

Intramolecular hydrogen bonds: common motifs, probabilities of formation and implications for supramolecular organization

Clair Bilton,^a Frank H. Allen,^b
Gregory P. Shields^b and
Judith A. K. Howard^{a*}

^aDepartment of Chemistry, University of Durham, South Road, Durham DH1 3LE, England, and ^bCambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, England

Correspondence e-mail:
j.a.k.howard@durham.ac.uk

Received 16 December 1999

Accepted 3 March 2000

A systematic survey of the Cambridge Structural Database (CSD) has identified all intramolecular hydrogen-bonded ring motifs comprising less than 20 atoms with N and O donors and acceptors. The probabilities of formation P_m of the 50 most common motifs, which chiefly comprise five- and six-membered rings, have been derived by considering the number of intramolecular motifs which could possibly form. The most probable motifs ($P_m > 85\%$) are planar conjugated six-membered rings with a propensity for resonance-assisted hydrogen bonding and these form the shortest contacts, whilst saturated six-membered rings typically have $P_m < 10\%$. The influence of intramolecular-motif formation on intermolecular hydrogen-bond formation has been assessed for a planar conjugated model substructure, showing that a donor-H is considerably less likely to form an intermolecular bond if it forms an intramolecular one. On the other hand, the involvement of a carbonyl acceptor in an intramolecular bond does not significantly affect its ability to act as an intermolecular acceptor and thus carbonyl acceptors display a substantially higher inclination for bifurcation if one hydrogen bond is intramolecular.

1. Introduction

Hydrogen bonds play a crucial role in supramolecular organization (Jeffrey, 1997; Nangia & Desiraju, 1998). Knowledge of hydrogen-bond geometries (Taylor & Kennard, 1984; Murray-Rust & Glusker, 1984), directionalities and motif formation is vital in the modelling of protein–ligand interactions (Tintelnot & Andrews, 1989; Böhm & Klebe, 1996), in crystal engineering (Aakeroy, 1997; Aakeroy & Seddon, 1993; Desiraju, 1989, 1995, 1997; Etter, 1991), and in *ab initio* crystal structure prediction (Gavezzotti & Filippini, 1994; Motherwell, 1999). Crystal-structure analyses are the principal source of this knowledge, either individually or accessed systematically through the Cambridge Structural Database (CSD: Allen & Kennard, 1993), which now records >200 000 structures, or through IsoStar, a knowledge base of intermolecular interactions derived from the CSD, the PDB (Protein Data Bank; RCSB, 2000) and other sources (Bruno *et al.*, 1997). Very recently, the CSD has been used to identify the most common motifs and to establish their probabilities of formation, and hence identify the most robust and reproducible intermolecular hydrogen-bonded motifs that might act as supramolecular synthons in crystal engineering applications (Allen *et al.*, 1998, 1999).

Sidgwick & Callow (1924) were among the first to recognize the importance of intramolecular hydrogen bonding on the physical properties of organic molecules, in particular *ortho-*

substituted phenols. Early studies of the phenomenon were summarized by Pimentel & McClellan (1960) and progress in theoretical studies reviewed by Schuster (1976). Schuster distinguished between intramolecular bonds where the donor and acceptor groups are separated by at least one sp^3 -hybridized C atom, which tended to be weaker than their intermolecular equivalent, and those in which the donor and acceptor are linked by a planar delocalized π -electron system, where the hydrogen-bonds tended to be considerably stronger than intermolecular bonds. This phenomenon in conjugated systems has been termed resonance-assisted hydrogen bonding (RAHB; Gilli *et al.*, 1989) and can be understood in terms of π -electron delocalization, enhancing the partial negative charge on the acceptor and the partial positive charge on the donor-H, strengthening the H \cdots A interaction and weakening the D–H bond. Intramolecular hydrogen bonding continues to be an important subject of current research, using both experimental techniques, *e.g.* vibrational spectroscopy (Palomer *et al.*, 1999), NMR spectroscopy (Gung *et al.*, 1999) and X-ray diffraction (Harmon *et al.*, 1999; Fakhraian *et al.*, 1991), and theoretical modelling (Chung *et al.*, 1997; Kovacs *et al.*, 1999; Luque *et al.*, 1998).

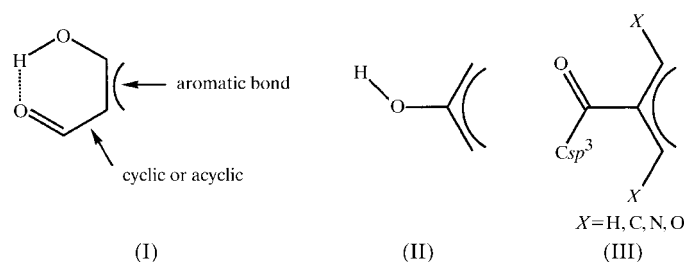
A number of factors can affect the ability of strong donors and acceptors to participate in predictable motif formation. Chief among these are steric accessibility, donor/acceptor competition, cooperativity and, most importantly, the removal of donor/acceptor combinations from the intermolecular domain through the formation of intramolecular hydrogen bonds. A number of recent studies have focused on competition between intra- and intermolecular hydrogen bonding in both the gas (Furlani & Garvey, 1997) and liquid (Missopolinou & Panayiotou, 1998) phases. Although intramolecular hydrogen bonds are ubiquitous in crystal structures and can have significant effects on intramolecular geometry, to our knowledge no general systematic structural study of intramolecular hydrogen bonding has so far been attempted. Hence, we have analysed structures in the CSD to discover the topologies, chemical constitutions and probabilities of formation of all intramolecular hydrogen-bonded motifs formed by N–H or O–H donors and N or O acceptors. Here we report the most common motifs located by this data-driven approach and we examine the interplay between intra- and intermolecular hydrogen bonding in some of these cases.

2. Methodology

A modified version of the CSD program *QUEST3D* has been developed (Allen *et al.*, 1998, 1999), which enables a thorough review of all inter- or intramolecular motifs represented in the CSD to be performed, subject to user-supplied geometric definitions of hydrogen bonding. This program was used to survey the entire CSD (April 1999 release comprising 197 481 database entries) and produce statistics for all intramolecular hydrogen-bonded motifs which occur for N and O donors and acceptors, *i.e.* the intramolecular motifs that are most likely to be significant, being formed by H-mediated interactions typically having energies of >20 kJ mol $^{-1}$. All non-polymeric

organic CSD entries with error-free coordinate sets and $R < 10\%$ were investigated, and duplicate structure determinations of the same compound were rejected. Intramolecular hydrogen-bonded rings which contained O/N–H donors and O or N acceptors with a D–H \cdots A angle $>75^\circ$ were tabulated. D–H distances were normalized to ideal values obtained from neutron diffraction studies, *viz.* 1.009 and 0.983 Å for N–H and O–H, respectively (Allen *et al.*, 1987). Initial CSD searches for intramolecular N/O–H \cdots N/O interactions <3.5 Å were performed with the same secondary search criteria, to establish the maximum distances which would be accepted as intramolecular hydrogen bonds (Figs. 1*a–d*). After inspection of these histograms, and by analogy with those for intermolecular hydrogen bonds (Allen *et al.*, 1999), distance limits of 2.30 Å for O–H \cdots N/O and 2.35 Å for N–H \cdots N/O contacts were adopted. All motifs which satisfied these criteria were collated and the number of occurrences (N_{obs}) of each motif was obtained from this list, together with the number of structures that contained each motif (S_{obs}).

Whilst these values are informative, they are dependent on the number of occurrences of the particular donor–acceptor combinations in the CSD, *i.e.* the number of times a motif could possibly occur (N_{poss}) and the number of structures which could possibly contain the motif (S_{poss}). Hence the probabilities of formation, $P_m = 100(N_{\text{obs}}/N_{\text{poss}})$ and $P_s = 100(S_{\text{obs}}/S_{\text{poss}})$, can be derived, which reduces bias due to the relative abundances of particular classes of compound in the CSD. N_{poss} values were obtained by conducting separate CSD searches for the fragments which could form each motif. This was restricted to the 50 motifs identified which occurred in ≥ 25 structures, using the same search conditions as in the automated motif search. In addition, torsion angles about non-rotatable multiple bonds were restricted to values of -90 to $+90^\circ$, to exclude fragments which could not possibly adopt the conformation required for intramolecular ring formation. Cyclic single bonds were similarly constrained. Fragments which were mutually exclusive were not included, *e.g.* formation of intramolecular hydrogen bonds by both H atoms of an NH $_2$ group to the same C=O acceptor. The resulting statistics for the 50 most common motifs, (1)–(50) (Fig. 2), ordered by the P_m value, are summarized in Table 1.



To assess the influence of the formation of intramolecular motifs on the ability of the donor or acceptor to form (additional) intermolecular hydrogen bonds, further searches were performed based on model fragment (I), a generic version of motifs (5) and (12) [which differ only by whether the C–C bond adjacent to the carbonyl acceptor is cyclic, (5), or acyclic, (12)]. The secondary search criteria noted above were used for

these searches, with a distance limit of 2.6 Å used to define both intra- and intermolecular N/O–H···O/N hydrogen bonds. To investigate the donor behaviour in the absence of the carbonyl acceptor, fragment (II) was used, and similarly, fragment (III) was chosen to examine intermolecular hydrogen bonding at the acceptor in the absence of an intramolecular donor. Initial searches provided three subsets comprising those structures which could form an intermolecular hydrogen bond: (a) (I), with an intramolecular

hydrogen bond, (b) (II), without an intramolecular hydrogen bond from the donor and (c) (III), without an intramolecular hydrogen bond to the acceptor but with at least one O/N–H donor present in the structure. Further searches located intermolecular hydrogen bonds formed by the donors and/or acceptors in (I)–(III), enabling the relative propensities with which the donors in (I) and (II), and similarly the acceptors in (I) and (III), form one or more intermolecular hydrogen bonds.

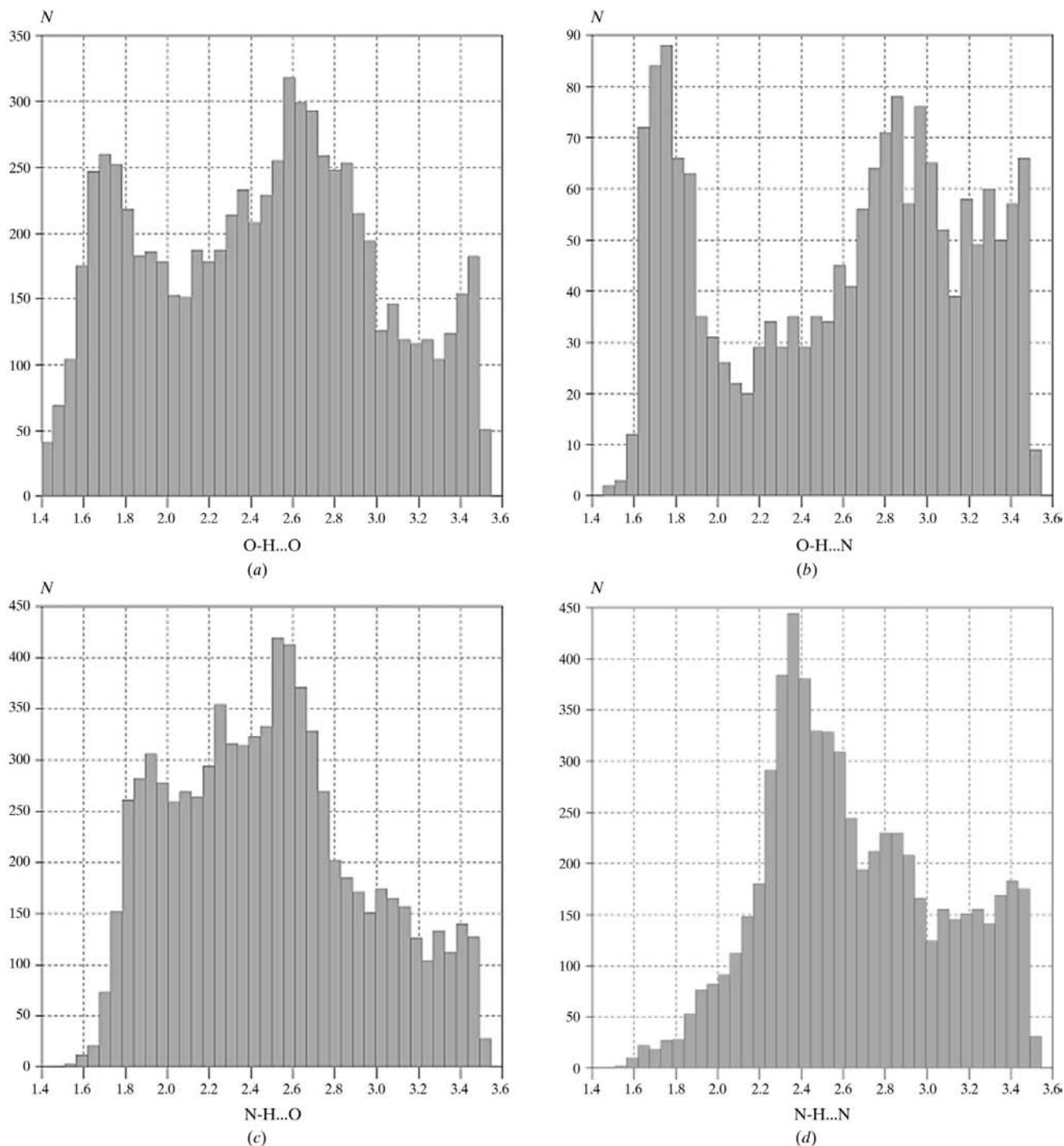


Figure 1
Histograms of intramolecular H···A distances (Å), for $D-H\cdots A > 75^\circ$: (a) O–H···O, (b) O–H···N, (c) N–H···O and (d) N–H···N.

3. Results and discussion

3.1. Motif statistics

The 10 most probable motifs are all six-membered rings and occur with $P_m > 90\%$. Features common to the most probable motifs are ring size and conjugation. Five-membered motifs and larger rings do occur, but are less probable. Motif (1) occurs in all possible cases, and in all 42 occurrences the atoms are arranged in the optimum geometry for intramolecular hydrogen-bonded ring formation (structures with an entirely different conformation were excluded from the derivation of N_{poss} , see above). The effect of conformational flexibility on P_m is significant. Pattern (22) has the same H—N—N=C—C=O atomic arrangement as (1), but has a considerably lower probability (*ca* 56%; it was assumed in the calculation of N_{poss}

that the C—C bond was flexible). The only difference between (1) and (22) is that the C—C bond is cyclic in (1), and thus the fragment has much less conformational flexibility and is less able to twist to form other motifs [the structures which could adopt motif (22) but do not, form 7 different alternative motifs instead].

For each of the next three most probable motifs, (2), (3) and (4), there is only one possible occurrence for which the motif is

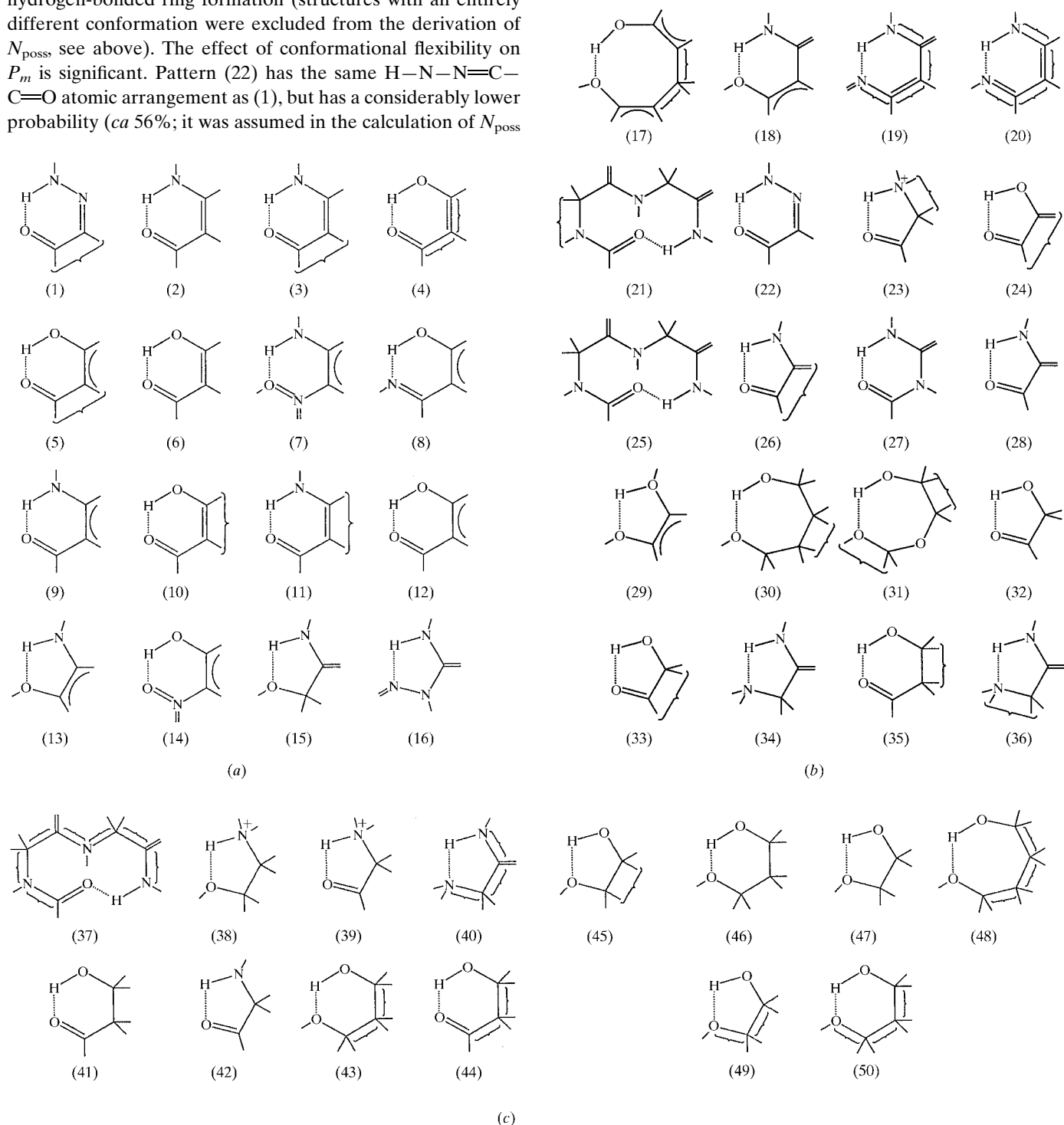


Figure 2
Intramolecular motifs found in ≥ 25 structures.

Table 1

Statistics for the 50 most common intramolecular hydrogen-bonded motifs.

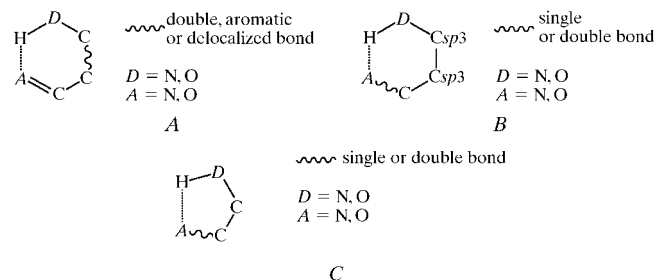
Definitions are given in §2.

Motif	S_{obs}	P_s	N_{obs}	P_m
(1)	37	100	42	100
(2)	67	98.5	86	98.9
(3)	35	97.2	43	97.7
(4)	32	97.0	40	97.6
(5)	199	97.1	287	97.3
(6)	50	98.0	67	97.1
(7)	147	93.6	235	95.1
(8)	102	93.6	147	94.8
(9)	77	91.7	118	93.7
(10)	71	91.0	89	90.8
(11)	59	88.1	66	88.0
(12)	186	83.8	259	86.0
(13)	43	76.8	61	79.2
(14)	32	74.4	45	76.3
(15)	54	70.1	71	73.2
(16)	101	82.8	119	70.0
(17)	41	89.1	106	67.1
(18)	55	65.5	59	62.1
(19)	88	93.6	126	60.6
(20)	86	87.8	126	57.8
(21)	39	61.9	40	56.3
(22)	34	56.7	37	56.1
(23)	31	55.4	33	55.0
(24)	75	54.7	97	54.2
(25)	99	63.1	199	53.6
(26)	33	56.9	34	51.5
(27)	30	69.8	28	40.6
(28)	33	33.7	58	39.7
(29)	165	54.5	228	37.9
(30)	46	64.8	61	35.9
(31)	29	30.2	38	26.8
(32)	122	28.8	143	23.4
(33)	106	24.3	114	22.2
(34)	147	31.1	212	22.2
(35)	30	20.7	35	20.0
(36)	35	22.2	40	19.1
(37)	49	48.5	65	19.0
(38)	33	14.6	52	16.9
(39)	82	16.3	96	14.4
(40)	65	17.5	92	12.7
(41)	35	10.0	44	8.9
(42)	123	14.5	147	8.7
(43)	133	16.9	155	7.6
(44)	33	8.2	35	7.4
(45)	206	16.7	239	7.2
(46)	34	15.2	38	5.2
(47)	35	6.4	38	2.8
(48)	25	3.5	35	2.5
(49)	52	3.5	65	2.4
(50)	52	3.5	58	2.4

not formed within the distance criteria, despite the correct atomic arrangement, and in each case an alternative intramolecular pattern is adopted. For (2), the alternative is the formation of an additional eight-membered ring motif (Fig. 3a). A seven-membered ring, H–N–N–C–C–C=O (where the C–C bond adjacent to the C=O is cyclic, Fig. 3b), is formed in preference to (3) in one structure, with a particularly short N–H···O distance of 1.60 Å. One compound which would be expected to form (4) actually adopts (44) (Fig. 3c). Interestingly, the alternative motif seems to form to allow the expected donor to participate in an intermolecular bond instead.

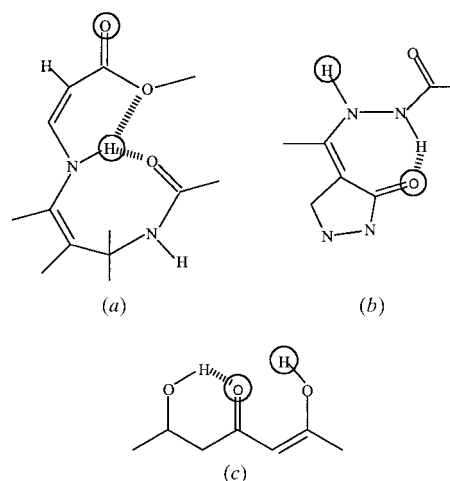
3.2. Generic motifs

Most of the motifs (1)–(50) comprise five- and six-membered rings and many of them can be grouped into generic motifs with features in common, enabling broad trends to be established (Table 2). With the exception of (20), all generic motifs **A** form with $P_m > 85\%$. As with motifs (1) and (22), motifs **A** are planar conjugated systems which may be stabilized by resonance-assisted hydrogen bonding. There does not seem to be any significant difference in probability for N and O donors and acceptors, except that (20) with N as both donor and acceptor is considerably less probable. A



histogram of H···O distances for fragments which could form motif (2) shows a sharp peak at *ca* 1.9 Å, indicating that the intramolecular hydrogen bonds are short and well within the distance criteria employed (Fig. 4a). Conversely, for generic motif **B**, with donors and acceptors connected with sp^3 – sp^3 single bonds, probabilities are all 20% or substantially less. Carbonyl (Osp^2) acceptors do not seem to form more favourable motifs than Osp^3 atoms in this case. The O–H distance distribution for the fragment which could form motif (41) (which has no cyclic bonds) is given in Fig. 4b. In contrast with (2), the distribution has no clear cut-off, although there is a minimum at *ca* 2.5 Å, consistent with the greater flexibility of the fragment and its lower P_m .

Generic motif **C** shows a much wider range of probabilities. With the exception of (15), the most probable motifs, including (23), (24) and (26) with P_m of *ca* 0.5, possess

**Figure 3**

Alternative intramolecular motifs formed instead of (a) (2), (b) (3) and (c) (4). Circled atoms are those which could form the expected motifs.

carbonyl acceptors. The O··H distance distribution for fragments which could form motif (24), which has two unsaturated C atoms linked by a cyclic bond and is thus relatively rigid (although the hydroxyl-H is free to rotate), is given in Fig. 4(c). This has a clear but relatively broad maximum centred around *ca* 2.2 Å, and therefore not all contacts in this region fall within the search criterion of 2.30 Å. The least favourable

motifs [(45), (47) and (49)] have *Osp*³ acceptors and their probabilities are comparable with those for saturated six-membered rings with the same donor and acceptor groups [B: (43), (46) and (50)]. The O··H distance histogram for fragments which could form motif (47) (Fig. 4d) does not show a clear primary maximum like that for (24) (Fig. 4c), but a bimodal distribution with maxima at *ca* 2.6 and 3.6 Å; many of

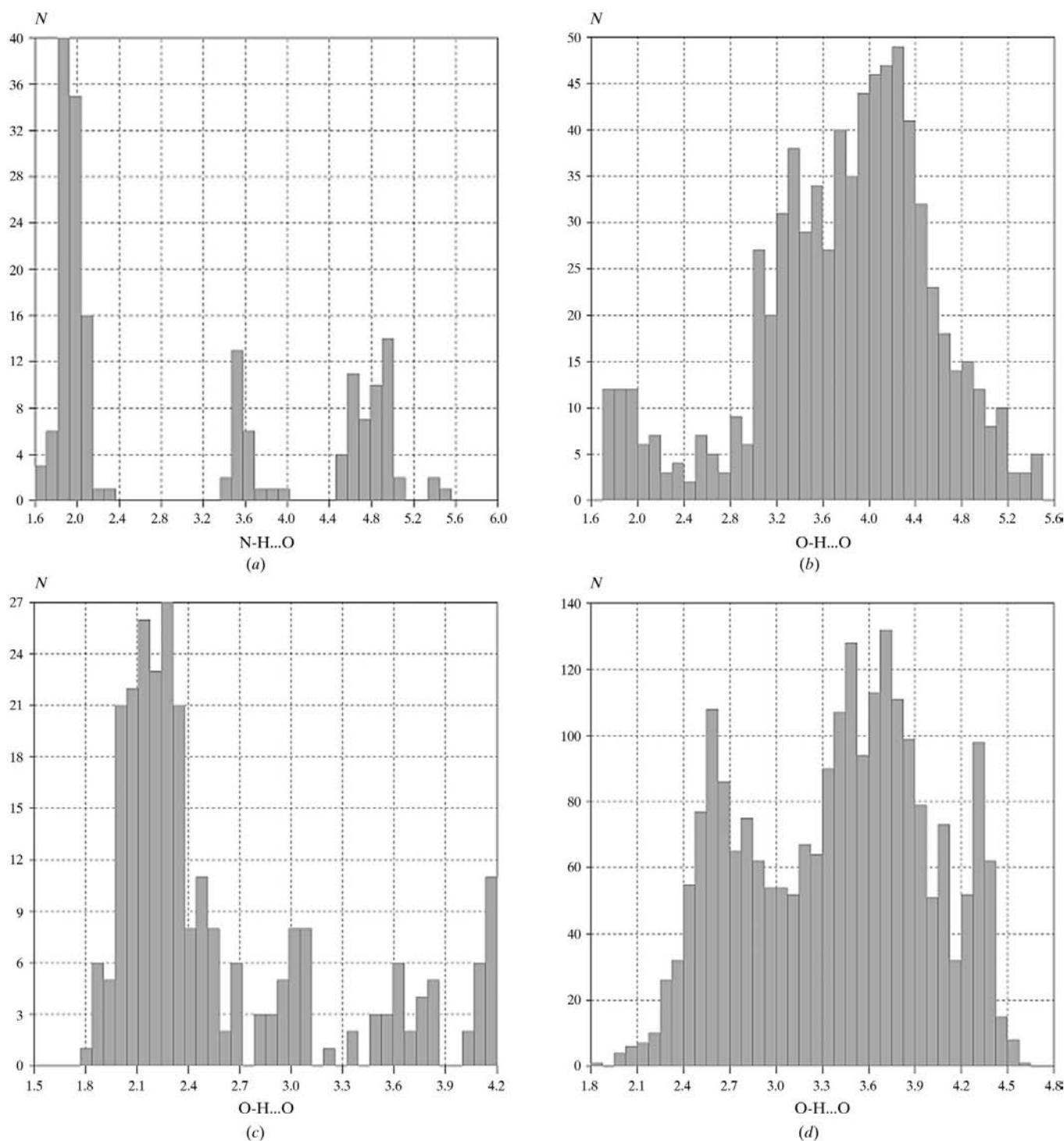


Figure 4
Histograms of intramolecular H···A distances for fragments which could form motifs (a) (2), (b) (41), (c) (24) and (d) (47).

Table 2
Statistics for generic motifs A–C.

Definitions are given in §2.

A			B			C		
Motif	<i>D, A</i>	<i>P_m</i>	Motif	<i>D, A</i>	<i>P_m</i>	Motif	<i>D, A</i>	<i>P_m</i>
(2)	N, O	98.9	(35)	O, =O	20.0	(15)	N, –O	73.2
(3)	N, O	97.2	(41)	O, =O	8.9	(23)	N, =O	55.0
(4)	O, O	97.6	(43)	O, –O	7.6	(24)	O, =O	54.2
(5)	O, O	97.3	(44)	O, =O	7.4	(26)	N, =O	51.5
(6)	O, O	97.1	(46)	O, –O	5.2	(28)	N, =O	39.7
(8)	O, N	94.8	(50)	O, –O	2.4	(32)	O, =O	23.4
(9)	N, O	93.7				(33)	O, =O	22.2
(10)	O, O	90.8				(34)	N, –N	22.2
(11)	N, O	88.0				(36)	N, –N	19.1
(12)	O, O	86.0				(38)	N, –O	16.9
(20)	N, N	57.8				(39)	N, =O	14.4
						(40)	N, –N	12.7
						(42)	N, =O	8.7
						(45)	O, –O	7.2
						(47)	O, –O	2.8
						(49)	O, –O	2.4

these longer interactions cannot be considered as hydrogen bonds.

Some saturated seven-membered rings [(30), 35.9% and (31), 26.8%] are rather more probable than their five- and six-membered analogues, which may suggest that seven-membered rings may be more favourable for an unsaturated system, although *P_m* for the highly constrained seven-membered ring (48) is only 2.5%. The only eight-membered ring in the top 50 is (17), with *P_m* \simeq 67%. This motif usually occurs in the structures of (hydroxy)calixarenes, which are often constrained in a conformation favourable for this intramolecular hydrogen bond. The only ten-membered intramolecular rings occur in the polypeptides, where (21) and (25) form in just over half of the possible cases, whereas substructure (37) with mainly cyclic bonds is less favoured, with *P_m* = 19%.

3.3. Effect on intermolecular hydrogen bonding

The results of searches described in §2 for substructures (I), (II) and (III) are summarized in Tables 3 and 4 for intermolecular hydrogen-bond formation to the donor and acceptor. From Table 3, it is clear that involvement of a donor-H in an intramolecular hydrogen bond of the type in fragment (I) makes it *ca* three times less likely to be involved in the formation of intermolecular hydrogen bonds than if the intramolecular hydrogen bond was absent, as in fragment (II). However, the formation of at least one inter- and one intramolecular hydrogen bond of the form in fragment (I) is considerably more favoured (by a factor of *ca* 10) than the formation of two or more intermolecular hydrogen bonds with the same donor [fragment (II)], *i.e.* the tendency for bifurcation at the donor increases considerably when one of the hydrogen bonds is intramolecular. This may be due in part to spatial effects, *viz.* the difficulty in arranging two acceptor molecules in mutually compatible positions with their acceptors both directed toward the H atom in the donor molecule;

Table 3

Statistics for intermolecular bond formation at hydroxyl donors in substructures (I) and (II).

N_{inter} = number of intermolecular hydrogen bonds formed; *cP* = cumulative probability; other definitions are given in §2.

<i>N_{inter}</i>	(I)				(II)			
	<i>N_{obs}</i>	<i>S_{obs}</i>	<i>cP_m</i>	<i>cP_s</i>	<i>N_{obs}</i>	<i>S_{obs}</i>	<i>cP_m</i>	<i>cP_s</i>
2	2	2	0.28	0.39	67	62	2.0	2.9
1	138	110	19.3	21.6	2081	1464	61.8	67.9
0	587	408	100	100	1288	692	100	100
Total	725	518	100	100	3369	2156	100	100

Table 4

Statistics for intermolecular-bond formation at carbonyl acceptors in substructures (I) and (III).

N_{inter} = number of intermolecular hydrogen bonds formed; *cP* = cumulative probability; other definitions are given in §2.

<i>N_{inter}</i>	(I)				(III)			
	<i>N_{obs}</i>	<i>S_{obs}</i>	<i>cP_m</i>	<i>cP_s</i>	<i>N_{obs}</i>	<i>S_{obs}</i>	<i>cP_m</i>	<i>cP_s</i>
3	1	1	0.14	0.19				
2	7	6	1.1	1.4	2	2	0.57	0.69
1	196	171	28.1	34.3	106	100	30.3	34.7
0	529	347	100	100	244	188	100	100
Total	725	518	100	100	350	288	100	100

where one acceptor is in the same molecule as the donor, only one additional acceptor molecule must be positioned favourably.

Conversely, the formation of intermolecular hydrogen bonds to a carbonyl acceptor is little affected by the presence of an intramolecular hydrogen bond (Table 4). This suggests that the acceptor is still sterically accessible, and resonance assistance may even enhance the acceptor ability of the carbonyl O atom. It is notable that >85% of the intermolecular bonds are formed to the opposite side of the C(CO)C bisecting plane from the intramolecular bond, *i.e.* in the other *sp*² lone-pair direction. Bifurcation is rare for the acceptor in fragment (III); only about 2% of the acceptors which form any intermolecular hydrogen bonds form two or more such bonds. This may be due both to the spatial effect noted above and the lack of resonance assistance. Perhaps surprisingly, acceptors forming an intramolecular hydrogen bond of the type in fragment (I) are more likely to form two intermolecular hydrogen bonds, but there are insufficient observations to draw firm conclusions.

4. Conclusions

This study has successfully identified the most common intramolecular ring motifs and shown that the most probable are planar six-membered conjugated systems, stabilized by RAHB, as might have been predicted. These seem equally favourable for both O and N donors and are characterized by short intramolecular H···O distances. Fully saturated five- and six-membered rings have considerably lower probabilities and exhibit much broader distance distributions, whilst *P_m* for some saturated seven-membered rings exceeds 50%.

Statistics for a model substructure suggest that whilst intramolecular hydrogen-bond formation does not significantly hinder the availability of an acceptor atom, the ability of a donor-H atom to engage in intermolecular bonding is significantly reduced. As a result, the predictable formation of certain intramolecular motifs would be expected to have a significant influence on the ability of the molecule to engage in intermolecular hydrogen bonding, particularly where there are no other potential strong donor-H atoms present. These results are of a preliminary nature and further studies into bi- and polyfurcation, both at the donor and acceptor, involving inter- and intramolecular hydrogen bonds are needed. Work in this area is in progress.

CB thanks the EPSRC (UK) and CCDC for funding, and JAKH thanks the EPSRC for a Senior Research Fellowship. The authors are indebted to Professor G. R. Desiraju for most useful discussions.

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