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Geometry of the N-H···O=C Hydrogen Bond. 2. Three-Center ("Bifurcated") and Four-Center ("Trifurcated") Bonds

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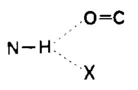
Abstract: A survey of 1509 N—H···O=C hydrogen bonds, observed by X-ray or neutron diffraction in 889 organic crystal structures, gave the following results. About one-fifth (i.e., 304) of the hydrogen bonds can be described as bifurcated, or "three-centered". In contrast, only six trifurcated (or "four-centered") bonds were found. Many of the bifurcated bonds are intramolecular. There is a formal positive charge on the proton-donor group in 152 of the bifurcated bonds and all of the trifurcated bonds. The H···O distances and N—H···O angles of bifurcated bonds tend to be longer and smaller, respectively, than those of linear ("two-center") hydrogen bonds. The proton usually lies within 0.2 Å of the plane containing the donor and acceptor atoms. In asymmetric bifurcated bonds, the shorter contact tends to be more linear than the longer contact.

This is the second[1] in a short series of papers describing the results of a statistical analysis of N—H···O=C hydrogen-bond geometries.[2] The analysis was based on 1509 bonds, taken from 889 organic crystal structures[3] (all crystallographic data were retrieved from the Cambridge Structural Database[4]). Some 1426 of the hydrogen bonds were observed by X-ray diffraction, the remainder by neutron diffraction. The X-ray hydrogen-bond geometries were "normalized",[5] i.e., the hydrogen atom position was moved along the observed N-H bond direction until the N-H distance was equal to 1.030 Å. This procedure corrects for systematic errors in the X-ray results.[6]

In this paper, we consider one of the least studied aspects of hydrogen bonding: the bifurcated hydrogen bond[7] (1; X = O, N, S, halogen; the study is necessarily confined to bifurcated bonds in which the shortest contact is of the type N—H···O=C). Trifurcated bonds (2; X, Y = O, N, S, halogen) are also examined.

Terminology

It was recently pointed out that the terms "linear", "bifurcated", and "trifurcated" (referring to 3, 1, and 2, respectively) are unsatisfactory.[8] The N-H···O angles of "linear" bonds are seldom equal to 180°.[9] The word "bifurcated" has been used to describe two entirely different types of arrangement (1 and 4). It was therefore suggested that 3, 1, and 2 should be termed "two-center", "three-center", and "four-center" hydrogen bonds, respectively.[8] These terms are used below.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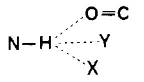
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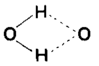
$N{-}H\cdots O{=}C$

3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The symbol $r(A\cdots B)$ is used to denote the distance between atoms A and B; $d(A\cdots B)$ denotes the difference between the sum of the van der Waals radii of A and B and the distance $r(A\cdots B)$, i.e.,

$$d(A\cdots B) = v(A) + v(B) - r(A\cdots B) \qquad (1)$$

where $v(A)$ and $v(B)$ are the van der Waals radii of A and B, respectively.[10] The symbol $\alpha(A{-}B{-}C)$ denotes the interatomic angle $\angle A{-}B{-}C$. The study is confined to three-center bonds in which the shorter of the two contacts is of the type N-H···O; this is termed the "major component" of the bond. The acceptor atom involved in the longer contact (the "minor component") is referred to as X throughout the text. Note that

$$d(H\cdots O) \geq d(H\cdots X) \qquad (2)$$

The acceptor atoms involved in the minor components of a four-center bond are referred to as X and Y, where

$$d(H\cdots O) \geq d(H\cdots X) \geq d(H\cdots Y) \qquad (3)$$

Three-Center Bonds: Preliminary Observations

For the purposes of the present study, we define a three-center bond as one in which the proton forms two contacts to hydrogen-bond acceptor atoms, such that both are in the "forward" direction [i.e., $\alpha(N{-}H\cdots O)$, $\alpha(N{-}H\cdots X) \geq 90°$] and shorter than the sum of the van der Waals radii of the atoms involved [i.e., $d(H\cdots O)$, $d(H\cdots X) > 0$]. By this definition, 304 of the 1509 N—H···O=C bonds in our sample are three centered. Thus, if an N—H···O=C hydrogen bond is chosen at random from a sample of organic crystal structures, the probability that it is three centered is 0.20 (1) (i.e., 304/1509). Symmetric three-center

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[†] Olga Kennard is a member of the external staff of the Medical Research Council.

[1] Part 1: Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761-5766.

[2] The symbol "N—H···O=C" signifies a hydrogen bond in which the acceptor is a carbonyl group or a carboxylate (CO_2^-) ion.

[3] A full list of references was deposited previously.[1]

[4] Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr., Sect. B* **1979**, *B35*, 2331-2339.

[5] Jeffrey, G. A.; Lewis, L. *Carbohydr. Res.* **1978**, *60*, 179-182.

[6] Taylor, R.; Kennard, O. *Acta Crystallogr., Sect B* **1983**, *B39*, 133-138.

[7] For previous studies, see: (a) Olovsson, I.; Jönsson, P.-G. In "The Hydrogen Bond"; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland: Amsterdam, 1976; Vol. II, pp 408-410. (b) Donohue, J. In "Structural Chemistry and Molecular Biology"; Rich, A., Davidson, N., Eds.; W. H. Freeman: San Francisco, 1968; pp 450-456.

[8] Jeffrey, G. A.; Maluszynska, H. *Int J. Biol. Macromol.* **1982**, *4*, 173-185.

[9] Koetzle, T. F.; Lehmann, M. S. In "The Hydrogen Bond"; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland: Amsterdam, 1976; Vol. II, pp 466-467.

[10] The van der Waals radius of hydrogen was taken to be 1.0 Å. This is claimed to be the best value for hydrogen atoms covalently bonded to electronegative atoms such as oxygen and nitrogen: Baur, W. H. *Acta Crystallogr., Sect. B* **1972**, *B28*, 1456-1465. All other van der Waals radii were taken from: Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441-451. They were as follows: N = 1.55, O = 1.52, F = 1.47, Cl = 1.75, Br = 1.85, I = 1.98, S = 1.80 Å.

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Table I. Geometry of Symmetric Three-Center Bonds Based on Normalized Hydrogen Atom Positions[a]

	atoms involved in bond									
structure	N	H	O	X	r(H···O)	r(H···X)	α(N–H···O)	α(N–H···X)	Δ	ref
N-acetyldehydroalanine	N	HN	O1	O1	2.188	2.222*	159.2	103.5	0.149	*b*
ammonium hydrogen oxalate hemihydrate	N1	H4	O4	O4	2.220	2.220	126.2	126.2	0.373	*c*
ammonium hydrogen oxalate hemihydrate	N2	H7	O1	O1	2.343	2.343	125.9	125.9	0.229	*c*
8-amino-5,7-dimethoxy-6-methylpyrrolo[1,2-*a*]indol-9-one	N2	H1N2	O3	O2	2.283	2.294*	165.2	102.8	0.067	*d*
α-(aminomethylene)glutaconic anhydride	N10	H110	O7	O8	2.104*	2.192	121.2	125.9	0.263	*e*
β-alanyl-L-histidine	N1	H23	O10	O9	1.980	2.038	154.5	134.7	0.131	*f*
β-*N*,*N*′-diacetylchitobiose trihydrate	N	HN	O7′	O1′	2.226	2.289	138.5	130.1	0.007	*g*
2-{benzoyl(aminocarbonyl)(methylimino)methyl}3,4,5,6-tetrachlorophenylbenzoate	N12	H12	O8	N10	2.209	2.289*	148.9	102.5	0.236	*h*
cyclobis(D-valylprolylvalyl-D-α-hydroxyisovaleryl) dihydrate	N7	H50	O7	N6	2.274*	2.348*	103.7	102.2	0.373	*i*
α-*S*-cysteinylthymine hydrochloride	Nam	HNam3	O4	O101	2.230	2.316	140.7	127.5	0.131	*j*
(7-chloro-1,3-dihydro-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl)oxamic acid *N*-methylamide	N3	H31	O1	O3	2.187*	2.244*	103.0	103.4	0.008	*k*
glycyl-L-tyrosine dihydrate	N5	H35	O9	O4	2.281*	2.356	97.9	143.5	0.085	*l*
α-L-glutamylglycine	N1	H11	O1ε1	O1ε2	2.243	2.335	116.1	128.1	0.223	*m*
glycyl-DL-alanine	N1	H1	O3	O1	2.214	2.268*	140.8	106.7	0.096	*n*
p-tolylglyoxylic acid *m*-trifluoroanilide	N	HN	O1	O1	2.125*	2.168	106.6	154.2	0.104	*o*
4-amino-1-(4-amino-2-oxo-1(2*H*)-pyrimidinyl)-1,4-dideoxy-β-D-glucopyranuronic acid monohydrate	N4A	HN41A	O6′B	O2′A	2.359	2.392	120.2	142.5	0.310	*p*
guanidinoacetic acid	N3	H5	O1	O1	2.324*	2.368	101.3	135.3	0.186	*q*
2,5-bis(2′-hydroxy(ethylamino))-1,4-benzoquinone	N	HN	O1	O1	2.081	2.160*	152.7	106.2	0.117	*r*
iboxyphylline monohydrate	N1	H1	O23	OW27	2.328*	2.357	114.4	140.4	0.216	*s*
α-phenylethylammonium 2-methoxyisoxazolidine-3,3-dicarboxylic acid *trans*-monomethylamide	N2	H5	O4	N1	2.139	2.170*	147.0	105.0	0.269	*t*
L-citrulline hydrochloride	N1	H3	O1	O3	2.159	2.163	131.9	131.8	0.154	*u*
L-Prolyl-L-tyrosyl-L-isoleucyl-L-leucine	N1	H201	O36	O7	2.052	2.118*	133.9	112.4	0.092	*v*
dimethylammonium hydrogen bis(hydrogen squarate)	N	H3	O1	O2	2.321	2.361	135.0	129.6	0.222	*w*
meso-3,3′-dithiobis(valine) dihydrate	N10	H29	O3	O4	2.194	2.207	151.6	120.6	0.338	*x*
L-methionyl-L-methionine	N2	H2	O1	O′2	2.267	2.339*	156.4	98.8	0.020	*y*
1-((1-morpholino-1-cyclohexen-6-ylidene)ammonio)-1-cyano-2-methoxy-2-oxoethanide	N2	HN2	O2	N1	2.119*	2.218*	112.3	101.1	0.351	*z*
2-methoxyisoxazolidine-3,3,5,5-tetracarboxamide	N5	H9	O6	O1	2.194	2.267*	139.1	99.0	0.095	*aa*
2-methyl-3-phenyl-4-(*N*-methyl-*N*-hydroxyamidin)isoxazolin-5-one hydrobromide	N2	H2N2	O3	O2	2.147	2.184*	138.2	102.4	0.154	*bb*
p-tolylglyoxylic acid *p*-chloroanilide	N	HN	O1	O1	2.104	2.145*	160.8	104.5	0.015	*cc*
1,2-naphthoquinone 1-(2-nitro-4-chlorophenyl)hydrazone	N1	H1	O1	O2	1.825*	1.893*	127.4	123.5	0.009	*dd*
DL-ornithine hydrobromide	N1	H3	O2	Br	2.297*	2.672	105.7	133.2	0.432	*ee*
3-(phenylamino)pyrrolidine-2,5-dione	N1	HN1	O1	O1	2.368*	2.435	110.9	122.7	0.518	*ff*
quisqualic acid	N2	HN2	O1A	O1B	2.068	2.089	151.4	143.7	0.052	*gg*
rubidium hydrogen iminodiacetate iminodiacetic acid	N21	H22	O14	O22	2.029	2.108*	155.5	112.1	0.071	*hh*
rugulovasine A	N12′	H12′	O20′	O18′	2.344	2.401*	139.1	101.4	0.287	*ii*
cyclo(L-*O*-(*tert*-butylseryl)-β-alanylglycyl-(*O*-methyl-β-aspartyl))	N2	HN2	O2	N1	2.201*	2.312*	120.7	104.5	0.201	*jj*
L-alanyl-L-alanyl-L-alanine hemihydrate	N1B	H11B	O3A	O1B	2.008	2.062*	143.3	114.4	0.009	*kk*
D-tryptophan hydrogen oxalate	N15	H15c	O21	O13	2.005	2.086	147.2	123.3	0.051	*ll*

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[a] Geometrical parameters defined in text. Distances in angstroms, angles in degrees. Asterisks indicate intramolecular contacts. Atom labels are those used in original literature, unless none were given (in which case, labels are those used in Cambridge Database). [b] Ajo, D.; Granozzi, G.; Tondello, E.; Del Pra, A.; Zanotti, G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 927–929. [c] Kuppers, H. *Acta Crystallogr., Sect. B* 1973, *B29*, 318–327. [d] Gruska, R. P.; White, J. C. *Acta Crystallogr., Sect. B* 1978, *B34*, 2052–2055. [e] Tsai, L.; Silverton, J. V.; Lingh, H. T. *J. Org. Chem.* 1978, *43*, 4415–4420. [f] Barrans, Y.; Bellocq, A. M.; Cotrait, M.; Richard, H. *J. Mol. Struct.* **1976**, *30*, 225–242. [g] Mo, F. *Acta Chem. Scand., Ser. A* **1979**, *33*, 207–218. [h] Friedrichsen, W.; Schroer, W.-D.; Debaerdemaeker, T. *Justus Liebigs Ann. Chem.* 1980, 1836–1849. [i] Pletnev, V. Z.; Galitskii, N. M.; Langs, D. A.; Duax, W. L. *Bioorg. Khim.* **1980**, *6*, 5–20. [j] Berman, H. M.; Zacharias, D. E.; Carrell, H. L.; Varghese, A. J. *Biochemistry* 1976, *15*, 463–467. [k] Fryer, R. I.; Earley, J. V.; Blount, J. F. *J. Org. Chem.* **1977**, *42*, 2212–2219. [l] Cotrait, M.; Bideau, J.-P. *Acta Crystallogr., Sect. B* **1974**, *B30*, 1024–1028. [m] Eggleston, D. S.; Valente, E. J.; Hodgson, D. J. *Acta Crystallogr., Sect. B* 1981, *B37*, 1430–1433. [n] Paton, W. F.; Paul, I. C. *Cryst. Struct. Commun.* **1979**, *8*, 275–279. [o] Hohne, E.; Seidel, I. *Krist. Tech.* 1980, *15*, 885–890. [p] Swaminathan, P.; McAlister, J.; Sundaralingam, M. *Acta Crystallogr., Sect. B* **1980**, *B36*, 878–885. [q] Berthou, J.; Laurent, A.; Nakajima, S. *Acta Crystallogr., Sect. B* **1976**, *B32*, 1529–1532. [r] Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1975**, *53*, 777–783. [s] Khuong-Huu, F.; Cesario, M.; Guilhem, J.; Goutarel, R. *Tetrahedron* **1976**, *32*, 2539–2543. [t] Kostyanovsky, R. G.; Rudchenko, V. F.; D'yachenko, O. A.; Chervin, I. I.; Zolotoi, A. B.; Atovmyan, L. O. *Tetrahedron* **1979**, *35*, 213–224. [u] Ashida, T.; Funakoshi, K.; Tsukihara, T.; Ueki, T.; Kakudo, M. *Acta Crystallogr., Sect. B* **1972**, *B28*, 1367–1374. [v] Cotrait, M.; Geoffre, S.; Hospital, M.; Precigoux, G. *Acta Crystallogr., Sect. B* **1979**, *B35*, 114–118. [w] Wang, Y.; Stucky, G. D. *J. Chem. Soc., Perkin 2* **1974**, 925–928. [x] Warner, L. G.; Ottersen, T.; Seff, K. *Acta Crystallogr., Sect. B* **1974**, *B30*, 1077–1082. [y] Stenkamp, R. E.; Jensen, L. H. *Acta Crystallogr., Sect. B* **1975**, *B31*, 857–861. [z] Toupet, L.; Delugeard, Y. *Acta Crystallogr., Sect. B* **1979**, *B35*, 1935–1936. [aa] Rudchenko, V. F.; D'yachenko, O. A.; Chervin, I. I.; Zolotoi, A. B.; Atovmyan, L. O.; Kostyanovskii, R. G. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, 850–859. [bb] Fanfani, L.; Nunzi, A.; Zanazzi, P. F.; Zanzari, A. R. *Acta Crystallogr., Sect. B* **1972**, *B28*, 2598–2604. [cc] Hohne, E.; Seidel, I. *Krist. Tech.* **1979**, *14*, 1097–1105. [dd] Guggenberger, L. J.; Teufer, G. *Acta Crystallogr., Sect. B* **1975**, *B31*, 785–790. [ee] Kalyanaraman, A. R.; Srinivasan, R. *Acta Crystallogr., Sect. B* **1971**, *B27*, 1420–1427. [ff] Argay, G.; Carstensen-Oeser, E. *Acta Crystallogr., Sect. B* **1973**, *B29*, 1186–1190. [gg] Flippen, J. L.; Gilardi, R. D. *Acta Crystallogr., Sect. B* **1976**, *B32*, 951–953. [hh] Herbertsson, H. *Acta Crystallogr., Sect. B* **1977**, *B33*, 830–834. [ii] Cole, R. J.; Kirksey, J. W.; Clardy, J.; Eickman, N.; Weinreb, S. M.; Singh, P.; Kim, D. *Tetrahedron Lett.* **1976**, 3849–3852. [jj] Karle, I. L.; Handa, B. K.; Hassall, C. H. *Acta Crystallogr., Sect. B* **1975**, *B31*, 555–560. [kk] Fawcett, J. K.; Camerman, N.; Camerman, A. *Acta Crystallogr., Sect. B* **1975**, *B31*, 658–665. [ll] Bakke, O.; Mostad, A. *Acta Chem. Scand., Ser. B* 1980, *34*, 559–570.

Table II. Number of Intermolecular and Intramolecular Contacts in Sample

type of contact	inter-molecular	intra-molecular
2 center, N-H···O	1112 (93%)	87 (7%)
all 3 center, N-H···O	242 (80%)	62 (20%)
all 3 center, N-H···X	144 (47%)	160 (53%)
symmetric 3 center,[a] N-H···O	26 (68%)	12 (32%)
symmetric 3 center,[a] N-H···X	19 (50%)	19 (50%)

[a] See Table I.

Table III. Means and Standard Deviations of Distributions[a]

type of bond	N^b	r(H···O)		α(N-H···O)		α(N-H···X)	
		μ^c	σ^d	μ	σ	μ	σ
all 2 center	1199	1.899	0.132	161.4	13.7		
intermolecular 2 center	1112	1.895	0.129	163.5	10.8		
all 3 center	304	2.004	0.149	146.8	16.3	113.4	16.1
3 center in which the H···O contact is intermolecular	242	1.994	0.148	150.6	12.2	not calculated	
3 center in which the H···X contact is intermolecular	144	not calculated		141.7	17.2	127.0	11.6

[a] Geometrical parameters defined in text. Distances in angstroms, angles in degrees. [b] N = number of bonds. [c] μ = unweighted mean, $\Sigma_i x_i/N$. [d] σ = sample standard deviation, $[\Sigma_i(x_i - \mu)^2/(N - 1)]^{1/2}$.

bonds are less common. In our sample, there are 83 three-center bonds in which $d(\mathrm{H}\cdots\mathrm{O}) - d(\mathrm{H}\cdots\mathrm{X}) \leq 0.2$ Å and only 38 in which $d(\mathrm{H}\cdots\mathrm{O}) - d(\mathrm{H}\cdots\mathrm{X}) \leq 0.1$ Å (these are listed in Table I).

Our definition of three-center bonding is necessarily arbitrary, because as X approaches H in **1**, there is no obvious point at which the bond becomes three centered. Thus, many of the bonds that are two centered by our definition are nevertheless in reasonably close proximity to a second hydrogen-bond-acceptor atom. For example, there are 216 two-center bonds in which the proton is within 2.8 Å of a second oxygen atom in the "forward" direction.

Occurrence of Three-Center Bonds

The above results give the *overall* rate of occurrence of three-center bonds. In practice, three-center bonds are more likely to occur in some types of structures than in others. We discuss below three factors that may be relevant.

Stoichiometry. A recent study of amino acid structures suggested that three-center bonds tend to occur in "proton-deficient" structures, i.e., structures in which there are not enough "active" protons (O-H, N-H) to satisfy the normal hydrogen-bonding requirements of the acceptor groups.[8] It was suggested that, in this situation, the acceptor groups "share" protons by forming three-center bonds. This possibility is not considered here because it cannot be confirmed or excluded without a detailed knowledge of the optimum hydrogen-bonding coordination numbers of various acceptor groups.

Intramolecular Interactions. The numbers of intermolecular and intramolecular contacts in our sample are summarized in Table II. χ^2 and binomial tests showed that the following observations are statistically significant at the >99.9% level: (1) The N-H···O contact in a three-center bond is more likely to be intramolecular than the N-H···O contact in a two-center bond. (2) The N-H···X contact in a three-center bond is more likely to be intramolecular than the N-H···O contact. The first of these observations can be rationalized as follows. Intramolecular bonds (whether they be two-centered or three-centered) are usually less linear than intermolecular bonds and are often longer.[11] Thus, the proton in an intramolecular N-H···O contact is likely to be more accessible to an approaching X atom than the proton in an intermolecular contact, provided that X lies close to the external bisector of the N-H···O angle (as is usually the case in three-center bonds). Observation 2 above suggests that many of the H···X contacts in our sample are due to the fortuitous proximity of a proton and an acceptor atom in the same molecule. These contacts may well be insufficiently attractive to occur in other circumstances. It may be argued that bonds in which the H···X contact is intramolecular and relatively long should not be described as three-centered.

Positively Charged Donor Groups. Exactly half (i.e., 152) of the three-center bonds in our sample involve donor nitrogen atoms that bear a formal positive charge. In contrast, only 395 of the 1199 two-center bonds involve positively charged $\mathrm{N^+}$–H groups. The difference between these proportions is statistically significant at the >99.9% level (χ^2 test). Thus, positively charged $\mathrm{N^+}$–H groups are more likely to form three-center bonds than uncharged N–H groups. There appears to be no difference between symmetric and asymmetric three-center bonds in this respect, e.g., 18 of the 38 bonds in Table I involve $\mathrm{N^+}$–H groups. The formal positive charge on the nitrogen atom is particularly important when both contacts in a three-center bond are intermolecular. Of the 115 bonds in this category, all but 25 involve $\mathrm{N^+}$–H groups.[12]

The above results may reflect a systematic crystal packing effect associated with the shape of ammonium and substituted ammonium ions. Alternatively, they may indicate that three-center bonds are more sensitive to the charge on the proton-donor group than two-center bonds. We tentatively suggest that intermolecular three-center bonds are unlikely to occur unless the relatively long H···X interaction is stabilized by an appreciable net positive charge on the hydrogen atom.

Geometry of Three-Center Bonds

The O···X nonbonded repulsion in three-center bonds forces at least one of the hydrogen bond contacts (N-H···O or N-H···X) to deviate considerably from linearity[7] and is likely to make very short H···O interactions unfavorable. The distribution of r(H···O) and α(N-H···O) for the 1199 two-center bonds and 304 three-center bonds in our sample are shown in Figure 1a–d. The means and standard deviations of the distributions are given in Table III. Mann–Whitney tests[13] showed that the tendency for three-center bonds to be longer, and less linear, than two-center bonds is statistically significant at the >99.9% level.[14] The difference between the geometries of two-center and three-center bonds is slightly less pronounced if intramolecular N-H···O contacts are excluded from the distributions (Table III) but is still highly (>99.9%) significant.

The distribution of α(N-H···X) for the 304 three-center bonds is shown in Figure 1e; the mean and standard deviation are given in Table III. The distribution is dominated by the large number of intramolecular N-H···X contacts, many of which have α(N-H···X) < 110°. Figure 1f shows the distribution of α(N-H···X)

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[11] Taylor, R.; Kennard, O.; Versichel, W., unpublished results.

[12] A detailed analysis of our dataset suggests that the tendency to form three-center bonds decreases in the order: $\mathrm{R_3N^+{-}H > R_2HN^+{-}H > RH_2N^+{-}H > H_3N^+{-}H > {>}N^+{-}H}$ (i.e., trigonal nitrogen). We note that the average H···O distances of two-center bonds involving these groups vary in the opposite order: $\mathrm{{>}N^+{-}H \simeq H_3N^+{-}H > RH_2N^+{-}H > R_2HN^+{-}H > R_3N^+{-}H}$.[11]

[13] Throughout the survey, nonparametric (i.e., distribution-free) statistical methods were used whenever possible. They are well documented in standard statistical texts, e.g.: (a) Siegel, S. "Nonparametric Statistics for the Behavioral Sciences", International Student Edition; McGraw-Hill Kogakusha: Tokyo, 1956. (b) Snedecor, G. W.; Cochran, W. G. "Statistical Methods", 7th ed.; Iowa State University Press: Ames, IA, 1980.

[14] These results are consistent with a study of three-center bonds in carbohydrate crystal structures: Ceccarelli, C.; Jeffrey, G. A.; Taylor, R. *J. Mol. Struct.* **1981**, *70*, 255–271.

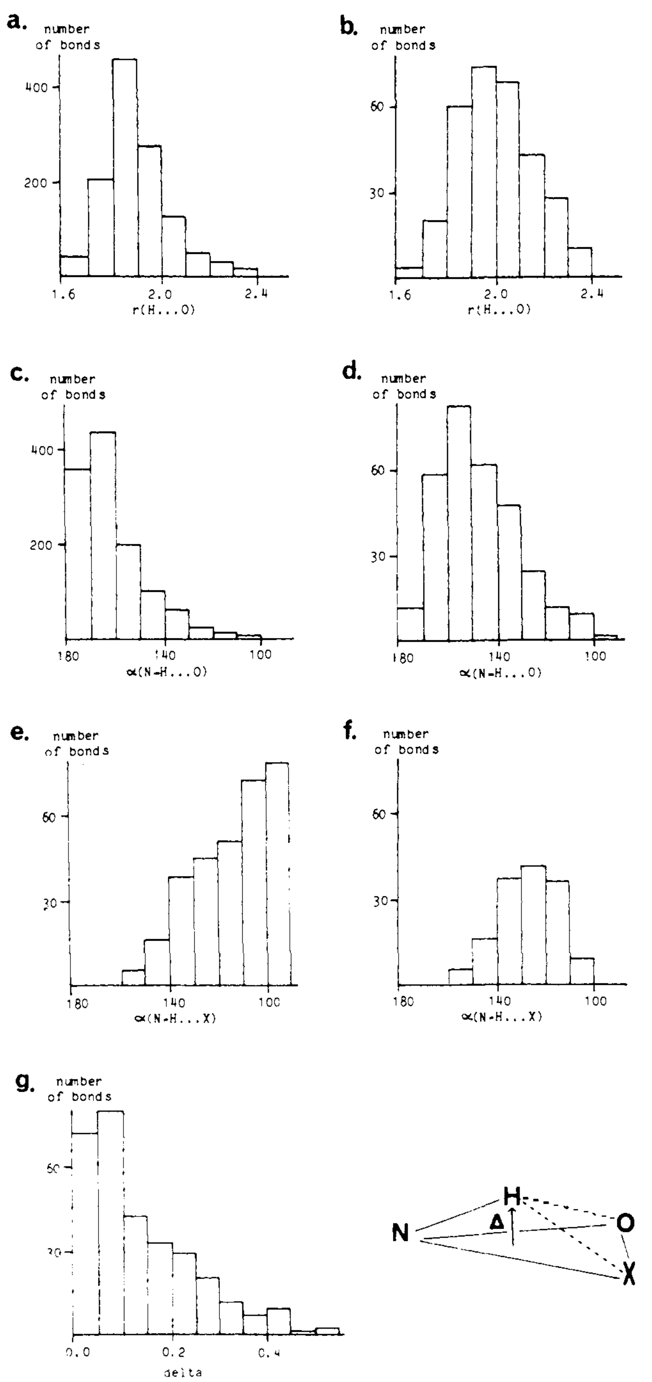


Figure 1. Distribution of (a) $r(\mathrm{H}\cdots\mathrm{O})$ (Å) for all two-center bonds in sample, (b) $r(\mathrm{H}\cdots\mathrm{O})$ (Å) for all three-center bonds in sample, (c) $\alpha(\mathrm{N{-}H}\cdots\mathrm{O})$ (°) for all two-center bonds in sample, (d) $\alpha(\mathrm{N{-}H}\cdots\mathrm{O})$ (°) for all three-center bonds in sample, (e) $\alpha(\mathrm{N{-}H}\cdots\mathrm{X})$ (°) for all three-center bonds in sample, (f) $\alpha(\mathrm{N{-}H}\cdots\mathrm{X})$ (°) for three-center bonds in which the H···X contact is intermolecular, (g) Δ (Å) for all three-center bonds in sample.

for the 144 three-center bonds in which the N–H···X contact is intermolecular. The mean values of $\alpha(\mathrm{N{-}H}\cdots\mathrm{O})$ and $\alpha(\mathrm{N{-}H}\cdots\mathrm{X})$ for these bonds are given in Table III. A paired Wilcoxon test showed that the difference between the mean values is statistically (>99.9%) significant. Thus, the major component of a three-center bond is usually more linear than the minor component, even when the minor component is intermolecular. This can be rationalized as follows. Since (by definition) $d(\mathrm{H}\cdots\mathrm{O}) \geq d(\mathrm{H}\cdots\mathrm{X})$, the N···O nonbonded repulsion is likely to be larger than the N···X repulsion in any three-center bond in which $\alpha(\mathrm{N{-}H}\cdots\mathrm{O})$ and $\alpha(\mathrm{N{-}H}\cdots\mathrm{X})$ are equal. Thus, the bond will tend to distort so as to increase $r(\mathrm{N}\cdots\mathrm{O})$ and decrease $r(\mathrm{N}\cdots\mathrm{X})$, i.e., α (N–H···O) will become

Table IV. Geometry of Four-Center Bonds Based on Normalized Hydrogen Atom Positions[a]

structure	atoms involved in bond					$r(\mathrm{H}\cdots\mathrm{O})$	$r(\mathrm{H}\cdots\mathrm{X})$	$r(\mathrm{H}\cdots\mathrm{Y})$	$\alpha(\mathrm{N{-}H}\cdots\mathrm{O})$	$\alpha(\mathrm{N{-}H}\cdots\mathrm{X})$	$\alpha(\mathrm{N{-}H}\cdots\mathrm{Y})$	ref
	N	H	O	X	Y							
1. ammonium orotate monohydrate	N	H4N	O4	O	O2	2.175	2.341	2.438	131.3	119.8	103.6	*b*
2. *N*,*N*-bis(2-hydroxyethyl)glycine	N4	H4	O43	O7	O1	2.114*	2.254*	2.257*	111.5	107.4	106.8	*c*
3. calcium nitrilotriacetate dihydrate	N	HN	O2	O3	O5	2.226*	2.260*	2.327*	104.7	101.9	99.9	*d*
4. L-homocitrulline hydrochloride	N1	H3	O1	O1	O3	1.934	2.383*	2.506	150.1	93.8	117.1	*e*
5. Histidine dihydrochloride	N1	H8	O1	O2	C12	1.978	2.305*	2.746	147.1	93.2	109.9	*f*
6. iminodiacetic acid hydroiodide	N	H5	O2	1	O4	2.269*	2.745	2.369*	101.8	141.2	100.4	*g*

[a] Geometrical parameters defined in text. Distances in angstroms, angles in degrees. Asterisks indicate intramolecular contacts. Atom labels are those used in original literature. [b] Solbakk, J. *Acta Chem. Scand.* 1971, *25*, 3006–3018. [c] Cody, V.; Hazel, J.; Langs, D. *Acta Crystallogr., Sect. B* 1977, *B33*, 905–907. [d] Whitlow, S. H. *Acta Crystallogr., Sect. B* **1972**, *B28*, 1914–1919. [e] Ashida, T.; Funakoshi, K.; Tsukihara, T.; Ueki, T.; Kakudo, M. *Acta Crystallogr., Sect. B* **1972**, *B28*, 1367–1374. [f] Kistenmacher, T.; Sorrell, T. *J. Cryst. Mol. Struct.* 1974, *4*, 419–432. [g] Oskarsson, A. *Acta Crystallogr., Sect. B* **1974**, *B30*, 780–783.

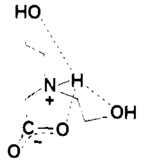
larger than α(N–H···X). The magnitudes of d(N···O) and d(N···X) are usually comparable in three-center bonds, e.g., in our sample, there are 165 bonds in which d(N···X) $\geq$ d(N···O) and 139 in which d(N···O) $\geq$ d(N···X). Thus, the major and minor components of a three-center bond cannot be distinguished reliably without a knowledge of the proton position.

Figure 1g shows the distribution of Δ (the deviation of the proton from the N, O, X plane, ignoring sign) for all three-center bonds in our sample.[15] The mean value of Δ is 0.137 (6) Å. The mean Δ value of the 18 three-center bonds determined by neutron diffraction is somewhat smaller [0.104 (19) Å], but the difference is not statistically significant. We conclude that the proton in three-center bonds usually lies within about 0.2 Å of the N, O, X plane. Surprisingly, Δ shows a small tendency to increase as the three-center bond becomes more symmetrical. Thus, the Spearman rank correlation coefficient of Δ and [d(H···O) – d(H···X)] is -0.148, which is significantly different from zero at the 99% level. Essentially the same result is obtained if the analysis is confined to three-center bonds in which both contacts are intermolecular.

Four-Center Bonds

We define a four-center bond as one in which the proton forms three contacts to hydrogen-bond-acceptor atoms. Each contact must be in the "forward" direction [α(N–H···O), α(N–H··X), α(N–H···Y) $\geq$ 90°] and shorter than the sum of the van der Waals radii of the atoms involved [d(H···O), d(H···X), d(H···Y) > 0]. This arrangement is very uncommon: there are only six four-center bonds in our sample (Table IV). Presumably, this is because of the unfavorable repulsions between N, O, X, and Y in **2**. All of the bonds involve positively charged donor nitrogen atoms. In contrast, only 395 of the 1199 two-center bonds involve N$^+$-H groups. These proportions are significantly different at the >99.9% level (χ^2 test). We conclude that a positively charged N$^+$–H group is far more likely to form a four-center bond than an uncharged N–H group.

Bonds 2 and 3 in Table IV are completely intramolecular. The molecules involved (**5** and **6**) are probably ideally suited to four-center bonding. Each contains a positively charged N$^+$–H group, surrounded by three acceptor atoms which "shield" the proton and prevent it from forming a normal, intermolecular two-center bond.



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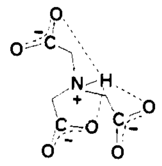

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Summary

Three-center hydrogen bonds, as defined in this study, are relatively common in organic crystal structures. However, many of the bonds involve intramolecular N–H···X contacts with α(N–H···X) < 110°. The energy associated with such interactions may well be small, and it is debatable whether they should be described as hydrogen-bonding contacts. We note that the definition of three-center bonding used above was an experimental convenience and is not necessarily recommended as the "best" definition.

Approximately 78% of the three-center bonds in which both contacts are intermolecular involve positively charged N$^+$–H groups. This suggests that intermolecular three-center bonds are unlikely to be a favorable packing arrangement in organic crystal structures unless the hydrogen atom carries an appreciable net positive charge. A similar result was found for four-center bonds, which are very rare and invariably involve N$^+$–H groups. Many aspects of the geometry of three-center bonds can be rationalized in terms of the N···O, N···X, and O···X nonbonded repulsions.

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(15) For an earlier investigation of the planarity of three-center bonds, see: Parthasarathy, R. *Acta Crystallogr., Sect. B* **1969**, *B25*, 509-518.

Communications to the Editor

Long-Range ^{1}H–^{1}H Spin–Spin Couplings through the Interglycosidic Oxygen and the Primary Structure of Oligosaccharides as Studied by 2D-NMR

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The potential of modern high-field two-dimensional nuclear magnetic resonance (2D-NMR) spectroscopy in sequencing organic oligomers has been clearly demonstrated in recent 2D NOE studies on small proteins,[1] oligopeptides,[2,3] and oligosaccharides.[4] In these works, sequence information was inferred from spectral correlations established via dipolar interactions (cross relaxations) between protons in contigous oligomeric units. Other, interresidual spin–spin interactions such as indirect homo- and/or heteronuclear long-range couplings may, under favorable conditions, also furnish the requested sequence information.[2] In this communication, we show that 2D correlations established via four-bond interglycosidic $^4J_{\mathrm{HCOCH}}$ couplings may represent a convenient, alternative route for the sequencing of small to medium-sized oligosaccharides.

Available literature data show $^4J_{\mathrm{HCOCH}}$ couplings to occur across ether linkages in simple organic molecules and assume values in the range between 0 and 1.5 Hz with moderate stereoselectivity.[5,6] The presence of the same type of couplings across glycosidic bonds in oligosaccharides, however, has not been analyzed yet. As shown in the sequel, the actual values of integlycosidic $^4J_{\mathrm{HCOCH}}$ couplings in a typical oligosaccharide are estimated to be lower than 0.2 Hz, still they are detectable by suitable experimental techniques. The latter are readily available from the so-called delayed COSY method[7] in which magnetization transfer between resonances

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