Heparin is infrequently used in this regard due primarily to the necessity for parenteral administration. This situation could possibly be changed by formulation of heparin with a nontoxic sulfated surfactant.

REFERENCES

(1) R. H. Engel and M. J. Fahrenbach, *Proc. Soc. Exptl. Biol. Med.*, **129,** 772(1968).

(2) R. H. Engel and S. J. Riggi, *ibid.*, **130,** 879(1969).

(3) D. S. Robinson and P. M. Harris, *Quart. J. Exptl. Physiol.*, **44,** 80(1959).

(4) G. E. P. Box and K. B. Wilson, *J. Roy. Stat. Soc., Ser. B.*, **13,** 1(1951).

(5) T. A. Loomis, *Proc. Soc. Exptl. Biol. Med.*, **101,** 447(1959).

(6) E. Windsor and G. E. Cronheim, *Nature*, **190,** 263(1961).

(7) D. M. Graham, T. P. Lyon, J. W. Gofman, H. B. Jones, A. Yankley, J. Simonton, and S. White, *Circulation*, **4,** 663(1951).

(8) H. Engelberg, *ibid.*, **10,** 604(1954).

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* Present address: Battelle Memorial Institute, Duxbury, MA 02332

† To whom all correspondence should be addressed.

Structural Studies on Complexes IV: Crystal Structure of a 1:1 5-Chlorosalicylic Acid and Theophylline Complex

ELI SHEFTER

Abstract □ Single crystal X-ray diffraction methods were utilized in obtaining the crystal and molecular structure of a 1:1 association complex between 5-chlorosalicylic acid and theophylline. The crystals are monoclinic (space group P $2_1/c$) with cell parameters of a = 7.845 Å.; b = 9.636 Å.; c = 21.185 Å.; and β = 92.20°. The crystals contain a significant fraction of the impurities 3,5-dichloro- and 3-chlorosalicylic acid. Hydrogen bonds are the major attractive forces between the components of the complex. A relatively strong hydrogen bond exists between the carboxyl group of 5-chlorosalicylic acid and N(9) of theophylline (2.682 Å.). The theophylline molecules are in a dimeric arrangement by virtue of centrosymmetrically related hydrogen bonds between N(7) and TO(10). The packing arrangement of the molecules suggests that the stacking forces are similar to those in a caffeine:5-chlorosalicylic acid complex.

Keyphrases □ Complexes—structural studies □ 5-Chlorosalicylic acid-theophylline complex—crystal, molecular structure □ Diffractometry—5-chlorosalicylic acid-theophylline complex □ Hydrogen bonding—5-chlorosalicylic acid-theophylline complex

Spectroscopic, kinetic, and a variety of other physical chemical methods have been used successfully to obtain valuable information on the nature and strength of intermolecular association complexes between a wide variety of biological compounds (1). However, these methods are generally unable to provide detailed descriptions of the complex at the atomic level. For this, one may in some instances resort to the direct method of X-ray diffraction. Though this technique requires crystalline complexes, whose structures may be somewhat different from those in solution, the results are quite useful when correlated to solution data. It is through such correlations that a clear picture of various molecular association complexes involving pharmaceutically important molecules may emerge.

The interactions of salicylates and other biological materials containing *pi* systems with xanthine derivatives have been studied quite extensively in solution. The thermodynamic parameters of such complexes obtained by Higuchi *et al.* (2, 3) suggest that "hydrophobic" forces aside from hydrogen bonding play a significant role. Donbrow and Jan (4) have indicated that xanthine–hydroxybenzoic acid complexes may involve a donor-acceptor-type mechanism. In a crystallographic study on the 1:1 complex between 5-chlorosalicylic acid and caffeine, the idea of "polarization bonding" was put forth (5). Although the primary intermolecular force in that solid-state complex is hydrogen bonding, some evidence was found for a localized interaction between the α-β unsaturated ketone portion of the xanthine and the *pi* system of the salicylic acid molecule. Even with the wide variety of experimental data now available on such complexes and postulated models for the interactions (for a theoretical model see reference (6)), the interactions in these complexes have not been elucidated with sufficient detail to draw definitive conclusions on their molecular nature.

The present report concerns a structural study on a 1:1 complex formed between theophylline and 5-chlorosalicylic acid. This structure was determined with the hope of providing further insight into the molecular nature of the "polarization" forces, and also to learn more about the role hydrogen bonds play in stabilizing such complexes.

EXPERIMENTAL

Prism-shaped crystals of the 1:1 complex were obtained by dissolving equal molar quantities of theophylline (Matheson, Coleman and Bell, Inc.) and 5-chlorosalicylic acid (Eastman Kodak practical grade) in an alcohol-water solution and allowing the solution to

Table I—Positional and Thermal Parameters with (in Parentheses) their Respective Standard Deviations × 10^{4a}

Atom	x/a	y/b	z/c	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
				Theophylline					
TN1	10848(5)	2307(4)	1478(2)	118(6)	100(5)	15(1)	14(9)	−12(4)	1(3)
TC2	10310(6)	3675(6)	1581(2)	128(8)	112(6)	17(1)	4(11)	−4(4)	−7(4)
TN3	9397(5)	4318(4)	1108(2)	135(6)	75(4)	20(1)	−2(8)	−13(4)	−20(3)
TC4	8975(5)	3602(5)	562(2)	109(7)	97(5)	15(1)	0(10)	−11(4)	2(4)
TC5	9519(6)	2269(5)	473(2)	126(7)	88(5)	16(1)	27(10)	−3(4)	−3(4)
TL6	10510(6)	1529(5)	937(2)	131(7)	92(5)	15(1)	13(10)	−23(4)	−8(3)
TN7	8800(5)	1870(4)	−99(2)	164(7)	89(4)	16(1)	70(9)	−25(4)	−9(3)
TC8	7909(6)	2952(5)	−321(2)	157(8)	109(6)	12(1)	21(12)	−35(5)	−8(4)
TN9	7977(5)	4044(4)	67(2)	148(7)	89(4)	19(1)	37(9)	−23(4)	−3(3)
TO10	11003(5)	337(4)	896(2)	242(8)	93(4)	19(1)	82(9)	−43(4)	−5(3)
TC11	11693(7)	1599(7)	2018(2)	176(10)	168(8)	16(1)	−29(15)	−38(5)	7(5)
TO12	10638(5)	4251(5)	2081(2)	236(8)	150(6)	20(1)	49(11)	−47(4)	−45(4)
TC13	8791(9)	5750(6)	1190(3)	283(4)	82(6)	30(2)	60(14)	5(8)	−23(5)
				5-Chlorosalicylic acid					
Cl5	6448(3)	−1149(2)	799(1)	373(5)	122(2)	54(1)	151(5)	−103(3)	5(2)
Cl3	7516(18)	2472(18)	2903(6)	354(30)	322(27)	29(3)	175(47)	−33(14)	44(14)
C1	5229(6)	2754(6)	1226(2)	124(8)	126(7)	20(1)	1(12)	−7(5)	14(5)
C2	5945(7)	2906(7)	1831(3)	159(9)	158(8)	19(1)	−11(14)	−25(5)	12(5)
C3	6809(7)	1792(8)	2118(3)	168(10)	220(11)	21(1)	−25(17)	−35(6)	30(6)
C4	6972(7)	5898(7)	1805(3)	178(10)	148(8)	31(1)	−1(15)	−44(7)	65(6)
C5	6250(8)	410(6)	1200(3)	191(11)	114(7)	32(2)	34(14)	−21(7)	38(6)
C6	5363(6)	1494(6)	915(2)	142(8)	128(7)	21(1)	18(12)	−32(5)	25(5)
C7	4301(6)	3927(6)	921(2)	136(8)	117(6)	20(1)	−1(11)	−7(5)	4(4)
O1	3637(5)	3665(4)	356(2)	195(7)	94(4)	23(1)	53(9)	−37(4)	12(3)
O2	4138(6)	5056(5)	1184(2)	282(10)	135(6)	27(1)	79(12)	−41(5)	−14(4)
O3	5818(7)	4074(6)	2166(2)	281(10)	207(8)	24(1)	28(14)	−52(5)	−29(5)

[a] Temperature factor = $\exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$.

evaporate. The following crystallographic data were measured for this material:

a = 7.845 (0.001) Å.
b = 9.636 (0.002) Å.
c = 21.185 (0.003) Å.
β = 92.20 (0.01)°

Density (measured by flotation) = 1.46 g./cm.[3]
Density (calculated assuming a 1:1 complex containing one full chlorine) = 1.468 g./cm.[3]
Z = 4 (number of molecules of complex in unit cell)
Space group $P2_1/c$

The stationary crystal–stationary counter method (7) was used to collect the intensity data on a diffractometer[1] equipped with goniostat. A set of balanced Ross filters (Ni against Co) were used for monochromatization of the Cu radiation. The crystal (dimensions 0.4 × 0.3 × 0.1 mm.) was mounted with [1 0 0] parallel to the *Phi* axis of the diffractometer. In the range of data measurement (limit 150° in *two theta*), 2,338 reflections of the 3,306 unique data had peak intensities that were significantly greater than their respective background. An approximate correction was made for absorption, based on the anisotropy of transmission of the X-rays as a function of the angle *Phi*. This function was measured for the (2 0 0) reflection at *Chi* equal to 90°. Aside from this correction, the appropriate Lorentz polarization factor and a factor to correct for α_1-α_2 splitting (25) were applied to convert an intensity to its structure factor amplitude, $|F_0|$. The $|F_0|$'s were placed on an absolute scale by Wilson's method, and normalized structure factors, $|E|$'s were computed.

The symbolic addition procedure was utilized to derive a set of phases for 292 reflections having $|E|$ values greater than 1.60. The method makes use of the Sayre relationship (8), which is essentially the same as the formula of Hauptman and Karle (9). Three linearly independent reflections (2 1 −3; 2 1 −2; 3 1 16) were selected as the origin-determining reflections on the basis that they have large values of $|E|$ and enter into many combinations for the application of the Sayre equation. Four reflections having a magnitude of $|E|$ greater than 3.0 (4 2 −5; 6 2 11; 6 3 −8; 2 8 7) were allowed to take up the 16 possible permutations of their phases. The phases of the other 285 reflections were determined for each of the 16 sets of starting phases using a program written by Robert Long (10). An E-map (11) was computed using the set of phases for the 292 data with the highest consistency index (10, 12). The position of 16 nonhydrogen atoms were positively located in this synthesis. A three-dimensional Fourier synthesis phased on these atoms enabled the other nonhydrogen atoms to be positioned in the lattice.

During the initial refinement by least-squares and difference electron-density maps, an atom other than hydrogen appeared to be attached to C3 of the salicylic acid molecule. The distance of this peak to C3 suggested that it was a chlorine atom with only a partial occupancy factor (peak height ~ 1 e/Å.[3]). The atomic site occupancy factor of the two chlorines were refined by least-squares along with their isotropic temperature factors. The site occupancy factor obtained for the chlorine bound to C3 was only 0.15 while that in Position 5 was 0.93. The practical grade of 5-chlorosalicylic acid in all likelihood is a mixture of the 5-chloro-, 3–5 dichloro- and 3-chloro- compounds, resulting from chlorination of salicylic acid. The crystalline complex reflects the varying portions of the chloro derivatives of salicylic acid, and can be considered as a solid solution of these compounds.

The hydrogen atoms were located in difference electron-density syntheses and included in the final cycles of least-squares refinement with isotropic temperature factors. All the other atoms were refined anisotropically, during which the site occupancy factors for the two chlorines were fixed at their respective values. A modification of the Gantzel, Sparks and Trueblood block diagonal least-squares program (unpublished) was utilized for this purpose. The weighting scheme in the final stages of refinement was $w^{-1} = (|F_0| - 3)/12^2 + 1$, designed such that $\langle w\Delta^2 \rangle$ is constant over the whole range of $|F_0|$'s.[2] The unobserved data were given zero weight. The final R value for the observed data is 0.087 (for all data 0.134). The atomic parameters and their estimated standard deviations (*ESD*'s) are listed in Tables I and II. A tabulation of the structure factors has been deposited in the Health Sciences Library of this University and may be obtained from the librarian on request.

With the exception of hydrogen, the atomic scattering factors used throughout the above calculations are those presented in *Reference 13*. The form factors for hydrogen are those published by Stewart *et al.* (14).

[1] General Electric XRD-6.

[2] $|F_0|$ is on absolute scale.

Table II—Parameters for Hydrogen Atoms with Their *ESD*'s in Parentheses

Atom	$x/a \times 10^3$	$y/b \times 10^3$	$z/c \times 10^3$	B_{iso}, Å.^{2}
H2	750(8)	−13(7)	199(3)	5.8(1.5)
H3	495(8)	152(7)	52(3)	5.8(1.5)
H4	331(9)	426(7)	25(3)	6.6(1.6)
H5	546(8)	475(6)	196(3)	5.2(1.4)
H6	1242(10)	104(8)	179(4)	8.1(2.1)
H7	1234(8)	207(7)	217(3)	5.2(1.5)
H8	1075(8)	104(7)	219(3)	6.3(1.6)
H9	880(9)	650(7)	65(3)	6.8(1.6)
H10	950(12)	616(9)	131(4)	9.7(2.5)
H11	769(14)	559(13)	122(5)	13.8(3.2)
H12	907(5)	123(4)	−25(2)	1.5(0.7)
H13	724(7)	290(6)	−72(3)	4.6(1.2)

The thermal parameters of the nonhydrogen atom were analyzed by the method of Schomaker and Trueblood (15). The *Uij's* calculated for the two molecular species, assuming that each behaves as a "rigid body," are in good agreement with their observed thermal parameters. The root mean-square difference between the calculated and observed values of the *Uij's* is 0.004 Å.^{2} for theophylline and 0.005 Å.^{2} for 5-chlorosalicylic acid including the partially occupied chlorine attached to C3; these differences are the same order of magnitude as the *ESD*'s of the *Uij's*. The translational and librational components of the thermal motion for theophylline are approximately 20% less than those computed for the salicylic acid residue. This reflects the greater number of intermolecular hydrogen bonds in which the theophylline molecule participates. The change in bond lengths and angles resulting from the thermal motion were all less than 1.5 times the *ESD*'s for the respective bonds, the corrections were therefore deemed to be unnecessary for the present discussion.

The bond lengths and angles obtained from the least-squares refined parameters are shown in Fig. 1. The *ESD*'s for the atom-to-atom distances are on the average 0.008 Å., and for the angles 0.4°. Those bonds involving hydrogens have an error of 0.1 Å. The angles about the hydrogen atoms are not given (because of their relatively high uncertainty, ±3°), except where the discussion warrants such information. Figure 1 also shows the atomic labels that are used throughout the discussion.

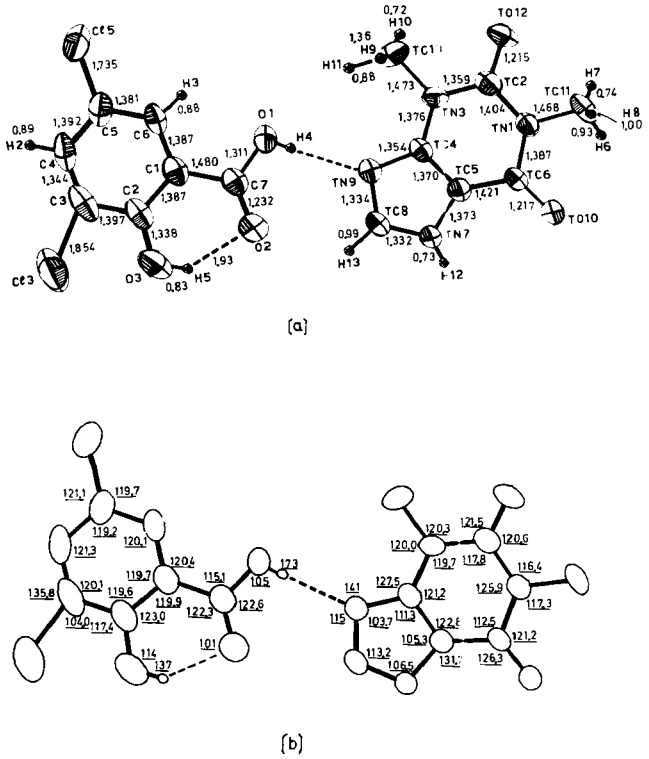

Figure 1—*Intramolecular bond lengths (a) and angles (b). The thermal motion of the individual atoms is represented by the ellipsoids.*

DISCUSSION OF RESULTS

The theophylline moiety has intramolecular bond distances and angles that are quite similar to those found in theophylline monohydrate crystals (16); none differ by more than 2 *ESD*'s. There is however, a significant difference between the planarity of the xanthine residues in the two structures. The atoms comprising the purine nucleus in the hydrated crystal are essentially coplanar, while in the complex there is a marked degree of puckering (see Table III). The pyrimidine and imidazole portions of the purine system are each planar within the limits of the errors in the atomic positions of the respective atoms. The 5- and 6-membered rings are however tilted from coplanarity about the C4—C(5) bond by 3.7°. This distortion of the purine system could possibly result from intermolecular packing forces, such as polarization bonding between the xanthine and the salicylic acid residue. In the 1:1 complex of caffeine with 5-chlorosalicylic acid (12), the pyrimidine and imidazole portions of the xanthine are also bent in a similar manner; distortion from planarity is 3.2°. TO12 and TC11 are significantly displaced from the plane of the pyrimidine ring, while TO10 and TC13 are essentially coplanar with this ring. Nonbonded intra- and intermolecular contacts may in all probability account for the distortions of these two exocyclic atoms from the pyrimidine ring.

In general the molecular parameters of the salicylic acid residue correspond with those found for the 5-chlorosalicylic acid moiety of the caffeine complex (12) and for salicylic acid itself (17). The differences that exist between the bond lengths and angles in this

Table III—Least-Squares Planes[a]

Atoms Comprising l.s. Plane	Displacement, Å.	Other Atoms	Displacement, Å.
TN1	0.027	TO10	0.009
TC2	0.035	TC11	0.216
TN3	−0.024	TO12	0.109
TC4	−0.035	TC13	−0.012
TC5	−0.045	H12	−0.010
TC6	−0.015	H13	0.241
TN7	−0.013		
TC8	0.037		
TN9	0.007		
−0.8422 X − 0.3381 Y + 0.4199 Z + 6.5311 Å. = 0			
TN1	0.001	TN7	0.098
TC2	0.009	TC8	0.143
TN3	−0.015	TN9	0.090
TC4	0.010	TO10	0.016
TC5	0.000	TC11	0.152
TC6	−0.006	TO12	0.051
		TC13	−0.002
−0.8551 X − 0.3385 Y + 0.3927 Z + 6.6999 Å. = 0			
TC4	0.004	TN1	0.156
TC5	−0.004	TC2	0.164
TN7	0.003	TN3	0.059
TC8	−0.001	TC6	0.072
TN9	−0.002	H12	−0.12
		H13	0.03
−0.8247 X − 0.3379 Y + 0.4536 Z + 6.4065 Å. = 0			
C2	−0.009	C7	−0.014
C2	−0.002	O1	0.014
C3	0.011	O2	−0.016
C4	−0.009	O3	0.023
C5	−0.003	Cl3	0.023
C6	0.011	Cl5	−0.014
		H2	0.02
		H3	−0.07
		H4	−0.04
		H5	−0.13
		TN9[b]	0.025
−0.8644 X − 0.3197 Y + 0.3881 Z + 3.2917 Å. = 0			

[a] The equations of the least-squares planes were calculated according to the method of Schomaker *et al.* (24). [b] This is the nitrogen that is involved in the hydrogen bond with O1.

structure and those observed in the other two salicylic acid structures are only significant about the C3, C4, and C5 atoms of the phenyl ring. The poorer agreement in this region of the molecule most likely reflects the solid solution phenomena, *i.e.* presence of 3-chloro- and 3,5-dichlorosalicylic acid.

The C5—Cl5 length is in excellent agreement with values reported (18) for a number of aromatic C—Cl bonds. The distance between C3 and Cl3, on the other hand, is considerably longer than the commonly found value. The angles about C3 deviate substantially from trigonal symmetry whereas those about C5 do not. An explanation for the unusual bonding parameters found for Cl3, undoubtedly resides in the small occupancy factor associated with this site. It is believed that the standard deviations for the positional parameters of Cl3 are greatly underestimated because of the use of the block diagonal approximation and the very low occupancy factor associated with this atom.

The least-square plane calculated through the phenyl ring of 5-chlorosalicylic acid indicates that the molecule is planar within experimental error (*cf.* Table III). The atomic displacements are greatest (but are not highly significant) in the vicinity of the intramolecular hydrogen bond between O2 and O3. A comparable situation also is found in the salicylic acid structure.

Hydrogen bonds appear to be the predominant stabilizing forces behind this solid-state association complex. These interactions are illustrated in Fig. 2. The weakly basic nitrogen (TN9) of theophylline participates in a relatively strong hydrogen bond with the proton from the carboxyl group of 5-chlorosalicylic acid. The 2.682 ± 0.006 Å. length between the N and O is somewhat longer than the similar interaction observed in the caffeine complex (2.644 ± 0.007). The difference in the strength of this hydrogen bond in the two crystalline complexes most probably reflects the variation in the basic character of N9 of the two xanthine molecules. There is also a hydrogen bond between the TN7 hydrogen of one theophylline and TO10 of a centrosymmetrically equivalent molecule. The same bonding situation also was found in theophylline monohydrate, but the N to O distance is 0.04 Å. shorter in the present instance. The hydrogen bonding scheme (*i.e.*, the two unique hydrogen bonds) is compatible with the infrared data of Cook (19, 26) on analogous solid-state complexes.

In Fig. 2 the dotted lines show the only other intermolecular contacts involving hydrogen atoms that are shorter than a nonbonded contact between the respective atoms. The sum of the van der Waals radii of hydrogen and oxygen is 2.6 Å. (20). A recent article on the topic of C—H hydrogen interactions by Donohue (21) suggests that

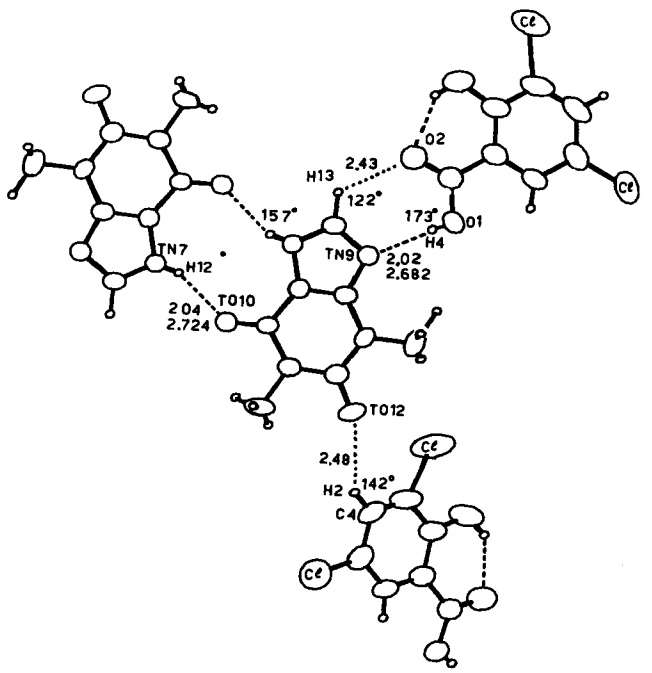

Figure 2—*A view of the molecular species in the crystal lattice showing the hydrogen bonding network (dashed lines). Dotted lines are relatively short C-H . . . O contacts.*

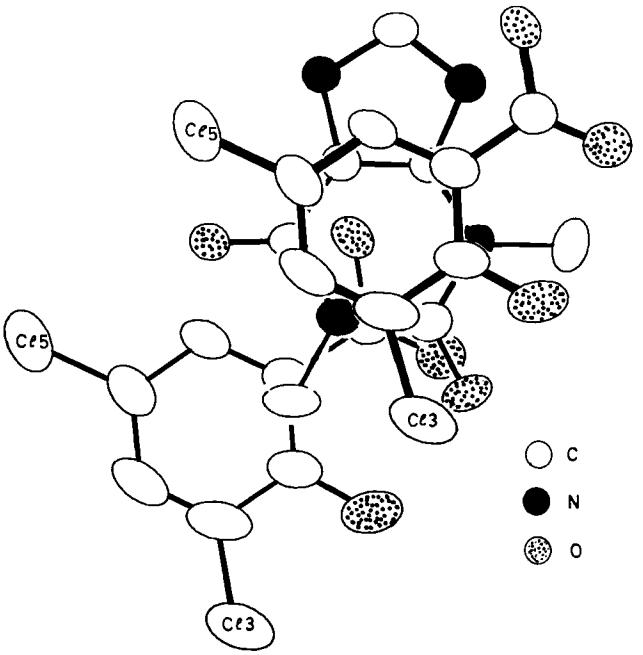

Figure 3—*The stacking arrangement of the 5-chlorosalicylic acid molecules about theophylline. The salicylic acid molecule with the heavier bonds is above the xanthine, while the other is below in this illustration.*

a 2.4 Å. contact between hydrogen and oxygen is a more realistic minimum value for a normal van der Waals contact between these two atoms. It is thus felt that the C—H . . . O contacts shown in Fig. 2 are not hydrogen bonds of the type postulated by Sutor (22). Verification of such hydrogen bonds must be determined by other physical chemical measurements, *e.g.*, infrared data.

In a previous report it was postulated that in certain association complexes (5), the α-β unsaturated ketone portion of a molecule may be involved in polarization bonding with the *pi* system of the other component of the complex. This was shown to be possibly valid in the case of the 1:1 crystalline complex between caffeine and 5-chlorosalicylic acid. In another crystallographic study on an acridine-cytosine complex (23), where neither component has the α-β unsaturated ketone residue, the only apparent intermolecular forces were of the hydrogen bond variety. The stacking arrangement about the theophylline molecule in the present structure, shown in Fig. 3, has certain features that are analogous to those observed in the caffeine complex. The phenyl ring of the salicylic acid moiety that is above theophylline in this illustration, overlaps the TC4, TC5, and TC6 atoms. In light of the variation in the hydrogen bonding schemes of the two xanthine complexes, the stacking orientations are remarkably homologous. The atoms TC5 and TC4 are closer to the phenyl ring (average 3.41 ± 0.01 Å.) than the other members of the xanthine system. The possibility thus exists that a weak attraction exists between the portion of theophylline containing these atoms and the *pi* electrons of the salicylic acid may cause the observed puckering of the xanthine. A parallel situation was also found in the caffeine-5-chlorosalicylic acid complex. The packing arrangement and the mode of puckering of the purine nucleus lend support to the idea that a localized attractive force polarization bonding exists between the phenyl ring and the α-β unsaturated ketone portion of the xanthine in this complex (5).

Other crystallographic analyses of complexes are underway in this laboratory, which hopefully will permit more definitive descriptions of these interactions to be made.

REFERENCES

(1) "Molecular Associations in Biology," B. Pullman, Ed., Academic Press, New York, N. Y., 1968.

(2) T. Higuchi and J. L. Lach, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 349(1954).

(3) T. Higuchi and D. A. Zuck, *ibid.*, **41**, 10(1952); *ibid.*, **42**, 132(1953).
(4) M. Donbrow and Z. A. Jan, *J. Pharm. Pharmacol., Suppl.*, **17**, 1295(1965).
(5) E. Shefter, *J. Pharm. Sci.*, **57**, 350(1968).
(6) R. S. Schnaare and A. N. Martin, *ibid.*, **54**, 1707(1965).
(7) T. F. Furnas and D. Harker, *Rev. Sci., Instr.*, **26**, 449(1955).
(8) D. Sayre, *Acta Cryst.*, **5**, 60(1952).
(9) H. Hauptman and J. Karle, "Solution of the Phase Problem I., The Centrosymmetric Crystal," ACA monograph No. 3, Polycrystal Book Service, Pittsburgh, Pa., 1953.
(10) R. E. Long, Ph.D. thesis, University of California, Los Angeles, 1965.
(11) I. L. Karle, H. Hauptman, J. Karle, and A. B. Wing, *Acta Cryst.*, **11**, 257(1958).
(12) E. Shefter, *J. Pharm. Sci.*, **57**, 1163(1968).
(13) "International Tables for X-ray Crystallography," vol. III, Kynoch Press, Birmingham, England, p. 202.
(14) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175(1965).
(15) V. Schomaker and K. N. Trueblood, *Acta Cryst.* **B24**, 63 (1968).
(16) D. J. Sutor, *ibid.*, **11**, 83(1958).
(17) M. Sundaralingam and L. H. Jensen, *ibid.*, **18**, 1053(1965).
(18) G. Gafner and F. H. Herbstein, *ibid.*, **15**, 1081(1962).
(19) D. Cook, personnal communication.
(20) L. Pauling, "The Nature of the Chemical Bond," 3rd ed., Cornell University Press, Ithaca, N. Y., 1960.
(21) J. Donohue, in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Eds., W. H. Freeman, San Francisco, Calif., 1968, p. 443.
(22) D. J. Sutor, *J. Chem. Soc.*, **1963**, 1105.
(23) E. Shefter, *Science*, **160**, 1351(1968).
(24) V. Schomaker, J. Waser, R. E. Marsh, and G. Bergman, *Acta Cryst.*, **12**, 600(1959).
(25) A. Tulinsky, C. R. Worthington, and E. Pignataro, *ibid.*, **12**, 623(1959).
(26) D. Cook and Z. R. Regner, *Can. J. Chem.*, **46**, 3055(1968).

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Nuclear Magnetic Resonance and Rheological Studies on the Thixotropic Properties of Montmorillonite–Water Systems

ARTHUR H. KIBBE and OSCAR E. ARAUJO

Abstract □ Several proposed mechanisms of the thixotropic behavior of montmorillonite-water systems were evaluated. The effects of temperature, reshearing, concentration, and storage time on these systems were studied by means of NMR and rheological measurements. The specific parameters used were the change in line width of the NMR spectrum and the static yield values obtained from the rheograms. The results indicate clear agreement with the theory that the colloidal particles upon contact adhere to form a spacious matrix resembling a house of cards.

Keyphrases □ Montmorillonite-water systems—rheology □ Thixotropic behavior—montmorillonite-water systems □ Stability—montmorillonite-water systems □ NMR spectroscopy—analysis

Montmorillonite–water systems have long been under study by physical chemists and more recently by the pharmaceutical industry because of their unique thixotropic behavior.

Hause and Reed (1) found that as little as 0.05% bentonite was sufficient to stop gas bubbles from rising to the surface.

Norton and Johnson (2) studied the properties of monodispersed clay-water systems and calculated the thickness of the water film, finding it to be approximately two molecules thick.

Freundlich (3), von Engelhardt (4), and Hause (5) assume that there are long-range electrical forces which permit the individual particles to act over distances of the order of 10^3 Å. This would be similar to the type of structure found in a magnet where all the free electrons of the iron are lined up in the same direction.

Usher (6), Kuhn (7), and Hofmann (8) prefer a mechanical picture of thixotropy in which the particles touch one another, adhere on contact, and build up a spacious matrix resembling a house of cards.

Macy (9), McBain (10), and Grim and Cuthbert (11) explain the rheological mechanism of montmorillonite mixtures by assuming that the aqueous layer which surrounds the clay particle becomes rigid as if it had crystallized into ice.

Williamson (12) reviewed the physical relationship between clay and water systems and concluded that the "ice" theory is the least satisfactory explanation for the rigidity of the water film on clay.

The strength of thixotropic gels increases with decreasing particle size. Brownian molecular motion is nonexistent in truly thixotropic systems and the particles which have ceased to move seem to be clearly separated from each other by water (12).

In 1945 Ewing (13) felt that bentonite had become of such importance in pharmaceutical preparations that he