/Ar-folded crystal structure of these aralkyl compounds.

Introduction

In 1996, Taylor and coworkers[1] analyzed the crystal conformation of a series of organic compounds in the Cambridge Structural Database (CSD) to investigate the effects of packing on the molecular structure.[2] They compared the crystal-structure conformer distributions of 12 substructures with MO data from the HF/6-31G*//HF/STO-3G level calculations. Least-squares regression showed that there was a statistically significant correlation between the crystal data and calculated potential-energy differences. It follows that the influence of the so-called packing force on the molecular structure is neither strong nor systematic.

Among the substructures they examined, there are compounds with an aromatic group at a terminus of the molecule, $ArCH_2XC$ and $ArXCH_2C$ ($X = CH_2$, O, S). It seemed interesting that the Ar/C *syn* conformation was frequently found by their database search. Recently we studied, by *ab initio* calculations [MP2/6-311G(d,p)//MP2/6-31G(d)], the conformation of a series of benzylic compounds $C_6H_5CH_2XR$ ($X = O$, CH_2, CO, S, SO, SO_2).[3] The most stable conformation has been shown to bear R and Ph in the *syn* relationship, with exceptions for several *tert*-butyl analogues. The conformation of 1-phenylethyl compounds $C_6H_5CHCH_3XR$ ($X = CO$,[4] SO,[5] CHOH,[6] S and SO_2[7]) was also studied. These molecules have been shown to prefer the conformation whereby the alkyl group (R) is *syn* to C_6H_5(Ph) and *anti* to the benzylic methyl group. The computational results agreed well with those obtained by NMR studies.[8]

Here, we examined crystal structures deposited in the CSD with our own hypothesis that such a R/Ar-folded motif is encountered, generally, in organic crystals since we felt the above result to be a consequence of the CH/π interaction.[9] The CH/π interaction is the weakest extreme of non-conventional hydrogen bonds.[10] The CH/π hydrogen bond occurs between soft acids and soft bases,[11] in contrast to the ordinary hydrogen bond that is the interaction between hard acids and hard bases. Recent molecular orbital calculations have established the theoretical basis of the CH/π interaction.[12,13]

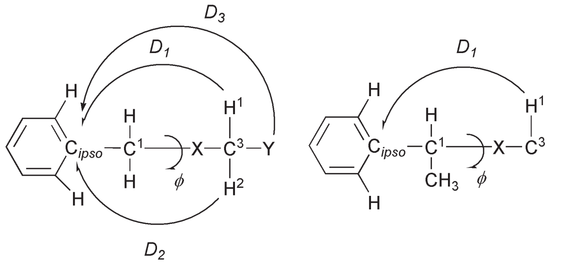
Method

Database study

The CSD version 5.24 (January 2003 release, 272 066 entries) was used. The torsion angle ϕ defined by the Ar-C^1–X-C^3 sequence in substructures $ArCH_2XCH_2Y$ **1** and $ArCHCH_3XC_{sp3}H$ **2** (Fig. 1) was inspected for organic crystals in the CSD. Only error-free structures with no disorder and $R < 10\%$ were accepted. Groups X and Y were any atoms in the initial survey and were replaced by an atom or group in the individual searches. X, Y and C_{sp3} in **2** were constrained not in a cyclic environment. Structures were inverted where necessary so that the torsion angle ϕ fell in the range $0 \sim 180°$. The C–H bond length was normalized to the standard value of 1.083 Å.

Ab initio calculations

A detailed description of the method is given in our previous papers.[3–7] Briefly, the geometry of $C_6H_5CH_2NHCH_3$,



1

2

Fig. 1 Substructures to be surveyed.

$C_6H_5CHCH_3CH_2CH_3$, $C_6H_5CHCH_3NHCH_3$ and $C_6H_5CHCH_3OCH_3$ was optimized at the MP2/6-31G(d) level of approximation. Using these geometries, single point calculations were performed at the MP2/6-311G(d,p) level to estimate the energies of the conformers. Vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization; all the eigenvalues were real for each conformer. Using these results, the thermal energy corrections were added to the total energy at 298.15 K and 1 atmosphere of pressure, with the principal isotope for each element type. All the calculations were performed by Gaussian 98 program.[14]

Results and discussion

First, organic crystals with substructures $ArCH_2XCH_2Y$ **1** were surveyed. 195 entries (268 fragments) were obtained from this search. Fig. 2 gives a histogram; the number of fragments is plotted against the torsion around the Ar-C^1–X-C^3 sequence. The peak at ϕ 180° (Ar/C^3 *anti*) is sharp but the cluster corresponding to the Ar/C^3 *syn* structure is broad. The number of fragments with the *syn* conformation (ϕ $0 \sim 90°$, 95 structures) is smaller than that of the *anti* conformation (ϕ $90 \sim 180°$, 173 structures). The ratio of the *syn vs. anti* conformation ($r_{syn/anti}$) is 0.55.

Fig. 3 shows a scattegram plotted for H^1/C_{ipso} distance (D^1) against the Ar/C^3 torsion angle (ϕ). Three clusters, centred at D^1 *ca.* 2.7, 3.3 and 4.0 Å, are found for the *syn* conformations. These correspond, in part, to the nearest, the second nearest and the remotest CH of a methyl group in CH_2Y, interacting with the aromatic ring, respectively. Superimposed on these clusters are CHs of other groups such as methylene or methine in CH_2Y. Fig. 4 is a scattegram plotted for H/C_{ipso} distances D^1 and D^2. It is noted that either D^1 or D^2 is in a short distance range with respect to C_{ipso}.

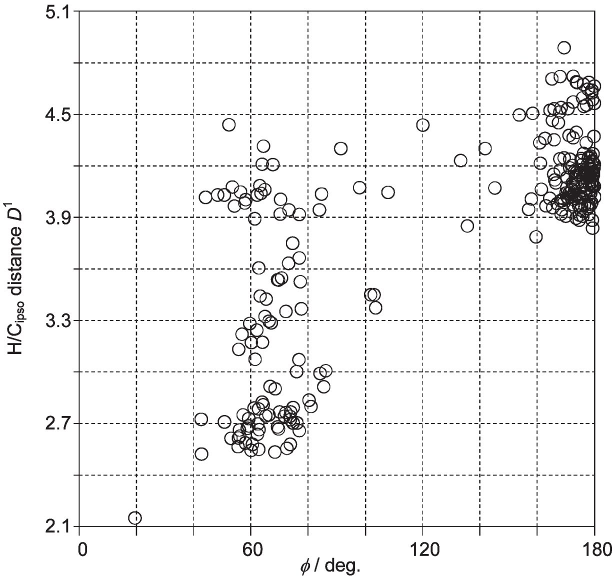


Fig. 3 Scattegram from a search of the substructure $ArCH_2XCH_2Y$ **1** plotted for H/C_{ipso} distance (D^1) against Ar/C^3 torsion angle (ϕ). VISTA ver. 2.0.

The above *syn* 95 fragments were analyzed to seek structure with at least one 5-member CH/π intramolecular distance D^1 shorter than 3.05 Å [= 2.9 Å (1.2 Å for H and 1.7 Å for sp^2 C) × 1.05][15] for entries with $\phi < 90$, 80, 70 and 60°. Many short H/C_{ipso} distances have been noted at the relevant atoms. Table 1 shows that almost every structure bears a CH/π contact shorter than 3.05 Å. A similar result was obtained for D^2.

Next, we surveyed the CSD by replacing group X with CH_2, NH, O and S. Table 2 summarizes the results. For X = CH_2, only 6 are in the *syn* conformation, whereas 61 fragments are *anti* with respect to Ar and C^3. For X = O, 21 and 40 are found *syn* and *anti* among 61 fragments, respectively. Figs. 5 and 6 give histograms for these surveys.

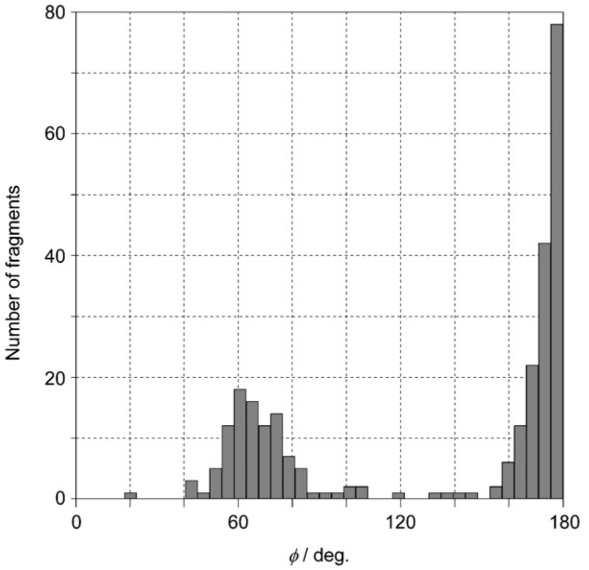


Fig. 2 Histogram obtained from a search of the substructure $ArCH_2XCH_2Y$ **1**. VISTA ver. 2.0.

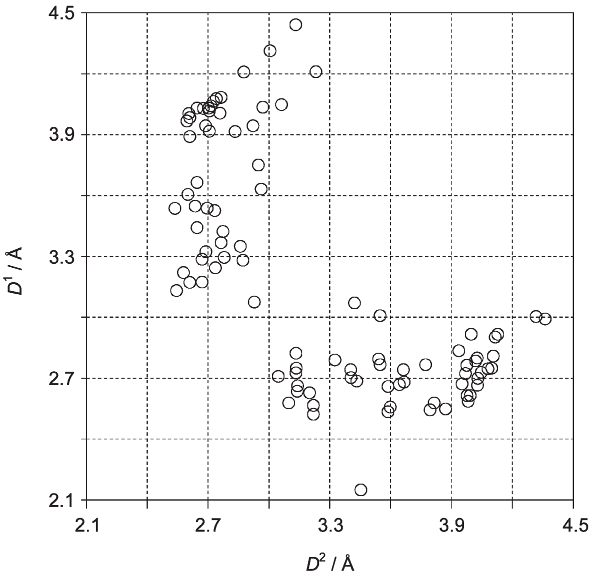


Fig. 4 Scattegram from a search of the substructure $ArCH_2XCH_2Y$ **1** plotted for H/C_{ipso} distances D^1 *vs.* D^2 ($\phi < 90°$).

Table 1 Number and proportion of structures with the *syn* conformation of $ArCH_2XCH_2Y$ **1** (X, Y: any atom), bearing 5-member CH/π intramolecular distances (H/C_{ipso}) shorter than 3.05 Å[a]

	$\phi/°$	Fragment[b]	Ratio (%)	D_{atm}/Å[c]
1	0 ~ 90	91	96	2.72 ± 0.14
	0 ~ 80	84	88	2.70 ± 0.13
	0 ~ 70	60	63	2.68 ± 0.13
	0 ~ 60	24	25	2.63 ± 0.13

[a] The C–H bond length was normalized to the standard value of 1.083 Å. [b] Number of observations with CH/C_{ipso} distance shorter than 3.05 Å. [c] Mean atomic distance ± SD.

Table 2 Crystal data of (a) $ArCH_2XCH_2Y$ and (b) $ArCHCH_3XCH$[a]

(a) $ArCH_2XCH_2Y$ (Y: any atom)	Fragment[b]	*syn*[c]	*anti*[d]	$r_{syn/anti}$[e]
X				
Any atom	268	95	173	0.55
Any C	109	27	82	0.33
CH_2	67	6	61	0.10
NH	2	0	2	—
O	61	21	40	0.53
S	14	6	8	0.75
(b) $ArCHCH_3XC_{sp3}H$				
X				
Any atom	159	125	34	3.68
Any C	41	34	7	4.86
CH_2	7	7	0	—
NH	13	12	1	12.00
O	4	2	2	1.00
S	0	0	0	—

[a] The C–H bond length was normalized to 1.083 Å. [b] Number of observations. [c] ϕ 0 ~ 90°. [d] ϕ 90° ~ 180°. [e] Ratio of the *syn vs. anti* conformation.

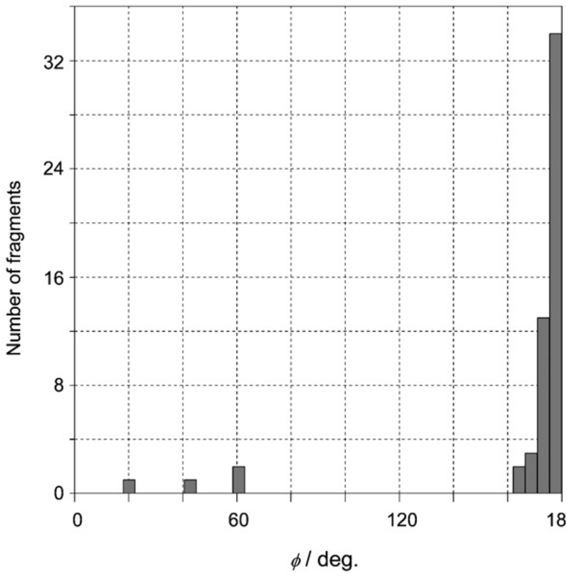


Fig. 5 Histogram obtained from a search of the substructure $ArCH_2CH_2CH_2Y$.

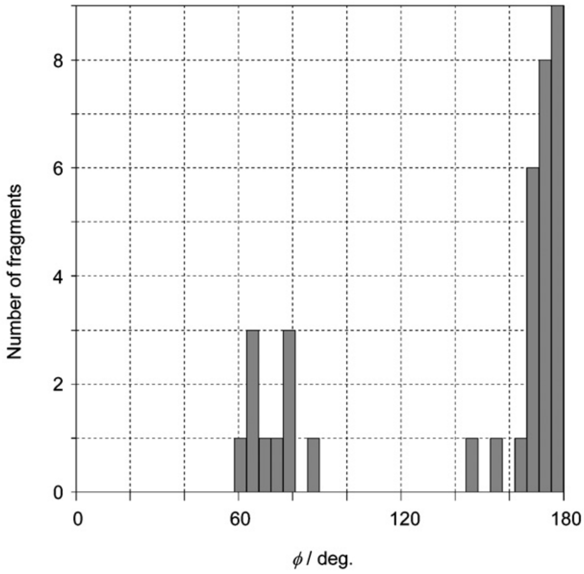


Fig. 6 Histogram obtained from a search of the substructure $ArCH_2OCH_2Y$.

For arylethyl compounds $ArCHCH_3XCH_2Y$ **2** (X, Y: any atom), only 14 entries were found in the database. We therefore surveyed, instead, the substructure $ArCHCH_3XC_{sp3}H$. Fig. 7 gives a histogram of this survey. The number of fragments with the *syn* conformation (ϕ 0 ~ 90°, 125 fragments) is larger than that of the *anti* conformation (ϕ 90 ~ 180°, 34 fragments). The ratio of the *syn vs. anti* conformation ($r_{syn/anti}$) is 3.68. Introduction of an alkyl group α to the aromatic ring greatly increased the abundance of the R/Ar-folded structure. This is reasonable in view of the unfavourable steric interaction, which may occur between the benzylic methyl group and R.

In Table 3 are listed the number of fragments and mean interatomic distances $D_1 \sim D_3$ in the crystal structure of Ar/C^3 *syn*-conformation. We note that the distance from the *ipso* carbon is shorter (around 1 Å) when the atom attached to C_3 is hydrogen than in the other cases. This is much shorter than might be expected by replacement of a C–H (bond length *ca.* 1.09 Å) to C–C (1.54 Å). The contribution from

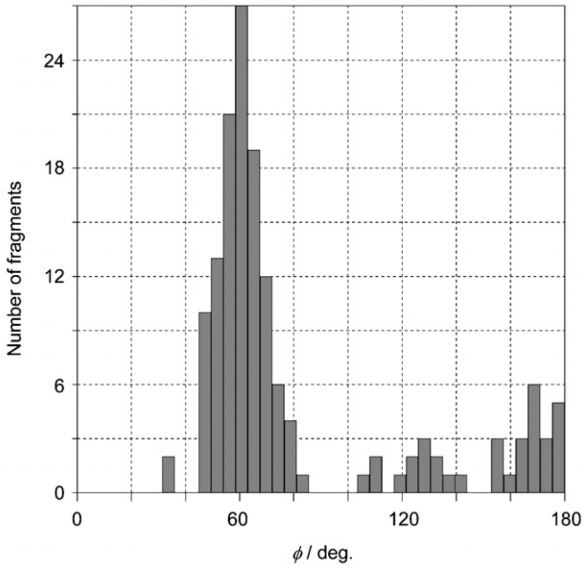
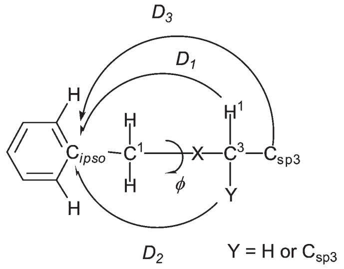


Fig. 7 Histogram obtained from a search of the substructure $ArCHCH_3XC_{sp3}H$ **2**.

Table 3 Number of fragments and mean interatomic (C_{ipso}/H^1, C_{ipso}/Y and C_{ipso}/C_{sp3}) distances (Å)in the crystal structure of Ar/C^3 *syn*-conformation[a]



(a) $ArC^1H_2XC^3H_2C_{sp3}$

	Fragment[b]	D_1	D_2	D_3
X = AA[c]				
Y: AA	95	3.20 ± 0.58	3.25 ± 0.55	4.16 ± 0.38
Y: Any C_{sp3}	58	3.21 ± 0.58	3.18 ± 0.53	4.18 ± 0.36
X = CH_2				
Y: AA	6	3.02 ± 0.51	2.96 ± 0.29	4.28 ± 0.42
Y: Any C_{sp3}	4	2.81 ± 0.50	3.10 ± 0.26	4.19 ± 0.51
X = O				
Y: AA	21	3.07 ± 0.44	3.17 ± 0.48	4.27 ± 0.32
Y: Any C_{sp3}	10	2.98 ± 0.36	3.13 ± 0.35	4.40 ± 0.08
X = S				
Y: AA	6	3.63 ± 0.72	3.16 ± 0.60	4.26 ± 0.34
Y: Any C_{sp3}	4	3.32 ± 0.67	3.27 ± 0.73	4.43 ± 0.22

(b) $ArC^1H_2XC^3H(C_{sp3})_2$
(Y = C_{sp3})

	Fragment	D_1	D_2	D_3
X = AA				
Y = C_{sp3}	33	2.66 ± 0.30	4.07 ± 0.29	4.11 ± 0.26

[a] The C–H bond length was normalized to 1.083 Å. [b] Number of observations. [c] Any atom.

the CH/π bond in making these conformations favorable seems apparent.

Comparison of the crystallographic data with the conformational energies calculated by the *ab initio* method

Table 4 compares the logarithm of *syn*/*anti*- ratio ($\ln r_{syn/anti}$) and the difference in the conformational energies ($\Delta G_{syn-anti}$). The greater the $\Delta G_{syn-anti}$, the greater the proportion of the *syn* conformation. A least-squares regression analysis shows a linear correlation to exist between $\ln r_{syn/anti}$ and $\Delta G_{syn-anti}$ (Fig. 8). This is consistent with the result reported by Taylor *et al.*

Table 4 Crystal conformer distributions ($\ln r_{syn/anti}$) and difference in the conformational energies ($\Delta G_{syn-anti}$, kcal mol^{-1}) calculated by the *ab initio* method for the *syn* and *anti* conformations of methyl benzyl and methyl 1-phenylethyl compounds

	$\ln r_{syn/anti}$	$\Delta G_{syn-anti}$	Reference
$C_6H_5CH_2CH_2CH_3$	−2.30[a]	0.04	3
$C_6H_5CH_2NHCH_3$	—	−0.35	this work
$C_6H_5CH_2OCH_3$	−0.63[a]	0.79	3
$C_6H_5CH_2SCH_3$	−0.29[a]	0.97	3
$C_6H_5CHCH_3CH_2CH_3$		1.09	this work
$C_6H_5CHCH_3NHCH_3$	2.48[b]	3.60[c]	this work
$C_6H_5CHCH_3OCH_3$	0.00[b]	2.05	this work
$C_6H_5CHCH_3SCH_3$	—	1.54	7

[a] $ArCH_2XCH_2Y$. [b] $ArCH(CH_3)XC_{sp3}H$. [c] *threo* isomer.

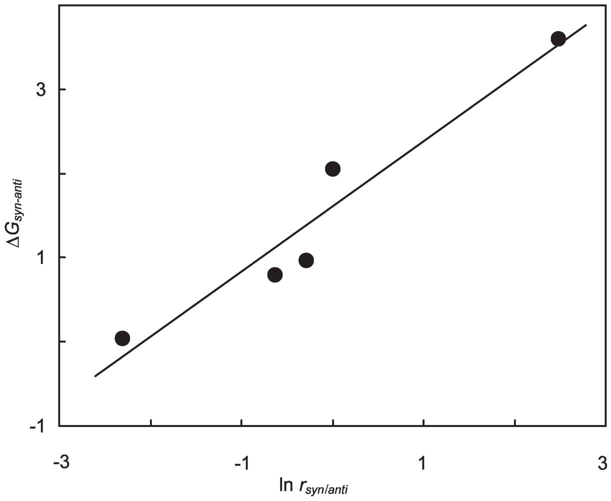


Fig. 8 Plot of $\ln r_{syn/anti}$ against calculated Gibbs energy difference $\Delta G_{syn-anti}$.

Conclusion

To summarize, crystal structures bearing CH and Ar in the *syn* relationship are often found in aralkyl compounds. Correlation of the crystal-structure conformer distribution with the computed conformational energy difference is statistically significant. As to the origin of the favoured *syn* R/Ar conformation, contribution from the CH/π hydrogen bond is suggested.

References

1 F. H. Allen, S. E. Harris and R. Taylor, *J. Comput.-Aided Mol. Des.*, 1996, **10**, 247.
2 F. H. Allen, *Acta Crystallogr. Sect. B*, 2002, **58**, 380; F. H. Allen, *Acta Crystallogr. Sect. A*, 1998, **54**, 758.
3 O. Takahashi, Y. Kohno, K. Saito and M. Nishio, *Chem. Eur. J.*, 2003, **9**, 756.
4 O. Takahashi, Y. Kohno, Y. Gondoh, K. Saito and M. Nishio, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1777.
5 O. Takahashi, Y. Kohno, Y. Gondoh, K. Saito and M. Nishio, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 369.
6 O. Takahashi, K. Saito, Y. Kohno, H. Suezawa, S. Ishihara and M. Nishio, *Bull. Chem. Soc. Jpn.*, 2003, **76** , in the press.
7 O. Takahashi, K. Saito, Y. Kohno, H. Suezawa, T. Yoshida, S. Ishihara and M. Nishio, *New J. Chem.*, 2003, **27**, DOI: 10.1039/b303268j.
8 S. Zushi, Y. Kodama, K. Nishihata, K. Umemura, M. Nishio, J. Uzawa and M. Hirota, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3631; Y. Kodama, S. Zushi, K. Nishihata, M. Nishio and J. Uzawa, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1306.
9 M. Nishio, M. Hirota and Y. Umezawa, *The CH/π Interaction. Evidence, Nature, and Consequences*, Wiley-VCH, New York, 1998. A comprehensive literature list for the CH/π interaction is available on the following website: http://www.tim.hi-ho.ne.jp/dionisio.
10 G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press, Oxford, 1999.
11 M. Nishio, *Tetrahedron*, 1989, **45**, 7201; M. Nishio, Y. Umezawa, M. Hirota and Y. Takeuchi, *Tetrahedron*, 1995, **51**, 8665.
12 Hydrogen bond nature of the CH/π interaction: J. J. Novoa and F. Mota, *Chem. Phys. Lett.*, 2000, **318**, 345; M. Hirota, K. Sakakibara, H. Suezawa, T. Yuzuri, E. Ankai and M. Nishio, *J. Phys. Org. Chem.*, 2000, **13**, 620; O. Takahashi, Y. Kohno, S. Iwasaki, K. Saito, M. Iwaoka, S. Tomoda, Y. Umezawa, S. Tsuboyama and M. Nishio, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 2421; O. Takahashi, Y. Kohno and K. Saito, *Chem. Phys. Lett.*, 2003, in the press.
13 Recent papers include: U. Samanta, P. Chakrabarti and J. Chandrasekhar, *J. Phys. Chem.*, 1998, **102**, 8964; S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami and K. Tanabe, *J. Am.*

Chem. Soc., 2000, **122**, 3746; S. Scheiner and S. J. Grabowski, *J. Mol. Struct.*, 2002, **615**, 209; A. Bagno, G. Saielli and G. Scorrano, *Angew. Chem. Int. Ed.*, 2001, **40**, 2532; F. Ugozzoli, A. Arduini, C. Massera, A. Pochini and A. Secchi, *New J. Chem.*, 2002, **26**, 1718; A. Bagno, G. Saielli and G. Scorrano, *Chem. Eur. J.*, 2002, **8**, 2047; S. Fomine, M. Tlenkopatchev, S. Martinez and L. Fomina, *J. Phys. Chem. A*, 2002, **106**, 3491.

14 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., 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. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, *GAUSSIAN 98 (Revision A.4)*, Gaussian, Inc., Pittsburgh PA, 1998.

15 L. Pauling, *The Nature of the Chemical Bond and the Structure of Molecules and Crystals; An Introduction to Modern Structural Chemistry*, Cornell University Press, Ithaca, New York, 3rd edn., 1960, p. 260.