Solid-state Dehydrochlorination and Decarboxylation Reactions. Part 2.[1] Reactions of Three Crystal Habits of *p*-Aminosalicylic Acid Hydrochloride and the Crystal Structure of *p*-Aminosalicylic Acid Hydrochloride

By **Chung-Tang Lin, Pik-Yen Siew, and Stephen R. Byrn,*** Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907, U.S.A.

Three crystal habits of *p*-aminosalicylic acid hydrochloride were obtained and the crystal structure determined. Crystals are monoclinic, space group $P2_1/c$, with a = 5.316(2), b = 8.464(3), and c = 17.888(9) Å, β = 93.30(3)°, and Z = 4. The structure was solved by direct methods and refined to R 0.099 for 923 observed reflections. The crystal packing of *p*-aminosalicylic acid is dominated by $H \cdots Cl^-$ hydrogen bonds and there are no carboxy-dimers. The carboxy-proton is instead hydrogen-bonded to a Cl^- ion.

Upon heating at 95 °C all three crystal habits lost HCl from one crystal face and then decarboxylated. The anisotropic behaviour of two of the three crystal habits is consistent with crystal packing while the third is not.

Crystals of all the three habits also lost HCl when placed in contact with Na_2CO_3 at room temperature and 60 °C. This reaction always started at the point of contact of the base and proceeded through the crystal anisotropically, resulting in dehydrochlorination and formation of the *p*-aminosalicylate anion. The anisotropic behaviour of two of the crystal habits is consistent with crystal packing. Different reactivity of these crystal habits with gaseous amines was also observed.

IN the preceding paper[1] we reported that the decarboxylation of *p*-aminosalicylic acid hydrochloride involves initial loss of HCl followed by electrophilic substitution and carbon dioxide loss to give *m*-aminophenol hydrochloride. In this paper we report a detailed study of three different crystal habits of *p*-aminosalicylic acid hydrochloride at 95 °C. In addition, we found that a solid–solid acid–base reaction of *p*-aminosalicylic acid hydrochloride can be initiated by placing these crystals in contact with sodium carbonate. This is an example of an organic solid–solid reaction. Such reactions are rare and are also models for drug-excipient reactions, which are sometimes observed in solid dosage forms.

EXPERIMENTAL

I.r. spectra were measured on a Beckman IR 33 or 4230 instrument. N.m.r. spectra were measured as in the preceding paper. *p*-Aminosalicylic acid hydrochloride crystallized in three habits: habit I from aqueous solution as thin small plates, habit II from dilute aqueous HCl solution as prisms, and habit III from dilute aqueous HCl solution as plates. All crystallographic calculations were carried out by use of '*X*-Ray '72,' Technical Report TR 192, Computer Science Center, University of Maryland.

Crystal Data.—$C_7H_7NO_3{\cdot}HCl$, M = 189.6. Monoclinic, a = 5.316(2), b = 8.464(3), c = 17.888(9) Å, β = 93.30(3)°, U = 803.5 Å^3, Z = 4, D_c = 1.567 g cm^{-3}, $F(000)$ = 392. Cu-K_α radiation, λ = 1.541 8 Å; μ(Cu-K_α) = 39.72 cm^{-1}. Space group $P2_1/c$ from systematic absences.

Data Collection.—Accurate unit-cell parameters were determined by least-squares analysis of the 2θ values of 14 independent accurately centred reflections. A crystal of habit I (0.113 × 0.143 × 0.050 mm^3) was aligned with its b axis (longest direction) parallel to the ϕ axis of a Picker four-circle card-driven diffractometer. Data were collected with β-filtered Cu-K_α radiation and a scintillation detector with a 2θ scan range of 2.2° and a scan speed of 30 s deg^{-1}. Background readings were taken for 10 s at each end of the scan range and data were collected to $2\theta_{max.}$ 132.23°. Data were scaled with respect to two reference reflections which were measured every 60 reflections, and which decayed <10% during data collection. Data were corrected for Lorentz polarization. The number of independent reflections was 1 516 of which 923 had $F_o > 3\sigma(F_o)$ and were considered observed.

Structure Analysis.—Application of the symbolic addition procedure (programs Singen and Phase) to those reflections with E values >1.4 gave phases which upon Fourier analysis gave an E map which revealed the co-ordinates of the chlorine and six other atoms. Remaining non-hydrogen atoms were located from a Fourier synthesis.

Refinement using first isotropic and then anisotropic temperature factors proceeded to R 0.109 and R' 0.078 when reflections with $F < 3\sigma(F) = W^{-1}$ were weighted out.

A difference-Fourier synthesis gave the positions of 5 of the 8 hydrogen atoms, and these were assigned isotropic temperature factors. With only the parameters of non-hydrogen atoms set to vary, least-squares refinement gave R 0.102 and R' 0.070. The hydrogen atoms missing in the structural model were those attached to C(5), O(3), and HCl. Positions of these atoms were calculated assuming H (HCl) to be the third hydrogen atom of the $R{-}\overset{+}{N}H_3$ group. When these hydrogen atoms were added to the least-squares calculation there was no improvement in the fit of the model to the data. A final difference map revealed two additional peaks of height comparable to hydrogen atoms but in chemically unreasonable positions. Consequently they were ignored. An isotropic extinction correction was applied giving a final R of 0.099 and R' 0.068, the extinction parameter being 1 573. Final observed and calculated structure factors and anisotropic thermal parameters are deposited in Supplementary Publication No. SUP 22239 (3 pp., 1 microfiche).*

Optical Goniometry of the Three Crystal Habits of p-*Aminosalicylic Acid Hydrochloride.*—The interfacial angles were measured on a Huber optical goniometer and compared to the calculated angles by use of a computer program. The assigned faces were confirmed using precession photography. These precession photographs also showed that the three crystal forms were different crystal habits with the

---

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

[1] C. T. Lin, P. Y. Siew, and S. R. Byrn, preceding paper.

same internal structure and not polymorphs. Figure 1 shows the Miller indices of these habits.

Solid-state Reactions.—Reactions were usually run on a Mettler FP 5 hot-stage sealed between two cover slides. The solid–solid reactions were run by placing crystals of Na_2CO_3 in contact with crystals of *p*-aminosalicylic acid hydrochloride. The solid–gas reactions were run by placing crystals of the hydrochloride salt and methenamine inside a steel ring sealed between two cover slides.

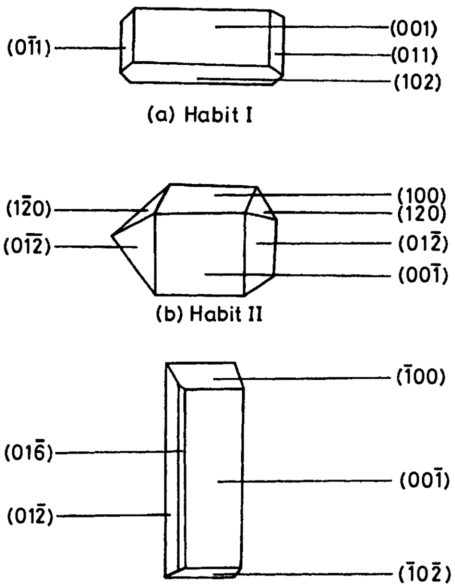
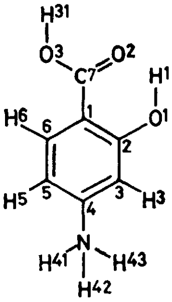


FIGURE 1 Schematic diagram of the Miller indices of the faces of (a) habit I, (b) habit II, and (c) habit III

RESULTS AND DISCUSSION

Crystal Structure of p-*Aminosalicylic Acid Hydrochloride* (I).—Table 1 lists bond lengths and angles and Table 2 atom parameters. Both are quite similar to those in *p*-aminosalicylic acid[1] itself (II). The biggest differences occur in bonds and angles involved in the amino group. The C(4)–N^+(1) bond in (I) is 1.46(1) Å while C(4)–N(1) in (II) is 1.36 Å. These differences are consistent with those observed in other aromatic amines. The expected C–N distance in aromatic amines[2,3] is 1.37 Å, and Ar-NH_2 distances of 1.37, 1.39, and 1.41 Å were observed for *p*-nitroaniline,[4] *p*-aminophenol,[5] and 2,5-dichloroaniline.[6] In contrast, Ar–NH_3^+ distances are much longer, *e.g.* 1.455 for *m*-toluidine hydrochloride,[7] 1.474 for *o*-aminophenol hydrochloride,[8] 1.49 for *p*-phenylenediamine hydrochloride,[2] 1.45 for *o*-phenylenediamine dihydrobromide,[3] and 1.45 Å for *p*-toluidine hydrochloride.[9]



(1)

TABLE 1

Bond lengths (Å) and angles for *p*-aminosalicylic acid hydrochloride (I)

(*a*) Bond lengths			
O(1)–C(2)	1.33(1)	C(1)–C(6)	1.42(1)
O(2)–C(7)	1.23(1)	C(1)–C(7)	1.45(1)
O(3)–C(7)	1.35(1)	C(2)–C(3)	1.38(1)
O(2)–O(1)	2.60(1)	C(3)–C(4)	1.41(1)
N(1)–C(4)	1.46(1)	C(4)–C(5)	1.42(1)
C(1)–C(2)	1.43(1)	C(5)–C(6)	1.35(1)
(*b*) Bond angles			
O(2)–C(7)–O(3)	120.0(9)	O(1)–C(2)–C(3)	117.9(8)
O(2)–C(7)–C(1)	124.0(8)	C(2)–C(3)–C(4)	119.7(7)
O(3)–C(7)–C(1)	115.9(7)	C(3)–C(4)–C(5)	122.2(8)
C(7)–C(1)–C(2)	118.8(7)	C(3)–C(4)–N(1)	120.5(7)
C(7)–C(1)–C(6)	123.7(8)	C(5)–C(4)–N(1)	117.3(7)
C(2)–C(1)–C(6)	117.4(7)	C(6)–C(5)–C(4)	116.2(7)
C(1)–C(2)–O(1)	122.3(7)	C(1)–C(6)–C(5)	124.6(8)
C(1)–C(2)–C(3)	119.8(9)		

TABLE 2

Atomic parameters for *p*-aminosalicylic acid hydrochloride ($\times 10^4$; for H $\times 10^3$), with estimated standard deviations in parentheses

	x	*y*	*z*
Cl	1 088(4)	4 216(3)	2 408(1)
O(1)	1 986(12)	1 402(9)	5 562(3)
O(2)	5 032(14)	2 959(10)	6 479(4)
O(3)	8 211(12)	4 349(9)	6 037(3)
N(1)	3 996(13)	1 079(9)	2 978(4)
C(1)	5 632(17)	2 831(13)	5 175(5)
C(2)	3 497(18)	1 832(12)	5 027(5)
C(3)	2 952(18)	1 274(12)	4 315(5)
C(4)	4 519(19)	1 683(12)	3 736(5)
C(5)	6 620(17)	2 708(12)	3 854(5)
C(6)	7 105(17)	3 211(12)	4 561(5)
C(7)	6 224(20)	3 355(14)	5 930(6)
H(31) *	845	483	656
H(11)	197	125	612
H(3)	147	48	411
H(43)	259	42	287
H(42)	325	185	276
H(41) *	562	81	273
H(5) *	770	304	343
H(6)	861	386	474

* Calculated as described in the text.

Only one other bond length and four bond angles in *p*-aminosalicylic acid (II) differ by $>3\ \sigma$ from those in (I); they are C(7)–O(3) 1.35(1) *vs.* 1.311, angles C(3)–C(4)–C(5) 122.2(8) *vs.* 118.7, C(5)–C(4)–N(1) 117.3(7) *vs.* 120.6, C(6)–C(5)–C(4) 116.2(7) *vs.* 120.1, and C(1)–C(6)–C(5), 124.6(8) *vs.* 122.0. The hydrogen bond is approximately the same strength in each, since the O(1) · · · O(2) distances are 2.60(1) and 2.620.

---

[2] R. Chandrasekaran, *Acta Cryst.*, 1969, **B25**, 369.

[3] C. Stalhandske, *Acta Chem. Scand.*, 1972, **26**, 3029.

[4] K. N. Trueblood, E. Goldish, and J. Donohue, *Acta Cryst.*, 1961, **14**, 1009.

[5] C. J. Brown, *Acta Cryst.*, 1951, **4**, 100.

[6] T. Sakurai, M. Sundaralingam, and G. Jeffery, *Acta Cryst.*, 1963, **16**, 354.

[7] F. Fowweather and A. Hargreaves, *Acta Cryst.*, 1950, **3**, 81.

[8] A. F. Cesur and J. P. G. Richard, *Z. Krist.*, 1965, **129**, 283.

[9] G. vonEller, *Bull. Soc. France Mineral. Cryst.*, 1959, p. 257.

Analyses of the least-squares planes (by use of '*X-Ray '72*' and Table 4 of ref. 10) showed that the probability that the aromatic ring [C(1)—(6)] was planar was 0.5. Atoms C(7), O(1), and N(1) were —0.058, 0.008, and —0.037 Å out of this best plane.

Table 3 lists dihedral angles involving the ring substituents. The O(1)–C(2)–C(1)–C(7) and O(1)–C(2)–C(1)–C(6) angles are consistent with O(1) being essentially in the plane of the ring. Similarly, the N(1)–C(4)–C(3)–C(2) and N(1)–C(4)–C(5)–C(6) angles indicate N(1) to be only slightly out of the plane of the ring.

TABLE 3

Dihedral angles (°) in *p*-aminosalicylic acid hydrochloride, with estimated standard deviations in parentheses

O(2)–C(7)–C(1)–C(2)	2(2)
O(2)–C(7)–C(1)–C(6)	−176(1)
O(3)–C(7)–C(1)–C(6)	5(2)
O(3)–C(7)–C(1)–C(2)	−178(1)
O(1)–C(2)–C(1)–C(7)	2(1)
O(1)–C(2)–C(1)–C(6)	−180(1)
N(1)–C(4)–C(3)–C(2)	179(1)
N(1)–C(4)–C(5)–C(6)	−178(1)

The dihedral angles which terminate in O(2) and O(3) indicate that both oxygen atoms of the carboxy-group are slightly out of the plane of the aromatic ring and that the angle between the carboxy-plane and plane of the aromatic ring is approximately 3.3°.

Crystal Packing.—The crystal packing is controlled by $\overset{+}{N}H \cdots Cl^-$, $OH \cdots Cl^-$, and $\overset{+}{N}H \cdots O$ intermolecular hydrogen bonds. Table 4 lists all non-hydrogen atom intermolecular contacts and Table 5 all important intermolecular contacts involving hydrogen atoms.

TABLE 4

Intermolecular contacts ⩽ 3.5Å not involving hydrogen atoms

$N(1) \cdots Cl$	3.029(5)	$O(1) \cdots C(4^{IV})$	3.40(1)
$O(3) \cdots O(1^{I})$	3.34(1)	$C(3) \cdots C(2^{IV})$	3.41(1)
$C(6) \cdots O(1^{I})$	3.43(1)	$C(3) \cdots O(1^{V})$	3.48(1)
$C(6) \cdots O(3^{II})$	3.45(1)	$Cl \cdots N(1^{VI})$	3.162(8)
$Cl \cdots O(3^{III})$	3.039(7)	$Cl \cdots N(1^{VII})$	3.171(8)
$C(6) \cdots C(7^{III})$	3.49(2)	$O(2) \cdots Cl^{VIII}$	3.308(8)
$C(4) \cdots O(1^{IV})$	3.40(1)	$O(1) \cdots Cl^{VIII}$	3.403(7)
$C(2) \cdots C(2^{IV})$	3.49(1)	$O(2) \cdots N^{VIII}$	2.88(1)
$C(2) \cdots C(3^{IV})$	3.41(1)		

Roman numeral superscripts denote the following equivalent positions relative to the reference molecule at *x*, *y*, *z*:

I	$x + 1, y, z$	V	$-x, -y, 1 - z$
II	$2 - x, 1 - y, 1 - z$	VI	$1 - x, \frac{1}{2} + y, \frac{1}{2} - z$
III	$1 - x, 1 - y, 1 - z$	VII	$-x, \frac{1}{2} + y, \frac{1}{2} - z$
IV	$1 - x, -y, 1 - z$	VIII	$x, \frac{1}{2} - y, \frac{1}{2} + z$

Figure 2 shows the packing of *p*-aminosalicylic acid hydrochloride, and together with Table 4 show that, surprisingly, there are no carboxylic acid dimers. The carboxylic acid hydrogen atom [H(31)] was not located from a difference map; however the non-hydrogen atom contacts show it to be involved only in $OH \cdots Cl^-$ hydrogen bond, thus its position was calculated assuming it was on the line connecting O(3) and Cl^- and 1.02 Å from O(3). The $O(3) \cdots Cl^-$ distance [3.039(7) Å] is shorter than a similar contact in the $OH \cdots Cl$ hydrogen bond in $CuCl_2 \cdot 2H_2O$ (3.18 Å), and in methylglyoxalbisguanyl hydrazone (3.09 and 3.15 Å).[11] Similarly, one hydrogen atom of the NH_3^+ group [H(43)] was not located from a difference map but its position was calculated assuming tetrahedral geometry and it is probably only involved in an $\overset{+}{N}H \cdots Cl^-$ hydrogen bond. The $\overset{+}{N}(1) \cdots Cl^-$ distances of 3.029(5) and 3.177(8) compare favourably with the $N^+ \cdots Cl^-$ distances of 3.10, 3.22, 3.26, and 3.26 in *m*-toluidine dihydrochloride,[7] 3.08 in procaine hydrochloride,[12] and 3.20, 3.21, and 3.25 Å in *p*-phenylenediamine dihydrochloride.[2]

TABLE 5

Hydrogen–chlorine or hydrogen–oxygen contacts less than the sum of the van der Waals radii

$H(42) \cdots Cl$	2.38	$H(42) \cdots O(2^{IV})$	2.53
$H(43) \cdots Cl^{II}$	2.24	$H(21) \cdots Cl^{V}$	2.41
$H(41) \cdots Cl^{III}$	2.23	$H(31) \cdots Cl^{VI}$	2.02
$H(41) \cdots O(2^{IV})$	2.48		

Roman numeral superscripts denote the following equivalent positions relative to the reference molecule at *x*, *y*, *z*:

I	$-x, -\frac{1}{2} + y, \frac{1}{2} - z$	IV	$1 + x, \frac{1}{2} - y, \frac{1}{2} + z$
II	$1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$	V	$1 - x, 1 - y, 1 - z$
III	$1 + x, \frac{1}{2} - y, -\frac{1}{2} + z$		

van der Waals radii were taken from A. I. Kitaigorodskii, 'Organic Chemical Crystallography,' Consultants Bureau, 1961, p. 6, as Cl + H = 2.95 Å and O + H = 2.53 Å. The positions of H(31) and H(43) were calculated as described in the text.

The other two hydrogen atoms attached to N(1) [H(41) and H(42)] and the hydroxy-hydrogen atom [H(21)] were located from difference maps and appear to be involved in bifurcated hydrogen bonds (see Tables 4 and 5). The H(21) bifurcated hydrogen bond involves an intramolecular $OH \cdots O$ hydrogen bond and an intermolecular $OH \cdots Cl^-$ hydrogen bond.

Solid-state Reactions.—The three crystal habits of *p*-aminosalicylic acid were studied at 95 °C and the behaviour of habits I and II is shown in Figure 3. The opaque region corresponds to disorder apparently caused by initial loss of HCl followed by decarboxylation. Parts (b) and (c) of Figure 3 (upper sequence) show that HCl exits the crystal parallel to the *b* direction in habit I. The crystals of habit I are quite thin, thus it is impossible directly to observe the reaction in the *c* direction; however, the photographs in Figure 3 give the impression that the reaction proceeds in thin layers of the crystal. If this were indeed the case, then the reaction would be slower in the *c* direction. Parts (b), (c), and (d) of Figure 3 (lower sequence) show that HCl exits the crystal parallel to the *a* direction in habit II.

Examination of Figure 2, which shows the crystal packing, shows that a hydrogen chloride molecule, once formed, could exit the crystal along the *a* or *b* crystallographic direction without encountering any nonpolar

---

[10] W. C. Hamilton, 'Statistics in Physical Science,' Ronald Press, New York, p. 207.

[11] W. C. Hamilton and J. A. Ibers, 'Hydrogen Bonding in Solids,' W. A. Benjamin, New York, 1968, p. 262.

[12] D. D. Dexter, *Acta Cryst.*, 1972, **B28**, 77.

functional groups. In these crystallographic directions HCl could pass through the crystal and exit remaining entirely in contact with amine and carboxy-functions.

Exit of HCl along the *c* crystallographic direction may also be possible because the crystallographic plane is lined with chloride ions, hydroxy-groups, amine groups,

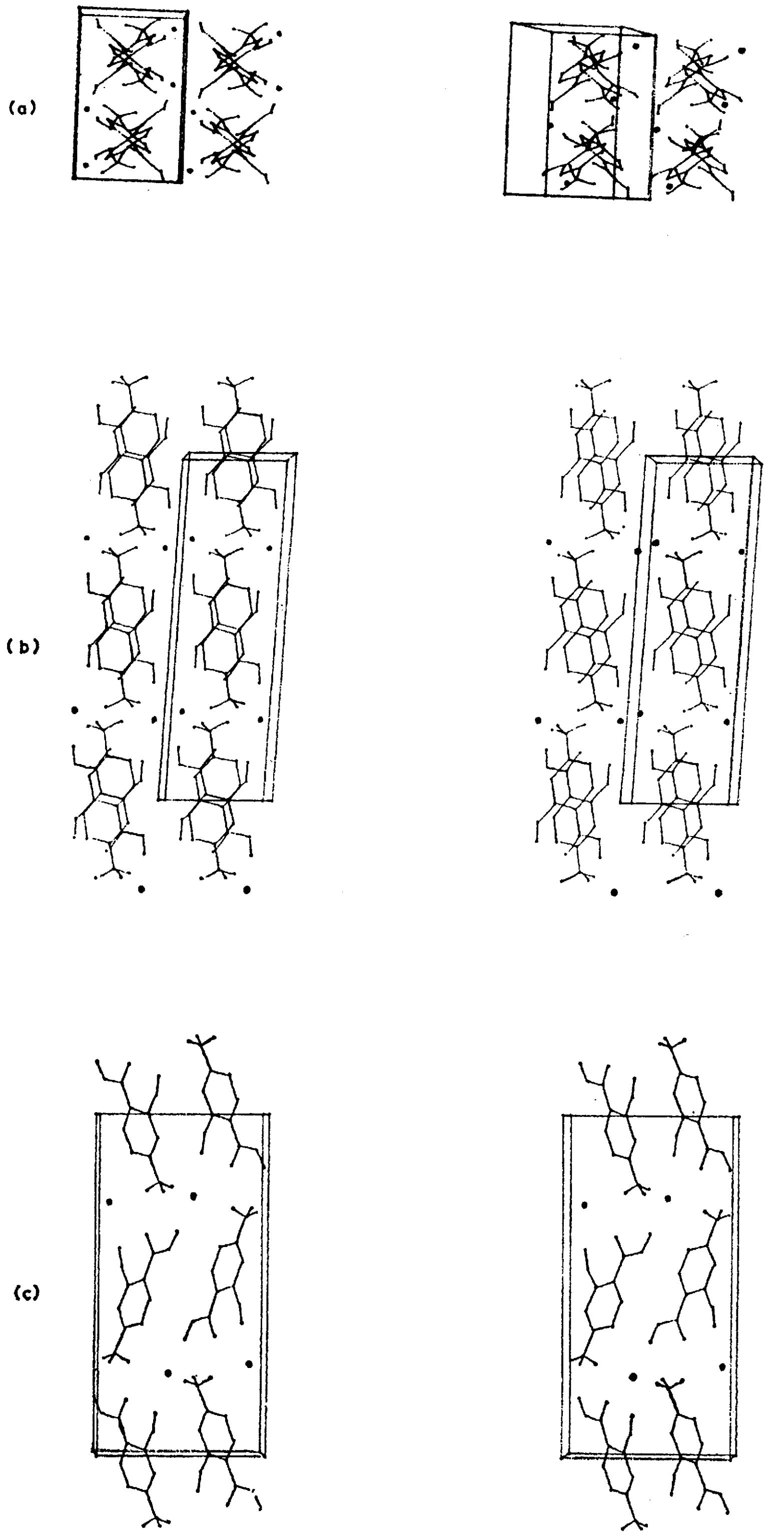


FIGURE 2 Stereoscopic drawings of the crystal packing of *p*-aminosalicylic acid hydrochloride viewed from the *a*, *b*, and *c* crystallographic directions. The axial directions are: (a) origin at lower left, *a* across, *b* up, and *c* out of plane of paper; (b) origin at upper left, *a* across, *c* down and, *b* out of plane of paper; and (c) origin at upper right, *b* across, *c* down, and *a* out of plane of paper

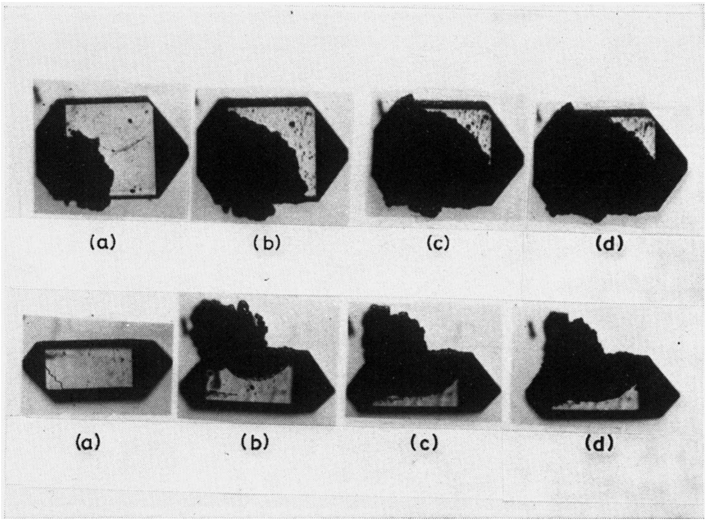


FIGURE 4 Upper sequence: reaction of a crystal of habit II with Na_2CO_3 (dark mass) viewed from the *c* crystallographic direction. (a) Start, (b) after 13 days, (c) after 21 days, and (d) after 30 days. Direction of the crystal axes *a* up, *b* across, and *c* into page.

Lower sequence: reaction of the same crystal viewed from the *a* crystallographic direction. This sequence was obtained by turning the crystal in the upper sequence on its side. (a) Start, (b) after 13 days, (c) after 21 days, and (d) after 30 days. Direction of crystal axes *b* across, *c* down, and *a* into page

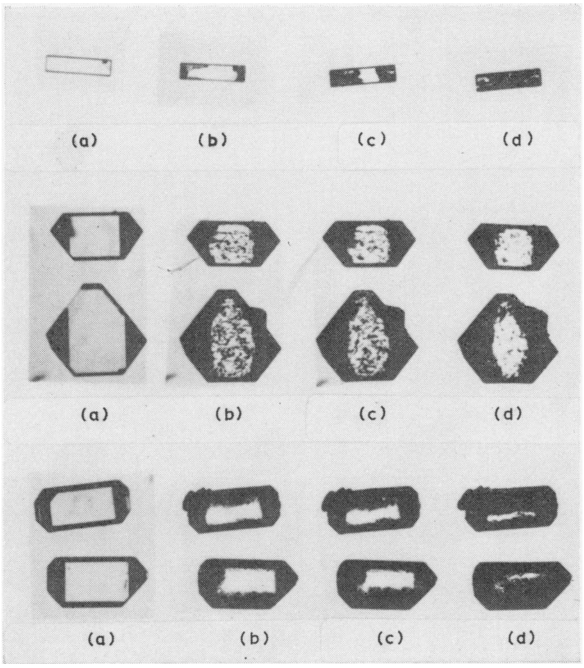


Figure 3 Upper sequence: reaction of crystals of habit I of *p*-aminosalicylic acid hydrochloride when heated at 95 °C. (a) Start, (b) after 38 h, (c) after 66 h, (d) after 86 h. Direction of crystal axes ***a*** down, ***b*** across, and ***c*** out of plane of paper. (See Figure 1 for illustration of crystal faces).

Middle sequence: reaction of crystals of habit II viewed from the ***a*** crystal direction when heated at 95 °C. (a) Start (b) after 18 h, (c) after 24 h, and (d) after 30 h. Direction of crystal axes ***c*** up, ***b*** across, and ***a*** out of plane of paper.

Lower sequence: reaction of crystals of habit II viewed from the ***c*** crystal direction when heated at 95 °C. (a) Start, (b) after 18 h, (c) after 24 h, and (d) after 48 h. Direction of the crystal axes is ***a*** up, ***b*** across, and ***c*** out of plane of paper and hydrocarbon functions which would be encountered by the HCl molecules.

Thus the crystal packing predicts that the dehydrochlorination reaction would occur along both the *a* and *b* crystallographic directions. Attempts to explain why the reaction of habit I occurred along the *b* direction in terms of the actual accessibility of the ammonium and chloride ions to the developed crystal faces $(0\bar{1}1)$, (011), or (102) failed. Careful examination of the crystal packing viewed from the $(0\bar{1}1)$, (011), and (102) faces showed no obvious hydrocarbon barriers to exit of HCl from any of these faces. Attempts to explain the behaviour of habit II using similar considerations also failed. Thus, the best available explanation for the anisotropic loss of HCl from habits I and II involves nucleation. We suggest that the reaction nucleates on the end of the crystals of habits I and II and, once initiated, moves from the ends where nucleation occurred toward the centre, because once initiated the loss of HCl is more favourable from the reacted and disturbed areas.

Nucleation was also used to explain the loss of water of hydration from crystal hydrates upon cutting with a razor blade [13] and the reaction of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate,[14] which began at one end of the crystal and proceeded through the crystal from the original site of reaction in a manner which could be explained by crystal packing. The important role of nucleation in dehydrochlorination reactions is further supported by the failure of habit III to behave as expected (see later).

Comparison of the upper and lower sequences of Figure 3 indicates that in the reaction of habit II (lower sequence) which begins on the *a* face, no fingers of reaction extend into the crystal. In the reactions of habit I, regions of disorder extend like fingers in the *b* direction [photo (b), upper sequence]. One possible interpretation of this behaviour is that the reaction is slightly faster in the *a* crystal direction than in the *b* direction. Thus, in the case where the reaction proceeds parallel to the *a* direction, a sharp front is observed while in the case where the reaction is parallel to the *b* direction the reaction proceeds more slowly giving the effect of fingers which are filled in by rapid reaction in the *a* direction.

This explanation is consistent with a careful analysis of the area of the tunnels available to exiting HCl (and CO_2) molecules along the *a* and *b* crystallographic directions. The tunnel area was calculated as follows: (1) a projection with the scale of 1 cm per Å was made along the *a* and *b* crystal directions, (2) it was assumed that H(43) and Cl had exited, (3) the atomic radii of H (1.17 Å) and O (1.36 Å) were used to determine the boundaries of the tunnels, and (4) the tunnel area was determined using a planimeter. These calculations showed that the tunnel parallel to the *a* direction had an area of 3.23 Å^2, while that parallel to the *b* direction had an area of 1.60 Å^2. These areas indicate that HCl loss should be faster parallel to the *a* than to the *b* direction, as observed. Furthermore, the ring–ring distances also indicate looser packing parallel to *a* (ring–ring contact of 5.316 Å) than to the *b* direction (4.232 Å). Thus, crystal packing is consistent with the slightly different rates of HCl loss in the *a* and *b* crystallographic directions.

The behaviour of habit III upon heating can best be explained in terms of nucleation and subsequent reaction from the disturbed and reacted areas. Crystals of habit III pitted on the (001) crystal face and then the crystal became opaque. As mentioned earlier, reaction from the (001) face is not expected, owing to the layers of hydrocarbon functions perpendicular to the *c* axis. This observation shows that the (001) face of habit III behaves differently from the same face in habits I and II. Unfortunately, the crystals of habit III were quite thin and it was impossible to view the reaction from other crystal faces. It is possible that the reaction is confined to the surface, since the time required for a crystal of habit III to become opaque was less than half that required by the crystals of other habits.

We have also investigated the reactions of habits I and II of *p*-aminosalicylic acid hydrochloride with gaseous primary, secondary, and tertiary amines. The reactions of primary and secondary amines were rapid and produced liquids. However, hexamethylenetetramine reacted with only the (001) face of habit I (30 min) while habit II [particularly the (001) and (100) crystal faces] did not react even after 72 h. In a possibly related instance, we have found that different crystal habits of aspirin reacted with hexamethylenetetramine at different rates.[15] In addition, crystals of enantiomorphs of acids were reported to react with optically active amines at different rates.[16]

Solid–Solid Reactions of p-*Aminosalicylic Acid Hydrochloride.*—All three habits of *p*-aminosalicylic acid hydrochloride underwent solid–solid reactions with sodium carbonate (see Figure 4 for photographs of a typical reaction). These reactions always began at the point where the acid crystal and base touched. They were quite slow and took more than 40 days to reach completion at 60 °C. If the reaction was run at room temperature droplets of water could be observed after a few days; however, at 60 °C no water droplets were observed. The water droplets resulted from the breakdown of carbonic acid and apparently at elevated temperatures the vapour pressure of water was sufficiently large to prevent condensation. Analysis of the end products of the reaction indicated that both *p*-aminosalicylic acid and *p*-aminosalicylate ion were present. Thus solid–solid acid–base reactions do occur and these reactions are slow in comparison to their solution counterparts. We suggest that the slow rate of

---

[13] S. R. Byrn and C. T. Lin, *J. Amer. Chem. Soc.*, 1976, **98**, 4004.

[14] S. R. Byrn, I. C. Paul, and D. Y. Curtin, *J. Amer. Chem. Soc.*, 1972, **94**, 890.

[15] S. R. Byrn and C. T. Lin, unpublished observations.

[16] C. T. Lin, I. C. Paul, and D. Y. Curtin, *J. Amer. Chem. Soc.*, 1974, **96**, 6199.

reaction is probably due to slow diffusion rates [17-20] of ions in the *p*-aminosalicylic acid hydrochloride crystal lattice. In addition, the fact that these reactions always began at the point of contact of the acid crystals and base and spread through the crystal from that point indicates that these reactions can be artificially nucleated and the reaction proceeds from the nucleation site which may involve a defect throughout the crystal. This behaviour is similar to that of single crystals of *p*-aminosalicylic acid hydrochloride at 95 °C, since once these crystals began to react the reaction spread from that nucleation site throughout the crystal. It should be noted that while the thermal reaction of *p*-aminosalicylic acid hydrochloride probably involves loss of HCl by diffusion, these solid–solid acid–base reactions could involve either diffusion of HCl to the sodium carbonate or counterdiffusion of the H^+ or Na^+ ions to form H_2CO_3 in the base and NaCl in the acid lattice.

Although organic solid–solid reactions are relatively rare, solid–solid reactions which form spinels from metal oxides (*e.g.* Al_2O_3 and MgO) at high temperatures have been carefully studied,[17-20] and the most probable mechanism of these reactions involves counterdiffusion of cations.

The behaviour of a crystal of habit I of *p*-aminosalicylic acid hydrochloride in contact with sodium carbonate on the (011) and $(0\bar{1}1)$ crystal faces, is quite similar to that of crystals of habit I upon heating, except that the reaction begins on only the end where the Na_2CO_3 is touching and moves to the other end. As in the thermal reaction of crystals of habit I, the photographs give the impression that the reaction is proceeding in layers and that it is slower in the *c* direction than in the *b* crystallographic direction.

When a crystal of habit I of *p*-aminosalicylic acid hydrochloride is placed in contact with sodium carbonate on the (102) face, the reaction begins at the point of contact and after five days the distance of the reaction front from the point of contact indicates the reaction is equally as fast in the *a* and *b* crystallographic directions. After 40 days the reaction stopped before it reached completion. The reaction rates in the *a* and *b* direction are consistent with crystal packing, which indicated that ion migration along either the *a* or *b* direction would be favourable (however, see above).

Figure 4 shows the behaviour of a crystal of habit II of *p*-aminosalicylic acid hydrochloride when Na_2CO_3 was placed on the *c* face. Measurement showed that the ratio of distances which the front had to move to reach completion in the *a* : *b* : *c* direction was 3.5 : 5 : 5. After 13 days the reaction had proceeded equally far in the *a* and *b* crystal directions and after 21 days the reaction had reached completion in the *a* and *b* direction but was not completed in the *c* direction. This data qualitatively shows that the reaction of habit II is faster in the *a* and *b* directions than in the *c* direction. These relative rates are consistent with crystal packing which showed that migrating ions encounter more hydrocarbon functions when migrating in the *c* than in the *a* and *b* directions.

This research was supported by a National Institutes of Health grant. We thank Professor D. Y. Curtin, Univ. of Illinois Urbana, for helpful discussions.

[7/936 *Received*, 30*th May*, 1977]

---

[17] For references on diffusion of ions see *e.g.* W. Jost, ' Diffusion,' Academic Press, New York, 1960, and L. A. Girifalco, ' Atomic Migration in Crystals,' Blaisdell, New York, 1964.

[18] H. Schmalzried, ' Solid-State Reactions,' Verlag-Chemie and Academic Press, New York, 1974 (English translation).

[19] H. Schmalzried, in ' Reactivity of Solids,' Proc. 6th Internat. Symposium, Schenectady, New York, August 1968.

[20] K. Hauffe, ' Reactionen in und an Festen Stoffen,' Springer-Verlag, Berlin, 1955.