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Intermolecular N—H···O Hydrogen Bonds Assisted by Resonance. Heteroconjugated Systems as Hydrogen-Bond-Strengthening Functional Groups

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Abstract

The crystal structures of seven compounds forming intermolecular N—H···O hydrogen bonds connected by π-conjugated systems are reported: (1) 2-methyl-*N*-phenylprop-2-enamide; (2) 2-methyl-*N*-benzylprop-2-enamide; (3) *p*-methoxyacetoacetanilide; (4) dibenzamide; (5) 3-methyl-4-(3′-methyl-1′-phenylpyrazol-5′-yl)-1-phenyl-4-pyrazolin-5-one; (6) 3-anilino-2-chloro-1,4-naphthoquinone; (7) 3-phenethyl-7-methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-one. 32 other structures of related compounds are surveyed in order to understand the reasons for the N—H···O bond presenting a range of N···O distances as wide as 2.70–3.05 Å. Data indicate that neutral intermolecular N—H···O hydrogen bonds shorter than 2.90 Å can occur only when the NH and C=O groups are connected by a π-conjugated system, which turns out to be increasingly delocalized while the N···O distance becomes shorter. All present findings are in agreement with the RAHB (resonance-assisted hydrogen bonding) model originally developed to explain strong hydrogen-bond formation in β-diketone enols and contribute to extending this model to the treatment of the strong intermolecular N—H···O bond.

Introduction

Intermolecular N—H···O hydrogen bonds are ubiquitous in biological systems such as DNA base pairs, proteins and ligand–receptor interactions (Jeffrey & Saenger, 1991; Saenger, 1984; Klebe, 1994). These weak bonds, which are essential for life as well as for many molecular recognition processes (Schneider, 1991; Rebek, 1990; Hamilton, 1990), display in crystals a large variety of distances and topologies which depend on both molecular properties and crystal packings (Bernstein, Etter & Leiserowitz, 1994; Taylor & Kennard, 1984; Olovsson & Jönsson, 1976). The knowledge of the factors determining how molecules self-aggregate in the solid state to give ordered patterns is important in designing organic structures able to produce new crystalline materials or control molecular association in solution (Lehn, Mascal, DeCian & Fischer, 1992; Panunto, Urbanczyk-Lipkowska, Johnson & Etter, 1987; Whitesides, Mathias & Seto, 1991; Etter, 1991; Desiraju, 1989).

Strong N—H···O hydrogen bonds are a well known driving force able to direct molecular aggregation in organic crystals and several attempts have been devoted to rationalize it (Jeffrey & Saenger, 1991; Etter, 1982, 1990; Taylor & Kennard, 1984; Berkovitch-Yellin, Ariel & Leiserowitz, 1983; Gavezzotti, 1994; Gavezzotti & Filippini, 1994). However, in spite of all efforts, the reasons why N···O distances display a large spectrum of

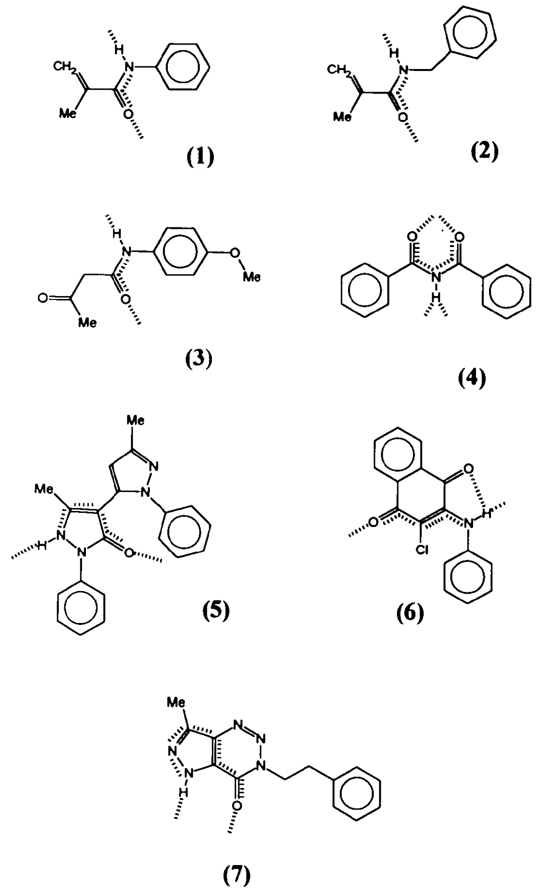

Fig. 1. Chemical formulae of compounds (1)–(7), whose crystal structures have been determined in the present paper. The hatchings indicate the π-conjugated systems.

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values, typically from 2.70 to 3.30 Å, are not yet fully understood.

Görbitz (1989), analysing N—H···O hydrogen bonds in amino acids and peptides, has shown that the intermolecular N···O distances are affected by the ionization of both hydrogen-bond acceptor and donor groups, ranging (on average) from 2.840 (6) Å for $NH_3^+\cdots{}^-OOC$ to 2.929 (9) Å for the interaction between N—H···O=C neutral groups. These results stress the importance of charges present on the atoms involved but, at the same time, indicate that having the donor and acceptor groups ionized is not enough to produce short N···O distances (2.70 Å), as observed in some strong intermolecular N—H···O bonds. It has also been recently suggested (Bertolasi, Ferretti, Gilli, Gilli, Issa & Sherif, 1993; Bertolasi, Nanni, Gilli, Ferretti, Gilli, Issa & Sherif, 1994; Bertolasi, Gilli, Ferretti & Gilli, 1994) that such very short N···O distances may depend on the NH and O partial charges, but only when they are generated by π-delocalization within a conjugated moiety connecting the two groups. Studies on the intramolecular N—H···O bond in ketohydrazones have in fact shown that the strengthening of the hydrogen bond is directly connected to the degree of π-delocalization along the O=C—C=N—NH*R* heterodienic chain ending with the N—H and C=O groups, suggesting that the N—H···O bond in these resonant systems is strictly similar to the O—H···O resonance-assisted hydrogen bonding (RAHB) proposed to explain the strong hydrogen-bond formation in β-diketone enols (Gilli, Bellucci, Ferretti & Bertolasi, 1989; Bertolasi, Gilli, Ferretti & Gilli, 1991; Gilli, Bertolasi, Ferretti & Gilli, 1993, 1994).

The main goal of this paper is to try to prove that the concept of RAHB is straightforwardly extensible to all conjugated (or resonant) intermolecular N—H···O hydrogen bonds by showing that conjugation is the most important factor determining their strengths and ways of affecting the molecular packing in neutral systems. The analysis is extended to amides, which are the simplest molecules able to give resonant hydrogen-bonded dimers or chains (Leiserowitz & Tuval, 1978; Berkovitch-Yellin & Leiserowitz, 1980) and to a variety of larger fragments where the NH and C=O groups are separated by an increasing odd number of carbons (or nitrogens) connected by alternating single or double bonds, *e.g.* enaminones (O=C—C=C—NH*R*), ketohydrazones (O=C—C=N—NH*R*) or more extended systems, and whose general formula can be related to the resonance forms (I*a*)⟷(I*b*) or, more generally (II), where *X* is a C or, sometimes, a N atom, *N* is a positive integer including zero and $n = 2N + 1$ is the total

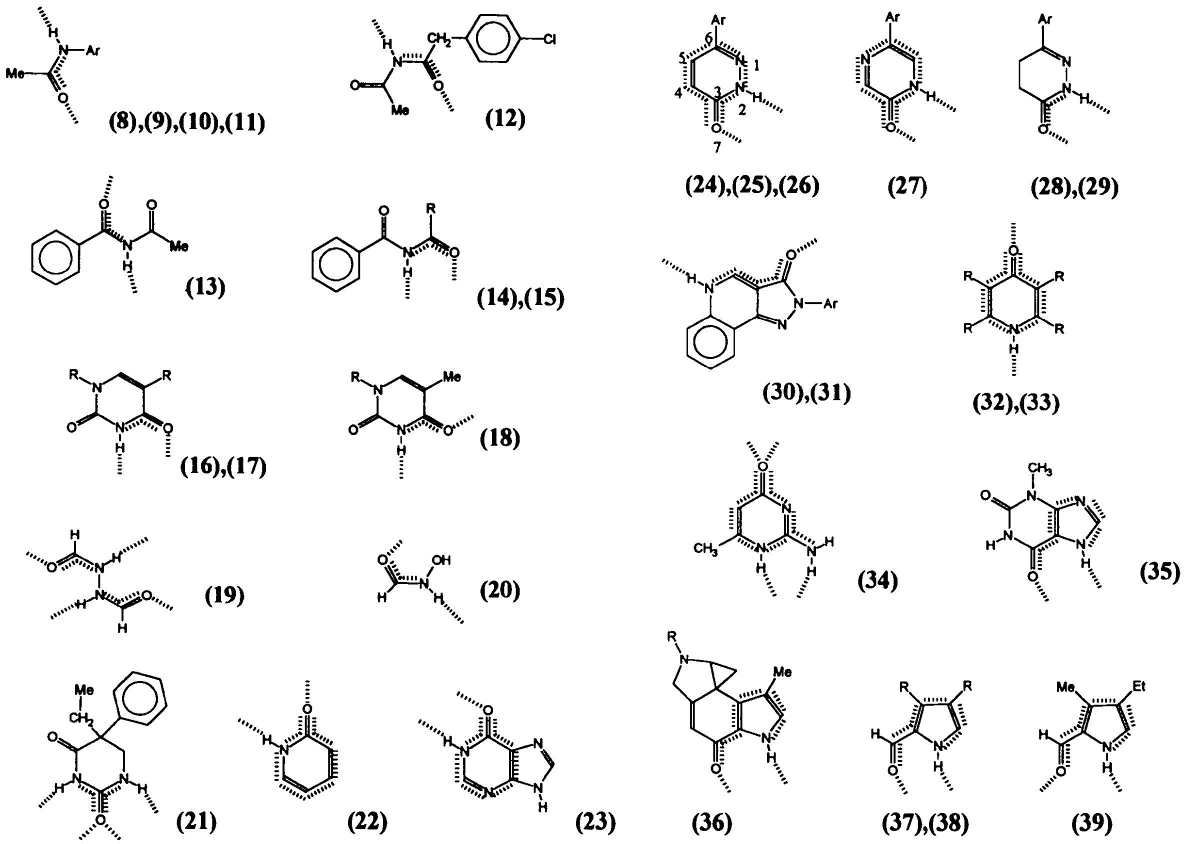

Fig. 2. Chemical formulae of compounds (8)–(39), which have been retrieved from the literature. The hatchings indicate the π-conjugated systems.

Table 1. *Crystal data*

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Formula	$C_{10}H_{11}NO$	$C_{11}H_{13}NO$	$C_{11}H_{13}NO_3$	$C_{14}H_{11}NO_2$	$C_{20}H_{18}N_4O$	$C_{16}H_{10}NO_2Cl$	$C_{13}H_{13}N_5O$
M_r	161.20	175.23	207.23	225.25	330.39	283.70	255.28
Crystal size (mm^3)	0.12 × 0.24 × 0.45	0.19 × 0.43 × 0.50	0.14 × 0.43 × 0.60	0.24 × 0.40 × 0.45	0.19 × 0.19 × 0.52	0.10 × 0.31 × 0.60	0.12 × 0.17 × 0.47
Space group	*Pbca*	$P\bar{1}$	*Pbca*	*Iba*2	$P2_1/a$	$P2_1/c$	$C2/c$
Crystal system	Orthorhombic	Triclinic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
a (Å)	9.132 (3)	10.004 (3)	9.469 (2)	8.469 (1)	11.793 (4)	4.823 (1)	18.970 (3)
b (Å)	12.931 (3)	10.482 (3)	8.530 (3)	15.783 (2)	7.920 (1)	22.371 (3)	5.770 (2)
c (Å)	15.514 (5)	11.506 (4)	27.149 (3)	9.003 (1)	18.366 (2)	11.814 (3)	23.578 (4)
α (°)	90	114.54 (2)	90	90	90	90	90
β (°)	90	111.28 (2)	90	90	100.01 (2)	97.04 (2)	97.22 (2)
γ (°)	90	88.16 (3)	90	90	90	90	90
V (Å^3)	1832.0 (9)	1013 (1)	2192.9 (9)	1203.4 (2)	1689.3 (6)	1265.1 (4)	2560 (1)
Z	8	4	8	4	4	4	8
D_x (Mg m^{-3})	1.17	1.15	1.26	1.24	1.30	1.49	1.32
F (000)	688	376	880	472	696	584	1072
μ (Mo $K\alpha$) (mm^{-1})	0.072	0.069	0.086	0.078	0.078	0.297	0.084
Independent reflections	1994	4417	2581	926	4075	2750	4354
Observed reflections (N_o)	602 [$I \geq 2\sigma(I)$]	2025 [$I \geq 2\sigma(I)$]	1263 [$I \geq 3\sigma(I)$]	625 [$I \geq 3\sigma(I)$]	2142 [$I \geq 3\sigma(I)$]	1792 [$I \geq 3\sigma(I)$]	1834 [$I \geq 3\sigma(I)$]
$\theta_{\min} - \theta_{\max}$ (°)	2–27	2–27	2–28	2–28	2–28	2–27	2–26
hkl ranges	0–11; 0–16; 0–19	0–12; −12–12; −14–14	0–12; 0–11; 0–35	0–11; 0–20; 0–12	0–15; −10–0; −24–24	0–8; 0–28; −15–15	0–23; 0–6; −27–27
*R**	0.054	0.057	0.040	0.034	0.044	0.045	0.043
wR†	0.055	0.077	0.046	0.044	0.052	0.053	0.049
p‡	0.04	0.07	0.03	0.04	0.04	0.04	0.04
No. of variables (N_v)	153	313	188	106	298	221	224
N_o/N_v	3.9	6.5	6.7	5.9	7.2	8.1	8.2
Max. shift/error	0.04	0.05	0.02	0.01	0.04	0.02	0.05
GOF§	1.64	1.60	1.75	1.50	1.59	1.66	1.44
Largest ΔF peak (e Å^{-3})	0.16	0.22	0.125	0.078	0.17	0.28	0.10

* $R = \Sigma|\Delta F|/\Sigma|F_o|$.
† $wR = (\Sigma w|\Delta F|^2/\Sigma w|F_o|^2)^{1/2}$.
‡ $w = 4F_o^2/[\sigma^2(F_o^2) + (pF_o^2)^2]$.
§ $\mathrm{GOF} = \Sigma|\Delta F|/(N_o - N_v)$.

number of C/N atoms in the *resonant spacer* R_n. For this purpose the present paper reports the crystal structures of seven compounds (Fig. 1) forming different molecular aggregates by means of resonant intermolecular N—H···O hydrogen bonds, together with a systematic analysis of the structures of a number of crystals whose packing is affected by this type of bond (Fig. 2).

$$\underset{(\mathrm{I}a)}{\mathrm{O{=}}X(\mathrm{-}X\mathrm{=}X)_N\mathrm{-NH}} \longleftrightarrow \underset{(\mathrm{I}b)}{\mathrm{O^-{-}}X(\mathrm{=}X\mathrm{-}X)_N\mathrm{=NH^+}}$$

$$\mathrm{O{=}}R_n\mathrm{-NH} \qquad (n = 2N + 1) \quad (\mathrm{II})$$

Experimental

The syntheses of (1), (2) and (7) have been described elsewhere (Cavicchioni, Scrimin, Veronese, Balboni & D'Angeli, 1982; Baraldi, Casolari, Guarneri, Manfredini, Pollini, Simoni & Zanirato, 1988) and crystals have been kindly provided by the authors. Compounds (3) and (6) were purchased from Aldrich Chemical Co. and (4) and (5) synthesized by the methods described in the literature (Titherley, 1904; Djerrari, Essassi & Fifani, 1991). Final structural data for (4) are statistically indistinguishable from those already determined by Mizrahi & Niven (1983), in spite of the rather high discrepancy factor of 0.75 given by these authors. The crystal structure of (4) has also been determined as part of its mixed crystal with triphenylphosphine oxide (Etter & Reutzel, 1991).

Crystal data, data collection and refinement details are given in Table 1.[*] All X-ray diffraction data were collected at room temperature on an Enraf–Nonius CAD-4 diffractometer using graphite monochromated Mo*Kα* radiation ($\lambda = 0.71069$ Å) with $\omega/2\theta$ scans. Lattice constants were determined by least-squares fitting of the setting angles of 25 reflections in the range $10 < \theta < 14°$. Intensities of three standard reflections were measured every 2 h and did not show significant variations for any of the seven compounds investigated. All intensities were corrected for Lorentz and polarization. Scattering factors were taken from *International Tables for X-ray Crystallography* (Cromer & Waber, 1974). The structures were solved by direct methods using the *SIR*88 (Burla, Camalli, Cascarano, Giacovazzo, Polidori, Spagna & Viterbo, 1989) system of programs and refined by full-matrix least squares. Compounds (1) and (3)–(7) were refined with anisotropic non-H atoms and isotropic H atoms. In (2) the asymmetric unit is formed by two molecules *A* and *B*; both molecules were refined in the usual way with the exception of the

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[*] Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA0069). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

disordered atoms C(1*B*) and C(3*B*), which were refined isotropically over two positions with 0.5 occupancy; the H atoms bonded to C(1*B*) and C(3*B*) were assigned fixed calculated positions. All calculations were performed using *MolEN* (Fair, 1990) and *PARST* (Nardelli, 1983).

Results and discussion

Final coordinates are given in Table 2, a selection of bond distances and angles is reported in Table 3, and hydrogen-bond parameters in Table 4. *ORTEP* (Johnson, 1976) views of the molecules, as well as of their intermolecular N—H···O hydrogen-bond motifs, are shown in Figs. 3–9. Table 5 reports the most important hydrogen-bond parameters for (1)–(7) and for a selection of other structures retrieved from the literature whose chemical formulae are shown in Fig. 2.

In Table 5 the hydrogen-bonded structures are named according to three methods: (*a*) by the symbols *chain* or *ring*, according to whether they are open or closed, and by the symbol R_n, which indicates the length of the resonant spacer (II) (R_1 for amides, R_3 for O=*X*—*X*=*X*—NH and R_5 for O=*X*—*X*=*X*—*X*=*X*—NH); (*b*) by the symbology proposed by Etter, MacDonald & Bernstein (1990); (*c*) by the same symbology but taking into account the effect of conjugation (*vide infra*). The 39 structures listed in Table 5 allow to define ten different types of R_n-rings or R_n-chains, which are summarized and displayed in Figs. 10(*a*)–(*k*).

According to RAHB rules (Gilli *et al.*, 1989, 1994) the strengthening of the N—H···O bond is to be associated with an increased contribution of (I*b*) to the ground state of the fragment, that is with a shortening and lengthening of all single- and double-bond distances, respectively. In the present case resonant chains contain different atoms (C or N) which may be included in rings of different dimensions and/or connected to other functional groups; moreover, there are resonant arrangements including more than one C—N bond for a single C=O bond. For this reason only the C=O distances have been chosen as indicators of π-delocalization within the fragment and Fig. 11 reports the scatterplot of N···O *versus* C=O distances for all compounds listed in Table 5.

In (1)–(3) and (8)–(13) amidic groups form infinite chains [R_1-chains or C(4) according to the nomenclatures chosen] of molecules linked by N—H···O bonds, while (14)–(17) and (28) and (29) are coupled in hydrogen-bonded dimers [R_1-rings or $R_2^2(8)$]. N···O distances range from 2.810 to 3.000 Å; they cannot be considered particularly short, but are on the short-distance side of the interval of 2.90–3.30 Å for non-resonant N—H···O bonds evaluated by a CSD (Cambridge Structural Database: Allen, Bellard, Brice, Cartwright, Doubleday, Higgs, Hummelink, Hummelink-Peters, Kennard, Motherwell, Rodgers & Watson, 1979) search on the $(Csp^3)_2N—H\cdots O=C(Csp^3)_2$ bonds observed in 42 structures of good accuracy.

Table 2. *Atomic coordinates and equivalent isotropic thermal parameters* (Å^2) *with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)\sum_i \sum_j B_{ij}\mathbf{a}_i\mathbf{a}_j$$

	x	*y*	*z*	B_{eq}/B
(1) 2-Methyl-*N*-phenylprop-2-enamide				
O(1)	0.6394 (3)	0.0939 (3)	0.6765 (2)	7.21 (8)
N(1)	0.8436 (3)	0.1385 (2)	0.7496 (3)	5.22 (6)
C(1)	1.0086 (5)	0.0248 (4)	0.6279 (3)	9.2 (1)
C(2)	0.8592 (4)	0.0129 (4)	0.6345 (3)	5.8 (1)
C(3)	0.7831 (5)	−0.0657 (4)	0.5895 (3)	8.4 (1)
C(4)	0.7721 (4)	0.0842 (3)	0.6878 (3)	5.3 (1)
C(5)	0.7838 (4)	0.2105 (3)	0.8082 (3)	4.9 (1)
C(6)	0.6725 (4)	0.2765 (3)	0.7831 (3)	6.7 (1)
C(7)	0.6182 (6)	0.3454 (4)	0.8426 (4)	9.4 (2)
C(8)	0.6697 (6)	0.3471 (4)	0.9250 (4)	10.1 (2)
C(9)	0.7812 (6)	0.2844 (4)	0.9481 (3)	8.3 (1)
C(10)	0.8409 (5)	0.2153 (3)	0.8905 (3)	6.2 (1)
H(N1)	0.924 (3)	0.117 (2)	0.762 (2)	5.0 (8)*
(2) 2-Methyl-*N*-benzylprop-2-enamide				
O(1*A*)	0.2215 (2)	0.8739 (2)	0.2018 (2)	6.05 (6)
N(1*A*)	0.4503 (2)	0.8649 (2)	0.2176 (2)	4.62 (6)
C(1*A*)	0.5366 (4)	1.1424 (4)	0.4323 (4)	7.7 (1)
C(2*A*)	0.3922 (3)	1.0785 (3)	0.3691 (3)	4.84 (8)
C(3*A*)	0.2839 (4)	1.1468 (4)	0.4106 (4)	8.9 (1)
C(4*A*)	0.3477 (3)	0.9305 (3)	0.2569 (2)	4.18 (7)
C(5*A*)	0.4264 (3)	0.7213 (3)	0.1127 (3)	5.10 (8)
C(6*A*)	0.4689 (3)	0.6165 (3)	0.1727 (3)	4.48 (7)
C(7*A*)	0.3744 (3)	0.5559 (4)	0.2030 (4)	6.7 (1)
C(8*A*)	0.4181 (4)	0.4638 (4)	0.2622 (4)	8.5 (1)
C(9*A*)	0.5556 (4)	0.4264 (4)	0.2878 (4)	7.6 (1)
C(10*A*)	0.6489 (4)	0.4850 (4)	0.2573 (3)	6.2 (1)
C(11*A*)	0.6070 (3)	0.5784 (3)	0.2010 (3)	5.05 (8)
H(N1*A*)	0.536 (3)	0.908 (2)	0.260 (2)	4.6 (6)*†
O(1*B*)	−0.2420 (2)	0.9295 (2)	0.2913 (2)	6.34 (6)
N(1*B*)	−0.0333 (2)	0.8730 (3)	0.2683 (2)	5.23 (6)
C(1*B*)	−0.1734 (8)	0.8949 (7)	0.0081 (7)	8.3 (2)*†
C(1*B*′)	−0.1057 (8)	0.9508 (8)	0.0492 (7)	5.0 (2)*†
C(2*B*)	−0.1935 (3)	0.9717 (3)	0.1234 (3)	5.54 (9)
C(3*B*)	−0.2731 (7)	1.0967 (6)	0.1404 (6)	6.7 (1)*†
C(3*B*′)	−0.3219 (11)	1.0398 (10)	0.0993 (10)	8.0 (3)*†
C(4*B*)	−0.1584 (3)	0.9234 (3)	0.2333 (3)	4.56 (7)
C(5*B*)	0.0128 (3)	0.8213 (3)	0.3731 (3)	5.58 (9)
C(6*B*)	0.0209 (3)	0.6649 (3)	0.3194 (2)	4.24 (7)
C(7*B*)	−0.0320 (3)	0.5722 (3)	0.1812 (3)	4.78 (8)
C(8*B*)	−0.0251 (3)	0.4292 (3)	0.1398 (3)	5.70 (9)
C(9*B*)	0.0337 (4)	0.3774 (4)	0.2346 (3)	6.7 (1)
C(10*B*)	0.0879 (4)	0.4686 (4)	0.3724 (3)	7.3 (1)
C(11*B*)	0.0820 (4)	0.6103 (3)	0.4147 (3)	6.01 (9)
H(N1*B*)	0.016 (3)	0.878 (2)	0.231 (2)	4.8 (6)*
(3) *p*-Methoxyacetoacetanilide				
O(1)	0.6452 (2)	0.3365 (2)	0.33295 (7)	8.38 (5)
O(2)	0.7922 (1)	0.4997 (2)	0.24309 (5)	6.03 (4)
O(3)	0.6452 (2)	0.3324 (2)	0.01704 (5)	6.05 (4)
N(1)	0.5695 (1)	0.4915 (2)	0.21391 (6)	4.01 (3)
C(1)	0.6141 (2)	0.4714 (3)	0.33826 (8)	4.80 (5)
C(2)	0.5806 (3)	0.5347 (4)	0.3876 (1)	8.24 (8)
C(3)	0.6086 (2)	0.5839 (2)	0.29634 (8)	4.31 (5)
C(4)	0.6651 (2)	0.5212 (2)	0.24895 (7)	4.03 (4)
C(5)	0.5958 (2)	0.4466 (2)	0.16462 (7)	3.64 (4)
C(6)	0.5040 (2)	0.4990 (2)	0.12829 (8)	4.02 (4)
C(7)	0.5228 (2)	0.4591 (2)	0.08017 (8)	4.46 (5)
C(8)	0.6348 (2)	0.3644 (2)	0.06644 (7)	4.33 (4)
C(9)	0.7263 (2)	0.3114 (3)	0.10199 (8)	4.76 (5)
C(10)	0.7068 (2)	0.3508 (3)	0.15076 (8)	4.43 (4)
C(11)	0.7582 (3)	0.2373 (4)	0.00124 (9)	8.20 (8)
H(N1)	0.487 (2)	0.514 (2)	0.2204 (6)	4.3 (4)*
(4) Dibenzamide				
N	1/2	1/2	0.0	4.21 (4)
O	0.4320 (2)	0.42028 (9)	−0.2012 (2)	5.42 (3)
C(1)	0.4111 (2)	0.4389 (1)	−0.0713 (2)	3.92 (3)
C(2)	0.2890 (2)	0.3945 (1)	0.0189 (2)	4.03 (3)
C(3)	0.2108 (3)	0.4328 (2)	0.1355 (3)	5.86 (5)
C(4)	0.0927 (3)	0.3879 (2)	0.2103 (3)	7.46 (7)

Table 2 (*cont.*)

	x	*y*	*z*	B_{eq}/B
C(5)	0.0567 (3)	0.3076 (2)	0.1713 (3)	6.87 (6)
C(6)	0.1348 (3)	0.2690 (1)	0.0578 (3)	6.34 (5)
C(7)	0.2486 (2)	0.3128 (1)	−0.0191 (2)	5.00 (4)
H(N)	1/2	1/2	0.091 (3)	3.8 (5)*
(5) 3-Methyl-4-(3′-methyl-1′-phenyl-pyrazol-5′-yl)-1-phenyl-4-pyrazolin-5-one				
O(1)	0.8226 (1)	0.2823 (2)	0.78503 (8)	4.23 (4)
N(1)	0.5405 (1)	0.1498 (2)	0.76139 (9)	2.98 (4)
N(2)	0.6365 (1)	0.2253 (2)	0.80291 (9)	2.84 (3)
N(3)	0.8824 (1)	0.0512 (2)	0.57023 (9)	3.50 (4)
N(4)	0.8410 (1)	0.0420 (2)	0.63525 (9)	2.97 (4)
C(1)	0.7249 (2)	0.2241 (3)	0.7619 (1)	2.92 (4)
C(2)	0.6777 (2)	0.1466 (3)	0.6931 (1)	2.75 (4)
C(3)	0.5646 (2)	0.1087 (3)	0.6949 (1)	2.80 (4)
C(4)	0.7380 (2)	0.1257 (3)	0.6305 (1)	2.88 (4)
C(5)	0.7136 (2)	0.1874 (3)	0.5601 (1)	3.45 (5)
C(6)	0.8049 (2)	0.1390 (3)	0.5252 (1)	3.47 (5)
C(7)	0.4746 (2)	0.0328 (3)	0.6380 (1)	4.01 (5)
C(8)	0.6369 (2)	0.2734 (3)	0.8770 (1)	3.00 (4)
C(9)	0.5508 (2)	0.2166 (4)	0.9133 (1)	4.24 (6)
C(10)	0.5492 (2)	0.2682 (4)	0.9847 (1)	5.63 (7)
C(11)	0.6321 (2)	0.3732 (4)	1.0207 (1)	5.64 (7)
C(12)	0.7182 (2)	0.4270 (4)	0.9851 (1)	5.29 (7)
C(13)	0.7212 (2)	0.3785 (3)	0.9132 (1)	4.31 (5)
C(14)	0.8235 (2)	0.1767 (4)	0.4483 (1)	5.15 (6)
C(15)	0.9047 (2)	−0.0502 (3)	0.6946 (1)	2.97 (4)
C(16)	1.0239 (2)	−0.0421 (3)	0.7070 (1)	3.60 (5)
C(17)	1.0863 (2)	−0.1314 (3)	0.7646 (2)	4.62 (6)
C(18)	1.0320 (2)	−0.2300 (3)	0.8092 (2)	5.18 (6)
C(19)	0.9147 (2)	−0.2417 (3)	0.7958 (1)	4.87 (6)
C(20)	0.8500 (2)	−0.1520 (3)	0.7389 (1)	3.80 (5)
H(N1)	0.470 (2)	0.178 (3)	0.770 (1)	4.8 (5)*
(6) 3-Anilino-2-chloro-1,4-naphthoquinone				
Cl(1)	−0.0938 (1)	0.24209 (3)	0.47778 (5)	3.21 (1)
O(1)	0.2417 (4)	0.1390 (1)	0.5465 (2)	4.17 (4)
O(2)	0.4824 (4)	0.2252 (1)	0.1500 (2)	4.37 (5)
N(1)	0.1532 (5)	0.2901 (1)	0.2595 (2)	3.44 (5)
C(1)	0.2881 (5)	0.1580 (1)	0.4532 (2)	2.94 (5)
C(2)	0.1620 (5)	0.2119 (1)	0.4041 (2)	2.68 (5)
C(3)	0.2358 (5)	0.2380 (1)	0.3075 (2)	2.68 (5)
C(4)	0.4257 (5)	0.2038 (1)	0.2384 (2)	3.02 (5)
C(5)	0.5341 (5)	0.1454 (1)	0.2803 (2)	2.94 (5)
C(6)	0.4762 (5)	0.1240 (1)	0.3854 (2)	3.02 (5)
C(7)	0.5939 (6)	0.0708 (1)	0.4270 (3)	3.97 (6)
C(8)	0.7618 (7)	0.0385 (2)	0.3632 (3)	4.52 (7)
C(9)	0.8132 (7)	0.0588 (2)	0.2578 (3)	4.66 (7)
C(10)	0.7042 (6)	0.1124 (1)	0.2166 (2)	3.94 (6)
C(11)	0.0392 (5)	0.3402 (1)	0.3096 (2)	3.25 (5)
C(12)	0.1548 (6)	0.3615 (2)	0.4144 (2)	4.14 (6)
C(13)	0.0419 (8)	0.4102 (2)	0.4601 (3)	5.34 (7)
C(14)	−0.1826 (8)	0.4389 (2)	0.4018 (3)	6.07 (8)
C(15)	−0.2934 (7)	0.4187 (2)	0.2963 (3)	5.56 (8)
C(16)	−0.1822 (6)	0.3696 (2)	0.2483 (3)	4.10 (6)
H(N1)	0.202 (5)	0.297 (1)	0.194 (2)	3.9 (6)*
(7) 3-Phenethyl-7-methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-one				
N(1)	0.1214 (1)	−0.1928 (3)	0.45018 (7)	4.89 (5)
N(2)	0.15869 (9)	−0.1567 (3)	0.49845 (8)	4.69 (4)
N(3)	0.14506 (9)	0.0344 (3)	0.53048 (7)	3.93 (4)
C(4)	0.0935 (1)	0.2022 (4)	0.51716 (9)	3.80 (5)
O(4)	0.08558 (8)	0.3618 (3)	0.55039 (6)	4.85 (4)
N(5)	−0.00110 (9)	0.2632 (3)	0.43370 (7)	4.31 (4)
N(6)	−0.02356 (9)	0.1478 (3)	0.38415 (7)	4.54 (4)
C(7)	0.0183 (1)	−0.0331 (4)	0.38276 (9)	4.31 (5)
C(8)	0.0684 (1)	−0.0363 (4)	0.43220 (9)	3.93 (5)
C(9)	0.0540 (1)	0.1536 (4)	0.46324 (8)	3.62 (5)
C(10)	0.0090 (1)	−0.2010 (5)	0.3344 (1)	6.25 (6)
C(11)	0.1920 (1)	0.0515 (4)	0.58485 (9)	4.30 (5)
C(12)	0.2518 (1)	0.2224 (4)	0.58233 (9)	4.77 (6)
C(13)	0.2906 (1)	0.2641 (4)	0.64106 (9)	4.08 (5)
C(14)	0.3431 (1)	0.1184 (5)	0.6639 (1)	6.54 (7)
C(15)	0.3764 (1)	0.1492 (5)	0.7189 (1)	7.51 (7)
C(16)	0.3582 (1)	0.3263 (5)	0.7514 (1)	6.18 (7)
C(17)	0.3062 (2)	0.4744 (5)	0.7295 (1)	6.97 (5)
C(18)	0.2726 (2)	0.4438 (4)	0.6747 (1)	7.51 (7)
H(5)	−0.024 (1)	0.381 (4)	0.443 (1)	5.9 (5)*

* Refined isotropically.
† Occupancy = 0.5.

Table 3. *Selected bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

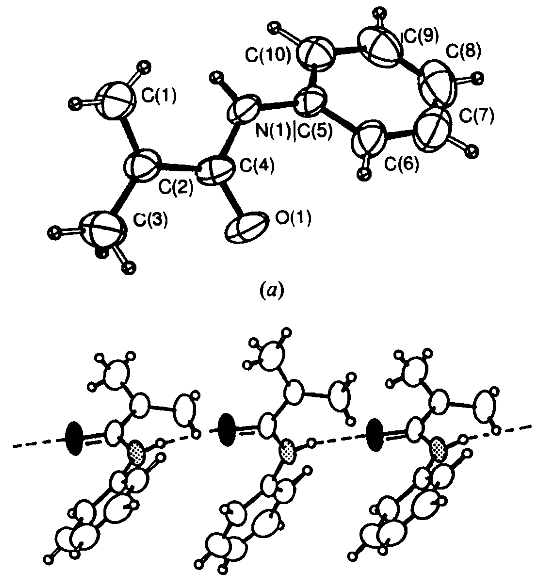
(1)			
N(1)—C(4)	1.356 (5)	C(4)—O(1)	1.231 (4)
N(1)—C(5)	1.411 (5)	C(2)—C(4)	1.472 (5)
C(4)—N(1)—C(5)	127.6 (4)	N(1)—C(4)—C(2)	117.4 (3)
N(1)—C(4)—O(1)	121.5 (4)	C(2)—C(4)—O(1)	121.1 (4)
(2)			
	Molecule *A*		Molecule *B*
N(1)—C(4)	1.329 (4)	N(1)—C(4)	1.333 (4)
N(1)—C(5)	1.444 (3)	N(1)—C(5)	1.443 (5)
C(4)—O(1)	1.226 (3)	C(4)—O(1)	1.232 (4)
C(2)—C(4)	1.495 (3)	C(2)—C(4)	1.475 (5)
C(4)—N(1)—C(5)	124.0 (2)	C(4)—N(1)—C(5)	123.4 (3)
N(1)—C(4)—O(1)	121.7 (2)	N(1)—C(4)—O(1)	120.8 (3)
N(1)—C(4)—C(2)	116.9 (2)	N(1)—C(4)—C(2)	118.1 (3)
C(2)—C(4)—O(1)	121.4 (3)	C(2)—C(4)—O(1)	121.1 (3)
(3)			
N(1)—C(4)	1.337 (2)	C(3)—C(4)	1.493 (3)
N(1)—C(5)	1.414 (2)	C(1)—C(3)	1.490 (3)
C(4)—O(2)	1.228 (2)	C(1)—O(1)	1.196 (3)
C(5)—N(1)—C(4)	127.2 (1)	C(3)—C(4)—O(2)	121.1 (2)
N(1)—C(4)—O(2)	122.9 (2)	C(1)—C(3)—C(4)	114.5 (2)
N(1)—C(4)—C(3)	116.0 (2)	C(3)—C(1)—O(1)	122.4 (2)
(4)			
N—C(1)	1.381 (2)	C(1)—C(2)	1.491 (3)
C(1)—O	1.219 (2)		
N—C(1)—O	122.4 (2)	C(1)—N—C(1′)	124.6 (1)
C(2)—C(1)—O	120.7 (2)	N—C(1)—C(2)	117.0 (1)
(5)			
N(1)—C(3)	1.341 (3)	C(2)—C(4)	1.463 (3)
N(1)—N(2)	1.386 (2)	N(3)—N(4)	1.368 (2)
N(2)—C(8)	1.412 (2)	N(3)—C(6)	1.319 (2)
C(1)—O(1)	1.245 (3)	N(4)—C(4)	1.373 (3)
C(1)—N(2)	1.388 (3)	N(4)—C(15)	1.415 (2)
C(1)—C(2)	1.428 (3)	C(4)—C(5)	1.365 (3)
C(2)—C(3)	1.373 (3)	C(5)—C(6)	1.399 (3)
C(3)—N(1)—N(2)	108.9 (2)	C(6)—N(3)—N(4)	105.2 (2)
N(1)—N(2)—C(1)	108.5 (2)	N(3)—N(4)—C(4)	111.4 (2)
N(2)—C(1)—C(2)	105.6 (2)	N(4)—C(4)—C(5)	105.8 (2)
C(1)—C(2)—C(3)	107.7 (2)	C(4)—C(5)—C(6)	106.5 (2)
N(1)—C(3)—C(2)	109.2 (2)	N(3)—C(6)—C(5)	111.2 (2)
(6)			
C(1)—O(1)	1.228 (3)	C(3)—C(4)	1.507 (4)
C(1)—C(2)	1.440 (4)	C(4)—O(2)	1.210 (3)
C(2)—Cl(1)	1.731 (3)	N(1)—C(3)	1.336 (4)
C(2)—C(3)	1.368 (3)	N(1)—C(11)	1.411 (4)
O(1)—C(1)—C(2)	122.5 (2)	C(2)—C(3)—C(4)	118.3 (2)
C(1)—C(2)—C(3)	123.5 (2)	C(3)—C(4)—O(2)	118.9 (3)
N(1)—C(3)—C(2)	129.1 (2)	C(3)—N(1)—C(11)	128.8 (2)
(7)			
N(1)—N(2)	1.279 (2)	N(5)—N(6)	1.366 (2)
N(1)—C(8)	1.378 (3)	N(5)—C(9)	1.340 (2)
N(2)—N(3)	1.379 (2)	N(6)—C(7)	1.314 (3)
N(3)—C(4)	1.384 (3)	C(7)—C(8)	1.408 (3)
C(4)—O(4)	1.230 (3)	C(8)—C(9)	1.364 (3)
C(4)—C(9)	1.420 (3)		
N(2)—N(1)—C(8)	117.9 (2)	N(5)—N(6)—C(7)	106.5 (2)
N(1)—N(2)—N(3)	119.8 (2)	N(6)—C(7)—C(8)	109.7 (2)
N(2)—N(3)—C(4)	127.6 (2)	C(7)—C(8)—C(9)	105.9 (2)
N(3)—C(4)—C(9)	110.1 (2)	N(1)—C(8)—C(9)	123.3 (2)
N(3)—C(4)—O(4)	121.2 (2)	C(4)—C(9)—C(8)	121.3 (2)
C(9)—C(4)—O(4)	128.7 (2)	N(5)—C(9)—C(8)	107.2 (2)
N(6)—N(5)—C(9)	110.7 (2)	C(4)—C(9)—N(5)	131.4 (2)

Table 4. *Hydrogen-bonding parameters* (Å, °) *with e.s.d.'s in parentheses*

	D···*A*	*D*—H	H···O	*D*—H···O
(1)	N(1)···O(1^{i}) 2.991 (4)	N(1)—H 0.80 (5)	H···O(1) 2.21 (5)	N(1)—H···O(1) 164 (2)
(2)	N(1*A*)···O($1B^{ii}$) 2.901 (4)	N(1*A*)—H 0.85 (5)	H···O(1*B*) 2.12 (5)	N(1*A*)—H···O(1*B*) 153 (3)
	N(1*B*)···O($1A^{iii}$) 2.916 (4)	N(1*B*)—H 0.77 (5)	H···O(1*A*) 2.20 (5)	N(1*B*)—H···O(1*A*) 154 (3)
(3)	N(1)···O(2^{iv}) 2.874 (2)	N(1)—H 0.83 (3)	H···O(2) 2.09 (3)	N(1)—H···O(2) 157 (1)
(4)	N···O^{v} 3.025 (2)	N—H 0.82 (3)	H···O 2.33 (2)	N—H···O 144 (1)
(5)	N(1)···O(1^{vi}) 2.733 (2)	N(1)—H 0.90 (2)	H···O(1) 1.83 (2)	N(1)—H···O(1) 175 (2)
(6)	N(1)···O(1^{vii}) 3.049 (3)	N(1)—H 0.85 (3)	H···O(1) 2.28 (2)	N(1)—H···O(1) 150 (2)
(7)	N(5)···O(4^{viii}) 2.746 (2)	N(5)—H 0.85 (2)	H···O(4) 1.90 (2)	N(5)—H···O(4) 169 (2)

Symmetry codes: (i) $\frac{1}{2}+x, y, \frac{3}{2}-z$; (ii) $x+1, y, z$; (iii) x, y, z; (iv) $x-\frac{1}{2}, y, \frac{1}{2}-z$; (v) $x, 1-y, \frac{1}{2}+z$; (vi) $x-\frac{1}{2}, \frac{1}{2}-y, z$; (vii) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (viii) $-x, 1-y, 1-z$.

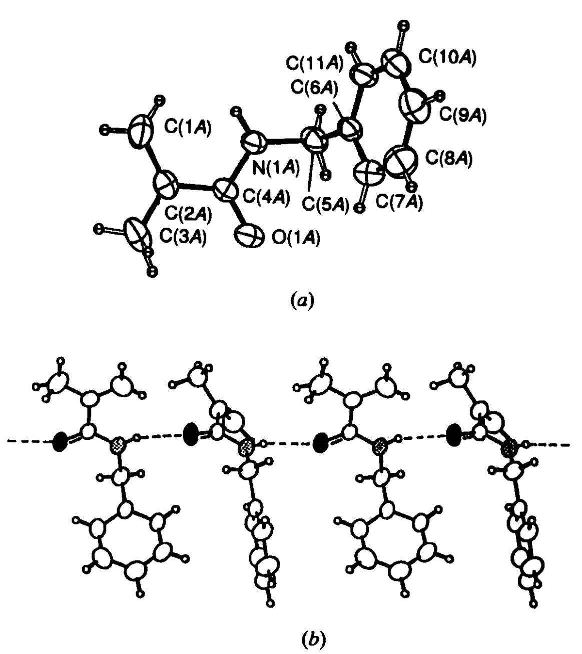
The mutual influence of hydrogen bonding and conjugation in simple amides has been studied using different experimental and theoretical methods (Jeffrey, 1984, 1985; Cheesman, Carroll & Bader, 1988; Popelier, Lenstra, Van Alsenoy & Geise, 1989; Asakawa, Kuroki, Kurosu, Ando, Shoji & Ozaki, 1992). All these studies agree with the conclusions that N—H···O bond formation is associated with the setting up of partial charges which are negative on the oxygen and positive on the NH moiety and with an enhancement of the π-delocalization of the amidic group, implying the lengthening of the C=O and shortening of the C—N



(*a*)

(*b*)

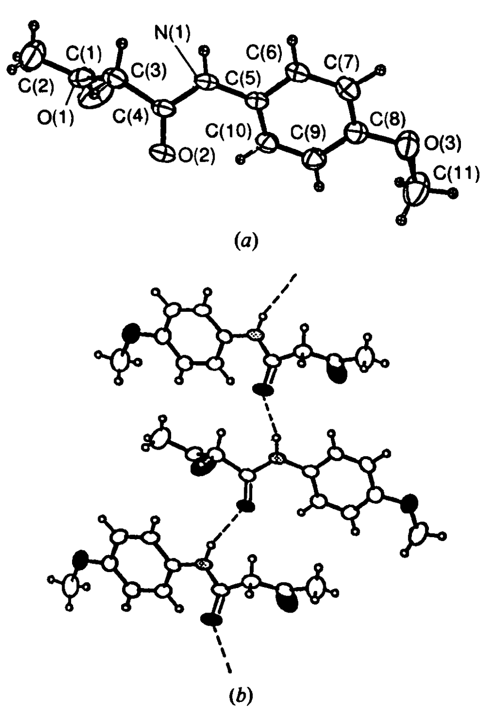
Fig. 3. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for (1). The thermal ellipsoids are drawn at the 30% probability level. (*b*) The hydrogen-bonding arrangement.



(*a*)

(*b*)

Fig. 4. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for one of the two independent molecules of (2). The thermal ellipsoids are drawn at the 30% probability level. (*b*) The hydrogen-bonding arrangement of the two alternating independent molecules.



(*a*)

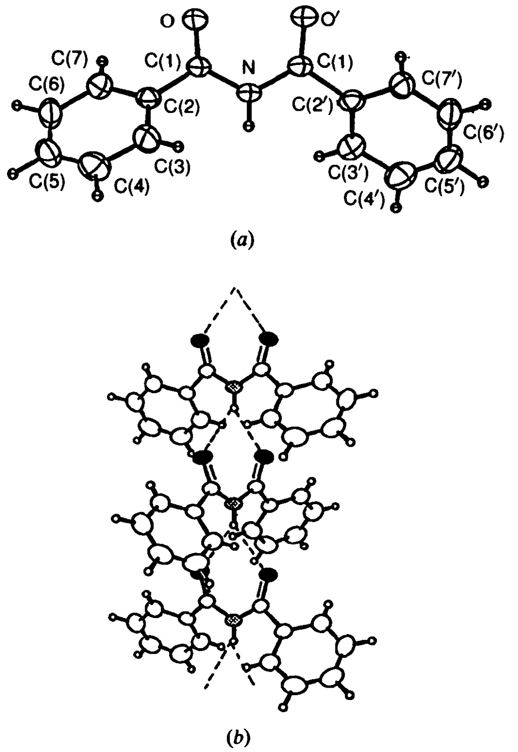
(*b*)

Fig. 5. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for (3). The thermal ellipsoids are drawn at the 30% probability level. (*b*) The hydrogen-bonding arrangement.

distances. These bond-distance effects are not fully verified here, essentially because they are very small and below the limit of accuracy of common crystal structure determinations. In fact, the C—N and C=O distances of 1.346 (11) and 1.229 (9) Å in tertiary amides (where hydrogen bonding is impossible) are only slightly shifted to the respective values of 1.329 (10) and 1.236 (9) Å in secondary and primary amides where the hydrogen bond is always observed (Allen, Kennard, Watson, Bremmer, Orpen & Taylor, 1987). Amides appear, therefore, to be scarcely susceptible to RAHB, most probably because the O=C—NH system is too short for being heavily π-polarizable.

In some cases, however, such polarizability turns out to be increased by specific factors. For example, in uracil derivatives (16–18) the increased polarization of the N—H bond due to vicinal groups causes a further shortening of the intermolecular hydrogen bond in dimers of 1-methyluracyl [16, Fig. 10*b*; $d(\text{C=O}) = 1.241$, $d(\text{N}\cdots\text{O}) = 2.810$ Å] and 1-acetylthymine [17; $d(\text{C=O}) = 1.232$, $d(\text{N}\cdots\text{O}) = 2.837$ Å], or in chains of 3′-*O*-acetylthymidine [18; $d(\text{C=O}) = 1.234$, $d(\text{N}\cdots\text{O}) = 2.857$ Å]. A similar situation is produced by linking to the amide nitrogen an electron rich and easily polarizable atom, such as nitrogen in (19) and oxygen in (20), both displaying unusually strong hydrogen bonds. *N,N*-diformohydrazide (19) contains two amidic groups linked by means of the hydrazinic N—N bridge and forms two antidromic chains of hydrogen bonds related by a centre of symmetry with distances N···O = 2.762 and C=O = 1.238 Å. Analogously, in formohydroxamic acid (20) the nitrogen is bonded to a OH group and the N···O and C=O distances are 2.784 and 1.257 Å, respectively.

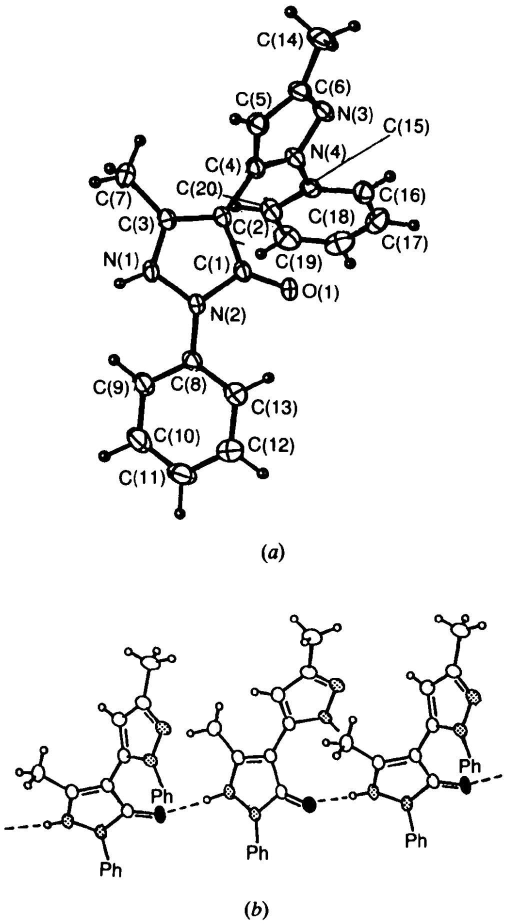
Stronger N—H···O hydrogen bonds occur also when the π-delocalization on the amidic moiety is coupled with and enhanced by other more extended π-conjugated cycles. The packing of 4-deoxyphenobarbital (21, Fig. 10*c*) is characterized by two cyclic intermolecular N—H···O bonds [R_1-rings or $R_2^2(8)$], where the oxygen O(2) is an acceptor of two hydrogen bonds [···H—N(1)—C(2)=O(2)···H—N(1)—C(2)=O(2)··· and ···H—N(3)—C(2)=O(2)···H—N(3)—C(2)=O(2)···] and which are superimposed to two conjugated intertwined hydrogen-bond chains [R_1-chains: ···O(2)=C(2)—N(1)—H···O(2)=C(2)—N(3)—H···]. The resulting C=O lengthening is remarkable (C=O = 1.248 Å), while the N···O hydrogen-bond



(*a*)

(*b*)

Fig. 6. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for (4). The thermal ellipsoids are drawn at the 30% probability level. (*b*) The hydrogen-bonding arrangement.



(*a*)

(*b*)

Fig. 7. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for (5). The thermal ellipsoids are drawn at the 30% probability level. (*b*) The hydrogen-bonding arrangement.

distance becomes 2.820 Å, on average. It is interesting to note that the other C=O group, which is not implied in any hydrogen bonding, is much shorter (C6=O6 = 1.227 Å).

A similar situation is found in hypoxanthine (23, Fig. 10*f*), where the short hydrogen bond N(1)···O(6) of 2.782 Å is assisted by two conjugated systems: the amidic R_1-ring [$R_2^2(8)$] H—N(1)—C(6)=O(6) and a more extended H—N(1)—C(2)=N(3)—C(4)=C(5)—C(6)=O(6) R_5-ring [$R_2^2(16)$] giving origin to a conjugated structure which can be called ($R_1 + R_5$)-ring [$R_2^2(8)R_2^2(16)$]. Other examples of double conjugation due to ($R_1 + R_5$)-rings are given in a recent paper (Prout, Bannister, Burns, Chen, Warrington & Vinter, 1994) reporting the structures of some pyridazinone and pyrazinone derivatives (24)–(29). N···O distances (2.890 and 2.909 Å) are longer in structures (28) and (29), where π-conjugation is confined to the amidic group, but become shorter when two conjugations are superimposed (24)–(27), with values in the range 2.756–2.835 Å. Strictly similar considerations hold when the ($R_1 + R_5$)-group forms chains instead of dimers and a typical example of such an ($R_1 + R_5$)-chain is illustrated for (22) in Fig. 10(*e*), where N···O and C=O distances are 2.761 and 1.251 Å, respectively.

In summary, amides display a rather large spectrum of N···O distances (Table 5 and Fig. 11), the longest ones being generally imputable to steric hindrance, a factor not discussed here but which can become particularly relevant when there is substitution at the amidic nitrogen. The present analysis suggests two reasons for abnormal shortening, *i.e.* substitution by a heteroatom (19 and 20) and accumulation of more than one resonant circuit on the same N—H···O bond (as in 21–27). Conversely, splitting of the resonant chain due to hydrogen-bond bifurcation can account for some very long N···O contacts. For instance, in (4) (Fig. 10*d*) the NH group is engaged in a bifurcated hydrogen bond and, accordingly, the intermolecular N—H···O bond is weaker than usual with a N···O distance of 3.025 Å.

Conjugated systems more extended than amides appear to be more efficient in strengthening the hydrogen bond. Compounds (5) (Fig. 7), (6) (Fig. 8), (30) (Fig. 10*g*) and (31) contain hydrogen-bonded chains of enaminonic O=C—C=C—NH*R* groups [R_3-chains or C(6)]. In comparison with amides, enaminones (5), (30) and (31) display greater π-delocalizations [d(C=O) = 1.245–1.252 Å] coupled with shorter hydrogen bonds having d(N···O) values from 2.694 (the shortest intermolecular bond so far observed) to 2.766 Å. Compound (6) must be considered an exception: its weaker delocalization [d(C=O) = 1.228 Å] and longer intermolecular hydrogen bond [d(N···O) = 3.049 Å] is clearly due to the concomitant presence of a second intramolecular bond which, by sharing the positive charge of the proton on two oxygens, weakens both N—H···O bonds (Taylor, Kennard & Versichel, 1984).

Combinations of the R_3-chain motif are also observed. Pyridone derivatives (32) and (33) for the 2 × R_3-chains displayed in Fig. 10(*h*), where the apparently unique N—H···O bonded chain actually consists of two chains passing on both sides of the six-membered cycle; N···O

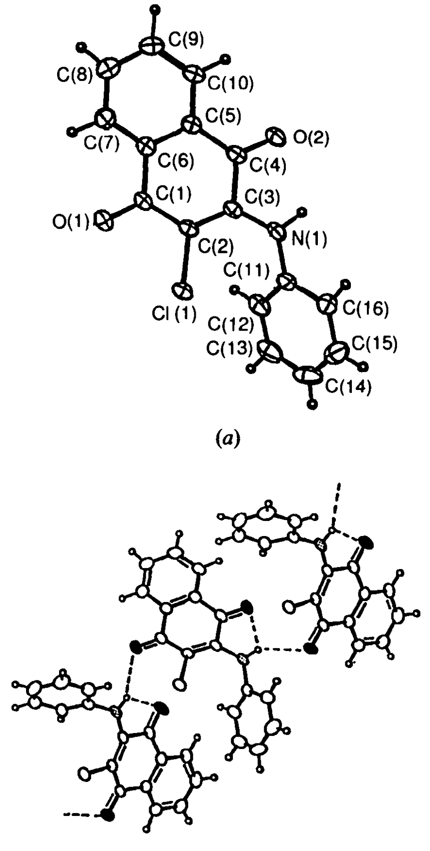


Fig. 8. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for (6). The thermal ellipsoids are drawn at the 30% probability level. (*b*) The hydrogen-bonding arrangement.

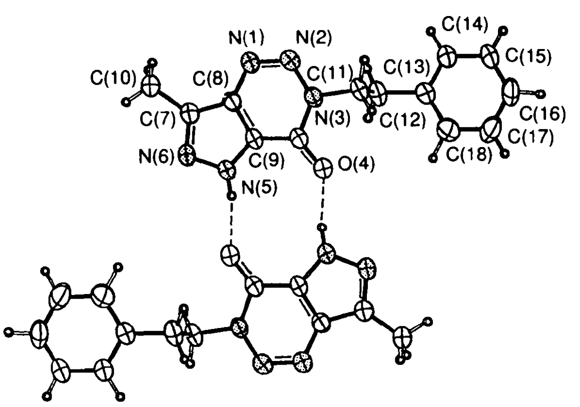


Fig. 9. (*a*) *ORTEP*II (Johnson, 1976) view and atom numbering for the dimer of (7). The thermal ellipsoids are drawn at the 30% probability level.

Table 5. *Structural data for a selection of compounds forming* N—H···O *intermolecular hydrogen bonding*

Bond distances in Å, e.s.d.'s in the range 0.001–0.007 Å. Hydrogen-bond topology: hydrogen-bond connectivities represented by means of: (*a*) our notation described in the text; (*b*) EMB notation (Etter *et al.*, 1990); (*c*) EMB notation but taking into account RAHB (Gilli *et al.*, 1989).

	REFCODE	*d*(C=O)	*d*(N···O)	Hydrogen-bond topology (*a*)	(*b*)	(*c*)	Ref.
(1)		1.231	2.991	R_1-chain	C(4)		Present work
(2)		⟨1.229⟩	⟨2.908⟩	R_1-chain	C(4)		Present work
(3)		1.228	2.874	R_1-chain	C(4)		Present work
(4)		1.219	3.025	2 × (R_1-chain)	$C^2_1(4)[R^2_1(6)]$		Present work
(5)		1.245	2.733	R_3-chain	C(5)	C(6)	Present work
(6)		1.228	3.049	R_3-chain*	C(6)S(5)		Present work
(7)		1.230	2.746	R_5-ring	$R^2_2(10)$	$R^2_2(16)$	Present work
(8)	ACACTA	1.228	2.905	R_1-chain	C(4)		(*a*)
(9)	ACACTB	1.224	2.865	R_1-chain	C(4)		(*a*)
(10)	ACAFLR01	1.234	2.954	R_1-chain	C(4)		(*a*)
(11)	JEPMAS	1.237	2.869	R_1-chain	C(4)		(*b*)
(12)		1.225	2.874	R_1-chain	C(4)		(*c*)
(13)	VIGXEO	1.221	2.910	R_1-chain	C(4)		(*d*)
(14)	VIGXIS	⟨1.212⟩	⟨3.000⟩	R_1-ring	$R^2_2(8)$		(*d*)
(15)	VIGXOY	1.215	2.990	R_1-ring	$R^2_2(8)$		(*d*)
(16)	METURA01	1.241	2.810	R_1-ring	$R^2_2(8)$		(*e*)
(17)	KOTCOL	1.232	2.837	R_1-ring	$R^2_2(8)$		(*f*)
(18)	GEXXIQ	1.234	2.857	R_1-chain	C(4)		(*g*)
(19)	FOMHAZ16	1.238	2.762	(R_1-chain)× 2	C(4)C(4)		(*h*)
(20)	SAGRUN	1.257	2.784	R_1-chain	C(4)		(*i*)
(21)	TAJXAD	⟨1.248⟩	⟨2.820⟩	2 × (R_1-chain) + R_1-ring	C(4)[$R^2_2(8)$]		(*j*)
(22)	PYRIDO04	1.251	2.761	(R_1 + R_5)-chain	C(4)	C(4)C(8)	(*k*)
(23)	GEBTUC	⟨1.246⟩	⟨2.782⟩	(R_1 + R_5)-ring	$R^2_2(8)$	$R^2_2(8)R^2_2(16)$	(*l*)
(24)		1.256	2.795	(R_1 + R_5)-ring	$R^2_2(8)$	$R^2_2(8)R^2_2(16)$	(*m*)
(25)		1.247	2.806	(R_1 + R_5)-ring	$R^2_2(8)$	$R^2_2(8)R^2_2(16)$	(*m*)
(26)		1.243	2.835	(R_1 + R_5)-ring	$R^2_2(8)$	$R^2_2(8)R^2_2(16)$	(*m*)
(27)		1.245	2.756	(R_1 + R_5)-ring	$R^2_2(8)$	$R^2_2(8)R^2_2(16)$	(*m*)
(28)		⟨1.236⟩	⟨2.890⟩	R_1-ring	$R^2_2(8)$		(*m*)
(29)		⟨1.234⟩	⟨2.909⟩	R_1-ring	$R^2_2(8)$		(*m*)
(30)	COVLII	1.252	2.694	R_3-chain	C(6)		(*n*)
(31)	COVLOO	1.250	2.766	R_3-chain	C(6)		(*n*)
(32)	MCHYPY10	1.252	2.753	2 × (R_3-chain)	C(6)	C(6)C(6)	(*o*)
(33)	SAVYAP	⟨1.262⟩	⟨2.705⟩	2 × (R_3-chain)	C(6)	C(6)C(6)	(*p*)
(34)	FETSEC	1.256	2.716	3 × (R_3-chain)	C(6)C(6)[$R^1_2(6)$]	C(6)C(6)C(6)[$R^1_2(6)$]	(*q*)
(35)	FADCUI	1.227	2.734	R_5-ring	$R^2_2(10)$	$R^2_2(16)$	(*r*)
(36)	GEXCOB	1.239	2.757	R_5-ring	$R^2_2(10)$	$R^2_2(16)$	(*s*)
(37)	DASRIY	1.234	2.806	R_5-ring	$R^2_2(10)$	$R^2_2(16)$	(*t*)
(38)	DASRUK	1.222	2.807	R_5-ring	$R^2_2(10)$	$R^2_2(16)$	(*t*)
(39)	DASROE	1.240	2.856	R_5-chain	C(5)	C(8)	(*t*)

⟨ ⟩ average values.

* Bifurcated (three-centre) hydrogen bond.

(8) *p*-Acetanisidide; (9) *N*-2-naphthylacetamide; (10) *N*-2-fluorenylacetamide; (11) *N*-methylnicotinamide; (12) *p*-chloroacetoacetanilide; (13) *N*-acetylbenzamide; (14) *N*-propionylbenzamide; (15) *N*-butyrylbenzamide; (16) 1-methyluracyl; (17) 1-acetylthymine; (18) 3′-*O*-acetylthymidine; (19) *N*,*N*′-diformohydrazide; (20) formohydroxamic acid; (21) 4-deoxyphenobarbital; (22) 2-pyridone; (23) hypoxanthine; (24) 6-(4-aminophenyl)-3(2*H*)-pyridazinone; (25) 6-(4-aminophenyl)-5-methyl-3(2*H*)-pyridazinone; (26) 6-(4-acetamido-2-methoxyphenyl)-3(2*H*)-pyridazinone; (27) 6-phenyl-3(2*H*)-pyrazinone; (28) 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone; (29) (*R*)-(−)-6-[bromopropionamido]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone; (30) 2-phenyl-2,5-dihydropyrazolo-[4,3-*c*]quinolin-3(3*H*)-one; (31) 2-(4-chlorophenyl)-2,5-dihydropyrazolo-[4,3-*c*]quinolin-3(3*H*)-one; (32) 3,5-dichloro-2,6-dimethyl-4-pyridinol; (33) 3,7,11-trioxa-17-azabicyclo(11.3.1)heptadeca-13,16-diene-15-(17*H*)-one; (34) 6-methylcytosine; (35) 3-methylxanthine; (36) 2-(4-chlorobenzoyl)-1,2,8,8a-tetrahydro-7-methyl-(7b*R*)-cyclopropa[c]pyrrolo-[3,2-*e*]indol-4(5*H*)-one; (37) 2-formyl-3-methylpyrrole; (38) 4-chloro-2-formyl-3-methylpyrrole; (39) 4-ethyl-2-formyl-3-methylpyrrole.

(*a*) Haisa, Kashino, Ueno, Shinozaki & Matsuoki (1980); (*b*) Srikrishnan & Parthasarathy (1990); (*c*) Kubozono, Kohno, Ooishi, Namazue, Haisa & Kashino (1992); (*d*) Etter, Britton & Reutzel (1991); (*e*) McMullen & Craven (1989); (*f*) Tari & Secco (1992); (*g*) Eccleston, Wilson & Howie (1988); (*h*) Jeffrey, Ruble, McMullan, De Frees & Pople (1982); (*i*) Kjoller Larsen (1988); (*j*) Mastropaolo, Camerman & Camerman (1991); (*k*) Ohms, Guth, Hellner, Dannöhl & Schweig (1984); (*l*) Schmalle, Hänggi & Dubler (1988); (*m*) Prout *et al.* (1994); (*n*) Ferretti, Bertolasi, Gilli & Borea (1985); (*o*) Boer (1972); (*p*) Bradshaw, Guynn, Wood, Wilson, Dalley & Izatt (1987); (*q*) Lowe, Schwalbe & Williams (1987); (*r*) Low, Tollin, Brand & Wilson (1986); (*s*) Watt, Martin, Duchamp, Mizsak, Nielson & Prairie (1988); (*t*) Smith, Bobe, Minnetian, Hope & Yanuck (1985).

distances register the remarkably short values of 2.70–2.75 Å. Moreover, 6-methylcytosine (34, Fig. 10*i*) can be classified as a 3 × R_3-chain because it displays three different conjugation pathways [O(8)=C(4)—C(5)=C(6)—N(1)—H, O(8)=C(4)—N(3)=C(2)—N(1)—H and O(8)=C(4)—N(3)=C(2)—N(7)—H], all passing through the same oxygen and two of them through the N(1) atom. Not unexpectedly, the N(1)···O(8) distance is very short, 2.716 Å, while N(7)···O(8) is longer, 2.855 Å.

In the remaining examples (7 and 35–39), N···O distances are rather short (2.734–2.856 Å), although the C=O and NH moieties apparently belong to a O=C—C—N—H non-conjugated moiety. This seems to be in disagreement with our previous considerations, which have tried to show that short hydrogen bonds are inevitably coupled with delocalization of a π-conjugated system. A more accurate analysis of bond distances reveals, however, that there are other conjugated chains including a larger number of atoms. This is illustrated in Figs. 9, 10(*k*) and (*j*) for (7), (35) and (39), respectively. In (7) (Fig. 9) and (35) (Fig. 10*k*) the conjugation pathway is along the seven-membered chains H—N(5)—N(6)=C(7)—C(8)=C(9)—C(4)=O(4) and H—N(7)—C(8)=N(9)—C(4)=C(5)—C(6)=O(6), respectively, both passing through the heterocyclic system and closing a resonant ring which, according to (II), can be called an R_5-ring [$R_2^2(16)$]. In (39) (Fig. 10*j*) the resonant chain consists of the H—N(1)—C(5)=C(4)—C(3)=C(2)—C(6)=O(1) seven-membered fragment and, accordingly, is definable as an R_5-chain [C(8)].

The metric aspects of all intermolecular N—H···O bonds previously discussed are summarized in the *d*(N···O) *versus* *d*(C=O) scatterplot of Fig. 11 and in the bar-chart of Fig. 12, which reports the intervals of N···O distances for the 39 cases studied, arranged according to the length of the resonant spacer R_n and compared with the corresponding distances belonging to the set of non-resonant hydrogen bonds previously described. Fig. 12 suggests that, in neutral molecules, intermolecular N—H···O bonds shorter than 2.90 Å must be associated with resonant systems, preferably longer than simple amides. On the other hand, the

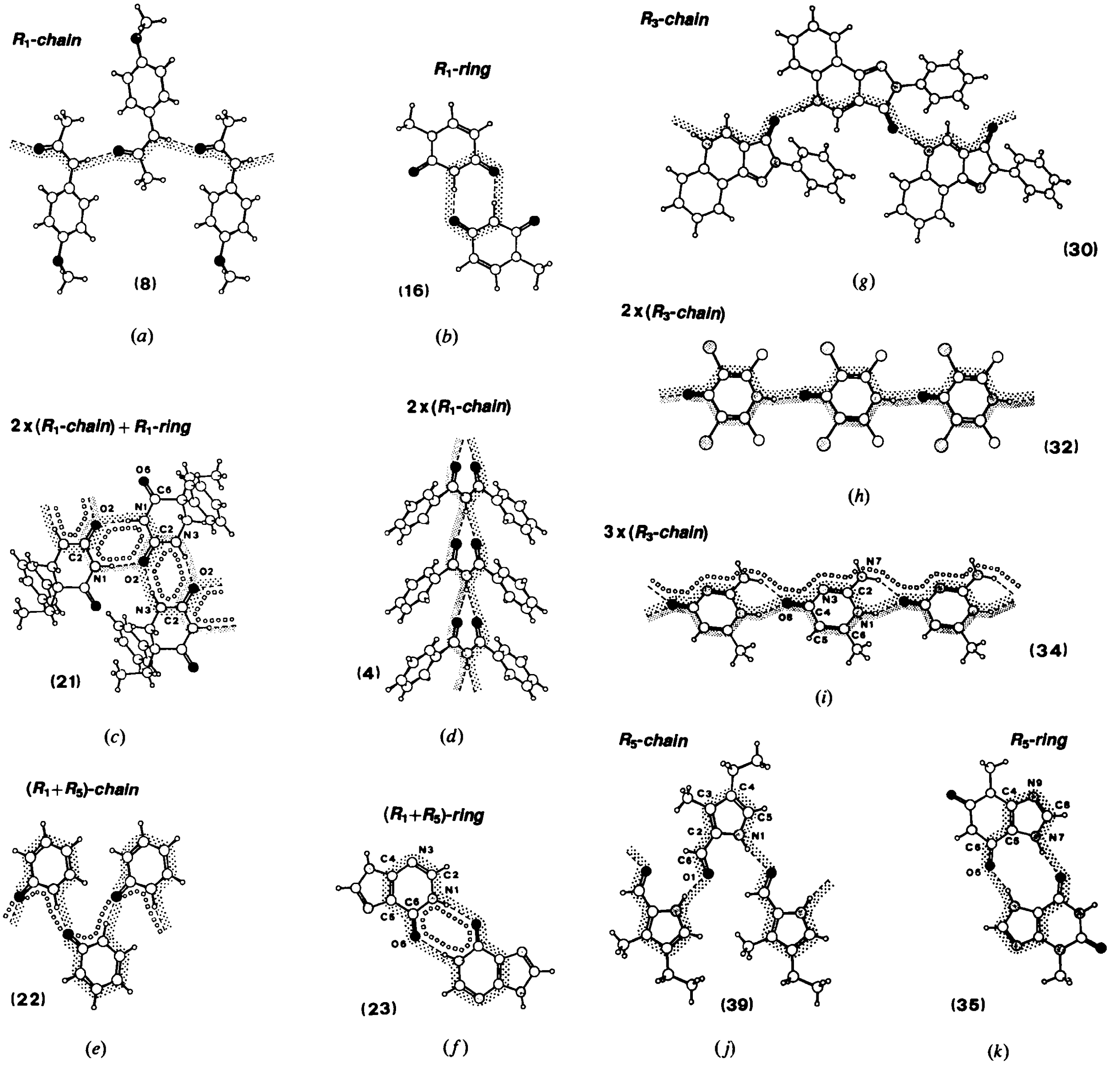


Fig. 10. A summary of the ten different resonant structures (chains or rings) identified by the analysis of the 39 cases of intermolecular N—H···O bonds listed in Table 5. Resonant chains and rings are marked by darker or lighter shading or by lines of small open squares.

scatterplot of Fig. 11 seems to establish a direct relationship between the shortening of the N···O contact distance, a measure of the hydrogen-bond strength and the lengthening of the C═O bond distance, taken as an indicator of π-delocalization in the ···O═R_n—NH··· heteroconjugated system.

Concluding remarks

The aim of this paper was to show that all the shortest (or strongest) N—H···O intermolecular hydrogen bonds between neutral molecules are controlled and determined by a synergism of hydrogen-bond strengthening and π-delocalization enhancement called RAHB or, in other words, that the molecular fragments involved must match the general formula ···O═R_n—NH··· defined in (II), where R_n is a resonant (or conjugated) chain of n atoms (n = odd number). The analysis of 39 cases of N—H···O bonds confirms that the shortest bonds are actually found in connection with the resonant systems R_1 (amides), R_3 (conjugated β-ketoamines and related compounds), R_5 (conjugated δ-ketoamines and analogues) or their combinations. Moreover, the scatterplot of d(N···O) *versus* d(C═O) seems to substantiate the idea that hydrogen-bond shortening and π-delocalization are directly related, in agreement with the hypothesis performed.

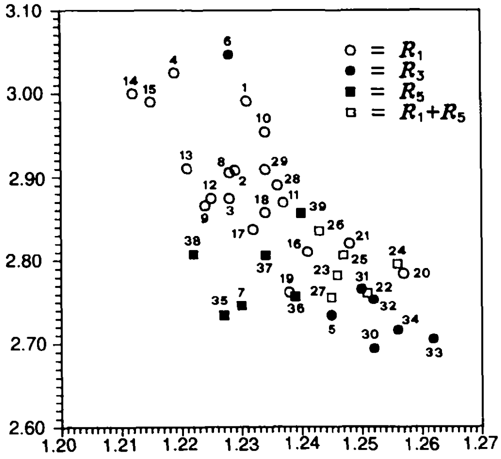


Fig. 11. d(N···O) *versus* d(C═O) scatterplot for the intermolecular N—H···O bonds discussed in the text classed according to the length of the resonant spacer R_n for each compound. Following the general formula ···O═R_n—N—H··· of (II), R_1 identifies amides and R_3 and R_5 conjugated β- and δ-ketoamines.

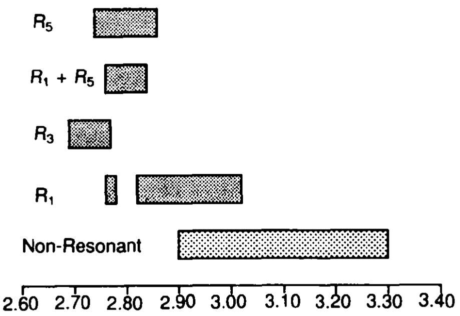


Fig. 12. Intervals of N···O distances for the intermolecular N—H···O bonds discussed in the text arranged according to the length of the corresponding resonant spacer R_n and compared with the interval observed in a set of non-resonant hydrogen bonds. Following the general formula ···O═R_n—N—H··· of (II), R_1 identifies amides, and R_3 and R_5 conjugated β- and δ-ketoamines. The small interval of 2.76–2.78 Å on the R_1 line refers to amides where the nitrogen is linked to a heteroatom (19 and 20).

The present results are consistent with those previously observed for the R_3 ketohydrazone fragment O═C—C═N—NHR, whose derivatives are found to form six-membered intramolecular cycles closed by N—H···O hydrogen bonds as short as 2.55 Å (Bertolasi *et al.*, 1993; Bertolasi, Nanni *et al.*, 1994; Bertolasi, Gilli *et al.*, 1994) and, moreover, parallel to that found for the O—H···O hydrogen bond (Gilli *et al.*, 1994) where O···O distances decrease from 2.70 (the non-resonant limit) to 2.40 Å in the order: carboxylic acids (R_1) > β-diketone enols (R_3) ≈ δ- and ξ-diketone enols (R_5 and R_7). The heteronuclear N—H···O bond is then affected by resonance in the same way as the homonuclear O—H···O bond, the main difference being that the latter can usually become much shorter because of the identical proton affinities of the donor and acceptor which favour the formation of a covalent three-centre–four-electron bond O·—·H···:O <-----> O:···H·—·O (Gilli *et al.*, 1994).

The fact that short N—H···O bonds between stoichiometrically neutral moieties can be produced only by resonance-assisted structures may have interesting implications in the self-assembling of molecules of biological interest and we have already commented (Gilli *et al.*, 1989, 1994) on the fact that the secondary structure of proteins is controlled by resonant chains of amide groups (a triplet of homodromic chains in α-helices and alternating antidromic chains in β-pleated sheets) and the base pairing in DNA is due to resonant-assisted amide–amidine complexes coupled with more extended heteroconjugated rings.

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