V

the nature of the substituent group in the thiophenyl ring.

In summary, it is clear that the acylals I, II, and III are undergoing hydrolysis with carbonyl attack by nucleophiles in a manner similar to typical esters. This difference in mechanism in comparison with usual types of acylals is most likely due to the ring structure in the case of I and to the fact that hydrolysis in the manner of acetals would demand formation of a rather unstable carbonium ion intermediate. The carbonium ion which would be produced in lysozyme-catalyzed reactions is a species that is not highly stabilized internally relative to simpler acetals. In a reaction sterically constrained by the active site of the enzyme, decomposition of an acylal intermediate to give a carbonium ion and a free carboxyl group (presumably aspartate-52) held in close

proximity, should lead to reversibility in the reaction, increasing markedly the normal stability of such an intermediate and necessitating involvement of solvent or other functional groups in its hydrolysis. Thus, it would be expected that if such an intermediate were being formed it would have more than transient existence and should be demonstrable. Therefore since there is no evidence for an acylal intermediate in lysozyme-catalyzed reactions, kinetic or otherwise, it is probable that it is *not* being formed. It will be noted that in hydrolysis of benzaldehyde disalicyl acetal,[30] an acetal having two substituent carboxyl groups properly positioned to participate in the reaction, a bell-shaped pH–rate constant profile is obtained. The enhancement in k_{obsd} in comparison with the dimethyl ester is 3 × 10^9, an enhancement of the magnitude obtained in enzymatic reactions. In that reaction the carboxylate anion of the monoanionic species contributes little if anything to the large rate facilitation although a stable acylal is the product. Consequently, it is not necessary to postulate involvement of aspartic acid-52 in the transition state to account for the observed kinetic data in lysozyme reactions.

The Nature of Intramolecular N···C=O Interactions. Crystal Structure of the *Senecio* Alkaloid Senkirkine

George I. Birnbaum

Contribution from the Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A 0R6. Received February 7, 1974

Abstract: The three-dimensional structure of senkirkine, $C_{19}H_{27}NO_6$, was determined by X-ray crystallography. The substance crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules in a unit cell with dimensions $a = 24.601 \pm 0.002$, $b = 9.133 \pm 0.001$, and $c = 8.708 \pm 0.001$ Å. Intensity data were collected with a diffractometer and the structure was solved by statistical methods. Refinement by least squares, which included hydrogen atoms, converged at R 0.045 for 2275 observed reflections. The transannular N···C distance was found to be 2.292 (4) Å. The extent of the partial bond in this and in several other structures is assessed. A correlation is established between the bond number and the frequency of the carbonyl peak in the infrared spectrum.

During the past years the crystal structures of three alkaloids in which there exists an intramolecular N···C=O interaction were determined in these laboratories, *viz.*, protopine,[1] cryptopine,[2] and clivorine.[3] More recently it was suggested[4] that such an interaction may be pertinent to the physiological activity of methadone. It seemed desirable, therefore, to obtain additional geometrical information and, if possible, to correlate it to the extensive chemical and spectroscopic

studies carried out in the past.[5] A transannular N··· C=O interaction has been known to exist in the *Senecio* alkaloid senkirkine;[6] this report describes the precise molecular geometry of senkirkine and presents an assessment of the extent of partial bonding in this alkaloid and in several others.

Experimental Section

Senkirkine, $C_{19}H_{27}NO_6$, was isolated from *Senecio vernalis* and crystallized from petroleum ether–chloroform (9:1) by Dr. F. Rulko. Precession photographs showed the colorless prisms (mp 199°) to be orthorhombic; the space group $P2_12_12_1$ was indi-

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Table I. Final Parameters and Their Standard Deviations

(a) Nonhydrogen Atoms[a]

Atom	x	y	z	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{13}$	$2U_{12}$
C(1)	3259 (1)	9382 (3)	5150 (3)	65 (1)	31 (1)	29 (1)	−5 (2)	−8 (2)	35 (2)
C(2)	3569 (2)	10456 (3)	5631 (4)	96 (2)	37 (1)	52 (1)	−27 (2)	−21 (3)	15 (3)
C(3)	4062 (2)	10939 (4)	4803 (6)	103 (3)	44 (1)	94 (3)	−34 (4)	−31 (5)	−35 (3)
N(4)	4094 (1)	10144 (3)	3331 (4)	77 (2)	44 (1)	67 (2)	22 (2)	−3 (3)	−12 (2)
C(5)	4526 (1)	9073 (4)	3128 (4)	53 (2)	66 (2)	64 (2)	22 (3)	7 (3)	−24 (3)
C(6)	4267 (1)	7666 (3)	2564 (3)	47 (1)	57 (1)	41 (1)	4 (2)	24 (2)	13 (2)
C(7)	3793 (1)	7286 (2)	3603 (2)	38 (1)	32 (1)	29 (1)	−7 (2)	−4 (2)	8 (2)
C(8)	3382 (1)	8559 (2)	3677 (2)	46 (1)	34 (1)	26 (1)	0 (2)	−5 (2)	15 (2)
C(9)	2726 (1)	9025 (3)	5885 (3)	64 (2)	58 (2)	34 (1)	6 (2)	7 (2)	63 (3)
O(10)	2751 (1)	7642 (2)	6715 (2)	58 (1)	55 (1)	29 (1)	0 (1)	3 (1)	26 (2)
C(11)	2900 (1)	7724 (3)	8188 (3)	51 (1)	49 (1)	28 (1)	−10 (2)	12 (2)	31 (2)
C(12)	2897 (1)	6220 (3)	8942 (2)	50 (1)	54 (1)	22 (1)	−4 (2)	4 (2)	−5 (2)
C(13)	3310 (1)	5228 (3)	8108 (3)	47 (1)	37 (1)	30 (1)	−8 (2)	−1 (2)	−11 (2)
C(14)	3877 (1)	5924 (3)	8186 (3)	46 (1)	39 (1)	33 (1)	−7 (2)	−15 (2)	3 (2)
C(15)	4271 (1)	5297 (3)	7038 (3)	38 (1)	37 (1)	48 (1)	9 (2)	−10 (2)	10 (2)
C(16)	4156 (1)	5577 (2)	5377 (3)	34 (1)	28 (1)	44 (1)	−1 (2)	0 (2)	13 (1)
O(17)	3968 (1)	6951 (2)	5154 (2)	45 (1)	31 (1)	34 (1)	−1 (1)	−11 (1)	16 (1)
C(18)	3947 (3)	10994 (6)	1974 (7)	123 (4)	78 (3)	103 (4)	105 (6)	−2 (6)	−7 (5)
O(19)	3070 (1)	8665 (2)	2604 (2)	60 (1)	64 (1)	34 (1)	−15 (2)	−25 (1)	51 (2)
O(20)	3020 (1)	8828 (3)	8844 (2)	103 (2)	49 (1)	42 (1)	−15 (2)	−5 (2)	35 (2)
O(21)	3067 (1)	6349 (2)	10487 (2)	94 (2)	55 (1)	24 (1)	−6 (2)	−6 (2)	6 (2)
C(22)	2317 (1)	5588 (5)	8876 (4)	51 (1)	89 (2)	46 (1)	4 (3)	28 (2)	−11 (3)
C(23)	3313 (2)	3676 (3)	8748 (4)	94 (2)	40 (1)	63 (2)	6 (3)	32 (4)	−16 (3)
C(24)	4700 (1)	4504 (4)	7449 (4)	52 (1)	63 (2)	64 (2)	20 (3)	−20 (3)	38 (3)
C(25)	5131 (2)	3853 (6)	6465 (6)	58 (2)	93 (3)	105 (3)	−9 (5)	−12 (4)	82 (4)
O(26)	4215 (1)	4715 (2)	4360 (3)	83 (1)	42 (1)	52 (1)	−15 (2)	−1 (2)	48 (2)

(b) Hydrogen Atoms[b]

Atom	x	y	z	B	Atom	x	y	z	B
H(21)	349 (2)	1092 (6)	654 (6)	5.8 (1.0)	H(182)	387 (3)	1039 (9)	82 (10)	9.6 (1.8)
H(31)	441 (4)	1093 (10)	512 (10)	11.4 (2.1)	H(183)	358 (3)	1170 (9)	219 (10)	9.9 (1.8)
H(32)	396 (2)	1208 (6)	451 (7)	6.8 (1.1)	H(211)	301 (2)	718 (6)	1072 (6)	6.5 (1.0)
H(51)	483 (2)	946 (6)	245 (6)	6.0 (1.0)	H(221)	225 (2)	540 (6)	768 (6)	5.8 (1.0)
H(52)	468 (2)	889 (5)	419 (5)	5.5 (0.9)	H(222)	232 (2)	474 (5)	958 (6)	5.4 (0.9)
H(61)	414 (2)	780 (7)	158 (7)	6.8 (1.2)	H(223)	210 (2)	627 (5)	926 (5)	5.0 (0.8)
H(62)	454 (2)	686 (5)	258 (5)	4.3 (0.7)	H(231)	336 (2)	377 (6)	982 (6)	5.5 (0.9)
H(71)	362 (1)	648 (3)	327 (3)	1.8 (0.4)	H(232)	365 (2)	314 (5)	830 (6)	5.2 (0.9)
H(91)	241 (3)	891 (4)	516 (5)	4.2 (0.7)	H(233)	298 (2)	308 (7)	860 (7)	7.0 (1.3)
H(92)	257 (2)	972 (5)	657 (6)	5.5 (1.0)	H(241)	474 (1)	439 (4)	860 (4)	3.7 (0.6)
H(131)	321 (1)	518 (3)	700 (4)	2.5 (0.5)	H(251)	544 (3)	421 (9)	668 (9)	11.7 (1.9)
H(141)	401 (1)	573 (4)	921 (4)	3.2 (0.6)	H(252)	517 (3)	280 (8)	656 (8)	8.2 (1.5)
H(142)	388 (1)	700 (4)	814 (4)	3.1 (0.6)	H(253)	506 (4)	383 (12)	533 (12)	12.9 (2.7)
H(181)	424 (3)	1145 (8)	172 (8)	8.6 (1.6)					

[a] The coordinates were multiplied by 10^4 and the thermal parameters by 10^3. The thermal parameters are expressed as $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{13}hla^*c^* + 2U_{12}hka^*b^*)]$. [b] The coordinates were multiplied by 10^3.

cated by systematic absences of reflections $h00$ for h odd, $0k0$ for k odd, and $00l$ for l odd. A crystal fragment with dimensions $0.32 \times 0.40 \times 0.50$ mm was mounted along the a axis on a manually operated G.E. XRD-5 diffractometer equipped with a Cu target. Cell dimensions were determined from angular settings of 11 high-angle reflections and both Cu Kα₁ (λ 1.54051 Å) and Cu Kα₂ (λ 1.54433 Å) radiations were used. The following crystal data were obtained: $a = 24.601 \pm 0.002$, $b = 9.133 \pm 0.001$, $c = 8.708 \pm 0.001$ Å; $V = 1956.5$ Å³; $D_x = 1.24$ g cm⁻³; $Z = 4$; $F(000) = 784$; $\mu = 7.7$ cm⁻¹.

The moving-crystal–moving-counter method (θ–2θ scan) was used to collect the intensity data and monochromatization was achieved by the use of a nickel filter and a pulse height analyzer. A net count of 100 or 5% of the background, whichever was higher, was determined as threshold intensity below which reflections were considered unobserved. There were 2446 unique reflections accessible to the diffractometer ($2\theta \leq 160°$) and 2287 (93%) of them had intensities above threshold values. The intensities were corrected for Lorentz and polarization factors; in view of the low value of μ and the regular shape of the crystal, absorption corrections were considered unnecessary.

The structure was determined by direct methods by use of a multisolution procedure similar to that described by Kennard, et al.[7] With $\alpha = 2.19$ and $t = 0.3$ one of the permutations yielded

$R_E = 0.20$ for 400 reflections with $E \geq 1.33$ after a tangent refinement carried out in four steps. The E map revealed the positions of all 26 nonhydrogen atoms. Atomic parameters were refined by block-diagonal least squares. The scattering factors for C, N, and O were those given by Hanson, et al.[8] and those of Stewart, et al.,[9] were used for bonded H. The oxygen curve was corrected for anomalous dispersion.[10] All hydrogen atoms were located on difference Fourier maps and their parameters were refined isotropically. Throughout the refinement the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized and a factor of 0.8 was applied to all shifts. The following weighting scheme was used during the final stages: $w = w_1 w_2$, where $w_1 = 1$ for $|F_o| \leq 8$, $w_1 = 8/|F_o|$ for $|F_o| > 8$; and $w_2 = \sin^2 \theta/0.7$ for $\sin^2 \theta < 0.7$, $w_2 = 1$ for $\sin^2 \theta \geq 0.7$. Twelve strong reflections suffered severely from extinction effects and they were given zero weights. After the final cycle the average parameter shift equalled 0.14σ and the largest one 0.90σ. The agreement index R ($\Sigma|\Delta F|/\Sigma|F_o|$) is 0.045 and the weighted index R' ($\Sigma w\Delta F^2/\Sigma wF_o^2$) is 0.061 for 2275 observed reflections. A final difference Fourier map was featureless.

Results

The final coordinates and temperature parameters,

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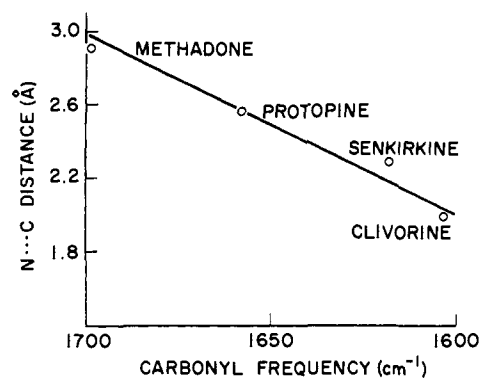(10) D. T. Cromer and D. Liberman, *J. Chem. Phys.*, 53, 1891 (1970).

Table II. Comparison of Bond Distances and Bond Numbers[a]

Compound	$D_{N\cdots C}$	$n_P{}^b$	$n_{BDS}{}^c$	$D_{C=O(BDS)}{}^c$	$D_{C=O(exp)}$	Ref
Methadone	2.910	0.005	0.14	1.234	1.214	16
Cryptopine	2.581	0.02	0.23	1.250	1.209	2
Protopine	2.555	0.02	0.23	1.250	1.218	1
Senkirkine	2.292	0.05	0.33	1.266	1.213	
Clivorine	1.993	0.15	0.50	1.301	1.258	3
Retusamine[d]	1.64	0.6	0.8	1.37	1.38	17

[a] Distances in ångströms. [b] Bond number calculated according to ref 13. [c] Calculated according to ref 16. [d] The structure determined was that of the α'-bromo-D-camphor-*trans*-π-sulfonate salt.

Figure 1. Molecular geometry. Top: torsional angles in degrees (their esd's are 0.2–0.4°). Center: bond lengths in ångströms (unless otherwise indicated their esd's are 0.003–0.004 Å). Bottom: bond angles in degrees (esd's 0.2–0.3°).

Figure 2. Perspective view of senkirkine; the thermal ellipsoids correspond to 50% probability.

Figure 3. Distances (Å) and angles (deg) in the bifurcated hydrogen bond system; O(19') is in the molecule displaced by *c*.

as well as their estimated standard deviations, are listed in Table I. A table of observed and calculated struc-

ture factors is available.[11] The precise molecular geometry can be seen in Figure 1 which gives torsional angles, bond lengths, and bond angles. Figure 2 shows the conformation of the molecule. As can be seen, the conformation of the eight-membered ring is very similar to that in clivorine: one-half, consisting of C(1), C(2), C(3), N(4), and C(8), is almost flat (within 0.07 Å), O(19) being displaced 0.950 (2) Å from the mean plane; the other half is envelope shaped, with C(6) below the mean plane through N(4), C(5), C(7), and C(8). The carbon atom of the carbonyl group does not lie in the plane defined by the three atoms to which it is bonded; it is displaced by 0.115 (2) Å toward the transannular nitrogen atom. The similarity with clivorine does not extend to the 12-membered ring, primarily because the endocyclic double bond in clivorine has migrated to an exocyclic position in senkirkine. The hydroxyl group is involved in a some-what asymmetric bifurcated hydrogen bond (Figure 3):

Figure 4. Correlation between carbonyl absorption maxima and distances of partial N···C bonds.

the hydrogen atom is donated intramolecularly to O-(20) and intermolecularly to O(19) in a molecule displaced by c. A hydrogen bond system with a similar geometry was found in a recent structure determination.[12] Apart from this, there are no unusually short intermolecular contacts.

Discussion

The transannular N···C distance, 2.292 (4) Å, is the second shortest observed thus far. The geometrical details therefore provide valuable data for the study of such interactions. Pauling's[13] equation, $D(n) = D(1) - 0.60 \log n$, can be used to calculate the bond number (n) of the partial N···C bond. Using the values 2.292 Å for $D(n)$ and 1.500 Å rather than 1.479 Å for an N^+–C bond in which N^+ is substituted,[14,15] one obtains $n = 0.05$. A similar calculation yields $n = 0.15$ for clivorine which is in excellent agreement with $n = 1.85$, the calculated bond number of the C=O bond. These values are in sharp contrast to those obtained from the equation derived by Bürgi, et al.[16] The two sets of bond numbers of the N···C bonds are shown in Table II. The differences are seen to be largest for the longer distances. In the fifth column C=O bond lengths are listed which were calculated according to eq 3 of Bürgi, et al.,[16] using the values of n shown in the fourth column. With the exception of retusamine,[17] where all bond lengths were determined with much lower precision, the calculated bond lengths are consistently longer than the experimental values given in the sixth column. In fact, the bond lengths found in the first

four alkaloids agree with the normal length of 1.215 ± 0.005 Å for a C=O bond in a ketone.[18] One would expect to find normal values for bonds which have 95% or more double bond character but not for C=O bonds with bond numbers as low as 1.67. In view of this it appears that the much smaller bond numbers for the partial N···C bonds calculated from Pauling's equation are more realistic than those derivable from the equations of Bürgi, et al.

It has long been known that an N···C=O interaction causes the carbonyl peak in the infrared spectrum to shift to a lower frequency.[5,19] A quantitative correlation between the N···C bond distances determined in recent crystal structure analyses and the carbonyl frequencies is now possible.[20] Figure 4 shows that a straight line can be drawn which is reasonably close to the experimental points. It may appear at first glance that a correction should have been applied in the cases of clivorine, senkirkine, and protopine since the carbonyl groups seem to be conjugated with a double bond or an aromatic ring. However, the X-ray analyses of these structures revealed that in each case the oxygen atom is displaced far from the plane of the double bond or the aromatic ring. Consequently, one can conclude that the carbonyl groups are essentially not conjugated. The bond lengths in these structures corroborate this conclusion. Although the correlation presented in Figure 4 will undoubtedly be refined as more relevant crystal structures become available, even a semiquantitative assessment of an N···C=O interaction on the basis of an ir spectrum should be valuable at this time.

Supplementary Material Available. A table of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-6165.

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