The Crystal Structures of a Ketone and Related Acetal Macrocycle containing 2,6-Pyridino and Polyether Subunits

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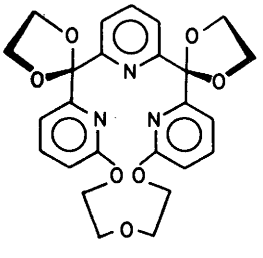
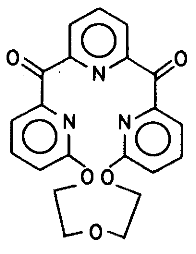
1,3,5-Tri[2,6]pyridina-6,9,12-trioxacyclododecaphane-2,4-dione, $C_{21}H_{17}N_3O_7$, crystallizes in space group $A2/a$ with $a = 20.124(6)$, $b = 12.194(3)$, $c = 15.385(2)$ Å, $\beta = 92.13(2)°$, and $Z = 8$. Refinement using 1 882 diffractometer-measured data yields R 0.038. The corresponding 2,4-bis(ethylenedioxy)-1,3,5-tri[2,6]pyridina-6,9,12-trioxacyclododecaphane, $C_{25}H_{25}N_3O_7$, crystallizes in space group $P2_1/c$ with $a = 10.454(4)$, $b = 27.144(7)$, $c = 9.168(3)$ Å, $\beta = 115.09(2)°$, and $Z = 4$. Refinement based upon 2 173 diffractometer-measured data yields R 0.054. The conformation of the diacetal macrocycle is globular; the main backbone of the molecule wraps around a central cavity in a shape somewhat like the seam of a tennis ball. The diketone molecule exhibits a much more open conformation. In both molecules, the linkage of the polyether chain to the pyridine ring is essentially *cis* to the nitrogen atom. A partial localization of double bonds of the asymmetrically substituted pyridine rings of both structures is noted.

DURING a synthetic study involving a series of macrocycles containing 2,6-pyridino and polyether subunits,[1] it was noted that diacetal macrocycles such as (1) exhibited varying ease of acid hydrolysis to the corresponding diketones (2) as a function of polyether chain length. Particularly mysterious is the fact that the ethylene glycol-bridged macrocycle (3) did not give the corresponding diketone, even under severe hydrolysis conditions, but instead forms products lacking macrocyclic character, while, further, the corresponding sulphide (4) is hydrolysed smoothly.


(1)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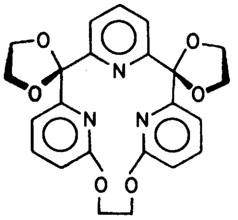
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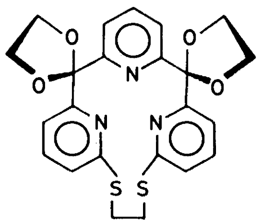
(4)

Attempts to gain understanding of the structure–reactivity correlation were hampered by lack of success in preparing suitable single crystals of (3), whereas (1) and (2) crystallized well. As the smallest members of this series for which both the diacetal and diketone are known, molecules (1) and (2) were excellent candidates for a study of structural changes which affect the anomalous hydrolysis reactions, and thus crystal structure determinations of these two compounds were undertaken.

Further reason to investigate these structures lies in their potential for convergence of the nitrogen lone pair electrons, leading to electron-rich cavities of particular interest.

EXPERIMENTAL

Crystals of (1) and (2) were grown from ethanol as plates and needles, respectively. Data for each compound were collected by an Enraf–Nonius CAD-4 diffractometer from a crystal glued to a glass fibre and mounted in random orientation. All measurements were made using graphite-monochromated Mo-K_α radiation at ambient temperature of 22 ± 2 °C. Unit cell dimensions and crystal orientation were determined from diffractomer co-ordinates of 15 accurately-centred reflections having $2\theta > 30°$. Crystal data and experimental constants for both compounds are listed in Table 1.

Intensity data were collected by the ω–2θ scan technique. Diffracted X-rays were detected by a scintillation counter equipped with a pulse height discriminator having its window adjusted to accept 95% of the Mo-K_α profile. Scan widths were computed for each reflection by the function given in Table 1, and extended at both ends by 25% with the counts collected during these extensions serving as background measurements. A rapid prescan of each reflection was made. If the prescan intensity exceeded the 'acceptance threshold', it was taken as the final measurement; if it was smaller than the 'unobserved limit', it was flagged as unobserved; if it was intermediate between these values it was remeasured at a scan speed appropriate to yield a 'standard intensity'. An upper limit was set on the time allotted for a single scan.

During data collection, check reflections were remeasured every 50 measurements as a monitor of crystal and instrumental stability and any decline in their intensities was used to correct measured intensities. Owing to diffractometer malfunction during collection of the diacetal data, the crystal was continuously irradiated and check reflections decreased rapidly in intensity. After *ca.* 800 measurements, a new crystal was mounted and data collection completed.

Reflections for which $I < 3\sigma(I)$ were flagged as unobserved. The variances $\sigma^2(I)$ were estimated from count-

TABLE 1

Crystal data and experimental parameters

	Ketone (2)	Acetal (1)
Formula	$C_{21}H_{17}N_3O_5$	$C_{25}H_{25}N_3O_7$
Formula weight	391.4	479.5
Crystal system	Monoclinic	Monoclinic
Space group	$A2/a$ *	$P2_1/c$
a/Å	20.124(6)	10.454(4)
b/Å	12.194(3)	27.144(7)
c/Å	15.385(2)	9.168(3)
β (°)	92.13(2)	115.09(2)
V/Å^3	3 773	2 356
Z	8	4
λ/Å	0.710 73	0.710 73
D_{calc}/g cm^{-3}	1.378	1.352
μMo-K_α/cm^{-1}	1.08	0.94
Crystal size (mm^3)	0.18 × 0.42 × 0.21	0.53 × 0.09 × 0.46 0.48 × 0.09 × 0.37
Data measured	6° ≤ 2θ ≤ 50°, one quadrant	6° ≤ 2θ ≤ 50°, one quadrant
Scan width	0.90° + 0.35 tan θ	1.0° + 0.35 tan θ
Prescan speed (° min^{-1})	$3\frac{1}{3}$	$3\frac{1}{3}$
Acceptance threshold (counts)	10^3	10^3
Unobserved limit (counts)	35	35
Standard intensity (counts)	10^3	10^3
Max. scan time (s)	300	180
Check reflections	$(\bar{8}\cdot0\cdot\bar{1}\bar{0})$, $(\bar{7}\cdot7\cdot5)$	$(\bar{1}\cdot16\cdot\bar{3})$, $(1\cdot\bar{1}\bar{2}\cdot4)$ †
Intensity decline (%)	4	10
Total data	3 586	3 781
' Observed ' data	1 882	2 173

* Nonstandard setting of space group $C2/c$, C_{2h}^6, #15. † $(36\bar{6})$ and $(4\cdot12\cdot2)$ for crystal 2.

ing statistics; variances for the diketone included a term [0.02 (counts)] ^{2} to account for non-statistical fluctuations. Lorentz and polarization corrections were applied to the data, but owing to the low value of the linear absorption coefficients, errors due to absorption were judged to be insignificant.

Structure Solutions and Refinements.—(A) 1,3,5-*Tri*[2,6]-*pyridina*-6,9,12-*trioxacyclododecaphane*-2,4-*dione* (2). Systematic absences hkl with $k + l$ odd and $h0l$ with h odd limit the space group to either the centrosymmetric $A2/a$ or the noncentric Aa. The former was confirmed by successful refinement. Eight molecules per unit cell necessitate one per asymmetric unit. The structure was solved by routine application of the multiple-solution direct phasing method,[2] using program MULTAN 74. Phasing of the 300 reflections with highest E values led to eight phase sets, the correct solution being best by all statistical criteria calculated by the program. An E map phased by this solution revealed the positions of all 29 non-hydrogen atoms of the molecule among the 30 largest peaks.

Hydrogen atoms were placed in calculated positions and the full model was refined by least-squares techniques. Hydrogen atoms were refined with isotropic temperature factors, while C, N, and O atoms were treated anisotropically. The function minimized in the least-squares procedure was $\Sigma\omega(|F_o| - |F_c|)^2$, where the weights are $\omega = \sigma^{-2}(F_o)$. Refinement was carried out using two blocks in the matrix, one containing all positional parameters, and the other containing all thermal parameters, the scale factor, and an extinction factor, which was deemed necessary in the latter stages of the process. Refinement was terminated when all shifts were small relative to appropriate standard deviations. The refined model produced discrepancy indices of R 0.038 and R_ω 0.038, based upon observed reflections, and goodness of fit of 1.22 for 1 882 observations and 331 variables. The refined value of the extinction coefficient is 4.4(1) × 10^{-6}. Definitions of these indicators are: $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$, $R_\omega = \Sigma\omega(|F_o| - |F_c|)^2/\Sigma\omega F_o^2$, and goodness of fit = $[\Sigma\omega(|F_o| - |F_c|)^2/(NO - NV)]^{\frac{1}{2}}$, where NO = number of observations, and NV = number of refined variables. A three-dimensional Fourier map computed at the conclusion of the refinement exhibited no residuals greater than ±0.16 eÅ^{-1}.

(B) 2,4-*Bis*(*ethylenedioxy*)-1,3,5-*tri*[2,6]*pyridina*-6,9,12-*trioxacyclododecaphane* (1). Systematic absences $0k0$ with k odd and $h0l$ with l odd uniquely determine the space group to be $P2_1/c$, and Z = 4 requires one molecule per asymmetric unit. The structure was easily solved by MULTAN 74 using 400 data and 2 500 phase relationships. The phase set with highest combined figure of merit yielded an E map from which 34 of the 35 non-hydrogen atoms were located among the top 35 peaks. The missing atom [C(22)] was placed in a reasonable position, hydrogen atom positions were geometrically calculated, and the structure was refined. Refinement was carried out as described for the diketone; however, no extinction correction was necessary. Convergence was attained with R 0.054, R_ω 0.060, and goodness of fit 1.89 for 2 173 observed data and 386 refined variables. A final difference map had no residuals larger than ±0.22 eÅ^{-3}.

RESULTS

Structure Descriptions.—The *X*-ray crystal structure of (1) was determined since it was the smallest member of this macrocyclic series in which *both* the diacetal *and* corresponding diketone are available for *X*-ray comparison purposes.

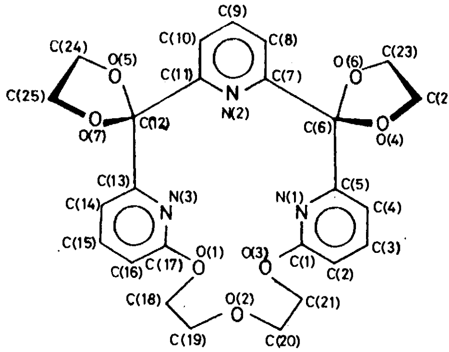

FIGURE 1 Numbering scheme for diacetal (1). Atoms of the diketone (2) are numbered similarly

Refined non-hydrogen atom co-ordinates for diacetal (1) are listed in Table 2 and anisotropic temperature factors and hydrogen atom parameters are given in Supplementary Publication No. SUP 23036 (23 pp.).* Diacetal (1) is shown in Figure 2 to exist in the crystal in such a conformation that the pyridine nitrogen lone pair electrons *do not* all point inwards towards a central cavity. Taking the C ⟶ N vector across the centre of the pyridine ring to be a

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* For details of Supplementary Publications, see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1980, Index Issue.

TABLE 2

Non-hydrogen atom positional parameters ($\times 10^5$) for diacetal (1)

Atom	*x*	*y*	*z*
O(1)	59 473(40)	52 997(12)	82 484(35)
O(2)	77 253(37)	57 494(11)	112 203(36)
O(3)	104 294(39)	58 044(13)	110 907(41)
O(4)	118 704(35)	71 131(11)	81 139(35)
O(5)	57 302(35)	65 203(13)	28 101(34)
O(6)	109 780(35)	67 670(12)	55 918(35)
O(7)	44 985(34)	66 491(12)	42 886(36)
N(1)	106 632(43)	62 657(15)	91 000(44)
N(2)	82 795(40)	67 039(14)	57 564(42)
N(3)	58 800(43)	58 664(13)	63 168(41)
C(1)	107 519(57)	58 368(21)	98 068(61)
C(2)	111 822(63)	54 027(21)	93 168(65)
C(3)	115 243(66)	54 270(20)	80 498(65)
C(4)	113 991(63)	58 720(20)	72 437(58)
C(5)	109 713(51)	62 787(17)	78 079(52)
C(6)	107 922(52)	67 938(18)	70 463(52)
C(7)	93 423(55)	69 873(18)	67 142(56)
C(8)	91 384(64)	74 210(20)	74 113(66)
C(9)	77 701(70)	75 470(21)	71 285(69)
C(10)	66 587(60)	72 555(21)	61 632(61)
C(11)	69 729(51)	68 402(17)	54 868(50)
C(12)	58 195(52)	64 902(18)	44 013(53)
C(13)	61 443(54)	59 566(19)	50 223(56)
C(14)	66 973(66)	56 240(23)	43 537(65)
C(15)	70 461(71)	51 600(23)	50 770(76)
C(16)	68 121(69)	50 620(20)	63 900(68)
C(17)	62 109(58)	54 199(20)	69 627(56)
C(18)	55 022(60)	56 877(21)	90 005(58)
C(19)	66 929(59)	60 248(18)	99 603(55)
C(20)	89 041(56)	60 245(19)	122 913(54)
C(21)	98 100(59)	62 262(19)	115 110(63)
C(22)	129 639(71)	71 147(23)	76 364(77)
C(23)	123 262(63)	69 623(25)	59 101(67)
C(24)	42 964(66)	64 409(28)	17 550(65)
C(25)	34 891(60)	64 656(22)	27 802(67)

TABLE 3

Non-hydrogen atom positional parameters ($\times 10^5$) for diketone (2)

Atom	*x*	*y*	*z*
O(1)	53 768(8)	84 369(11)	55 135(9)
O(2)	55 117(7)	65 503(11)	66 285(10)
O(3)	67 374(8)	55 495(11)	67 613(10)
O(4)	69 835(10)	80 908(14)	92 738(10)
O(5)	57 434(10)	126 309(13)	70 111(12)
N(1)	68 359(8)	70 764(13)	76 568(11)
N(2)	63 959(9)	102 106(14)	79 111(11)
N(3)	56 377(9)	100 408(14)	62 570(11)
C(1)	69 391(10)	66 007(17)	69 042(14)
C(2)	72 630(12)	71 003(20)	62 335(15)
C(3)	74 608(12)	81 672(21)	63 303(16)
C(4)	73 257(12)	87 083(19)	70 967(16)
C(5)	70 229(10)	81 363(17)	77 422(13)
C(6)	68 846(11)	86 183(18)	86 166(14)
C(7)	65 694(11)	97 380(17)	86 688(13)
C(8)	64 399(12)	101 879(21)	94 673(15)
C(9)	60 945(13)	111 718(23)	94 870(18)
C(10)	59 024(12)	116 655(20)	87 126(18)
C(11)	60 642(11)	111 632(17)	79 417(15)
C(12)	59 119(12)	116 744(19)	70 712(16)
C(13)	59 952(12)	109 789(17)	62 753(15)
C(14)	64 111(14)	112 959(20)	56 411(17)
C(15)	64 810(14)	105 960(23)	49 266(17)
C(16)	61 254(13)	96 414(21)	48 951(16)
C(17)	57 146(11)	94 043(18)	55 686(14)
C(18)	49 505(13)	81 562(20)	62 136(17)
C(19)	48 985(12)	69 362(20)	62 667(18)
C(20)	55 412(13)	53 972(19)	67 541(17)
C(21)	61 864(14)	51 547(20)	72 483(18)

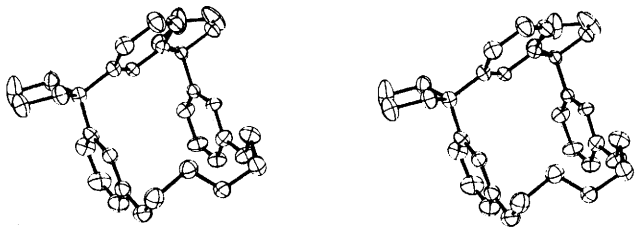

FIGURE 2 Stereoprojection for the diacetal (1). Atoms are represented by 30% probability contours. Hydrogen atoms are omitted

good approximation to the direction of the nitrogen lone pair, it can be seen that the nitrogen lone pairs on the two pyridine rings substituted by the polyether chain are approximately parallel and separated by *ca.* 4.5 Å. The central pyridine ring points its lone pair approximately anti-parallel to the other two. The overall conformation of

TABLE 4

Bond distances (Å)

Atoms	Diketone (2)	Diacetal (1)
N(1)–C(1)	1.318(3)	1.316(7)
N(1)–C(5)	1.351(3)	1.353(7)
N(2)–C(7)	1.335(3)	1.330(5)
N(2)–C(11)	1.341(3)	1.333(6)
N(3)–C(13)	1.351(3)	1.350(7)
N(3)–C(17)	1.327(3)	1.329(6)
O(1)–C(17)	1.362(3)	1.359(7)
O(1)–C(18)	1.443(3)	1.440(7)
O(2)–C(19)	1.415(3)	1.415(5)
O(2)–C(20)	1.420(3)	1.420(6)
O(3)–C(1)	1.360(3)	1.358(7)
O(3)–C(21)	1.444(3)	1.444(7)
C(1)–C(2)	1.383(3)	1.401(7)
C(2)–C(3)	1.367(4)	1.354(9)
C(3)–C(4)	1.388(4)	1.393(7)
C(4)–C(5)	1.374(3)	1.372(7)
C(5)–C(6)	1.503(3)	1.538(6)
C(6)–C(7)	1.508(3)	1.508(7)
C(7)–C(8)	1.379(3)	1.398(7)
C(8)–C(9)	1.385(4)	1.384(9)
C(9)–C(10)	1.377(4)	1.374(7)
C(10)–C(11)	1.383(4)	1.391(7)
C(11)–C(12)	1.499(3)	1.526(6)
C(12)–C(13)	1.504(3)	1.541(6)
C(13)–C(14)	1.365(4)	1.351(8)
C(14)–C(15)	1.404(4)	1.398(8)
C(15)–C(16)	1.367(4)	1.353(9)
C(16)–C(17)	1.379(3)	1.376(7)
C(18)–C(19)	1.494(4)	1.494(7)
C(20)–C(21)	1.509(4)	1.513(9)
C(6)–O(7)	1.209(3)	1.430(5)
C(12)–O(5)	1.218(3)	1.424(6)
C(6)–O(6)		1.429(6)
C(12)–O(7)		1.408(6)
O(4)–C(22)		1.387(9)
C(22)–C(23)		1.492(9)
C(23)–O(6)		1.416(8)
O(5)–C(24)		1.414(7)
C(24)–C(25)		1.508(11)
C(25)–O(7)		1.427(6)
C(2)–H(2)	0.98(2)	0.99(5)
C(3)–H(3)	1.00(2)	0.94(5)
C(4)–H(4)	0.91(2)	1.00(4)
C(8)–H(8)	1.01(2)	0.90(5)
C(9)–H(9)	0.96(2)	0.99(5)
C(10)–H(10)	0.96(2)	1.11(5)
C(14)–H(14)	0.97(2)	0.99(4)
C(15)–H(15)	0.94(2)	0.92(5)
C(16)–H(16)	1.03(2)	0.88(4)
C(18)–H(181)	1.11(2)	1.08(5)
C(18)–H(182)	1.06(2)	1.00(5)
C(19)–H(191)	1.09(2)	1.16(5)
C(19)–H(192)	1.02(2)	1.10(5)
C(20)–H(201)	1.15(2)	0.96(4)
C(20)–H(202)	1.09(2)	1.28(5)
C(21)–H(211)	1.15(2)	0.99(5)
C(21)–H(212)	0.95(2)	1.18(5)

TABLE 5

Bond angles (°)

Atoms	Ketone (2)	Acetal (1)
C(1)–N(1)–C(5)	117.0(2)	117.4(4)
C(7)–N(2)–C(11)	117.2(2)	117.7(4)
C(13)–N(3)–C(17)	115.7(2)	116.5(4)
C(17)–O(1)–C(18)	117.9(2)	117.7(4)
C(19)–O(2)–C(20)	114.4(2)	114.2(4)
C(1)–O(3)–C(21)	117.4(2)	119.1(4)
N(1)–C(1)–O(3)	120.1(2)	119.4(4)
N(1)–C(1)–C(2)	123.8(2)	123.4(5)
O(3)–C(1)–C(2)	116.1(2)	117.2(4)
C(1)–C(2)–C(3)	118.8(2)	118.1(5)
C(2)–C(3)–C(4)	118.7(2)	119.8(5)
C(3)–C(4)–C(5)	118.6(2)	118.0(5)
C(4)–C(5)–N(1)	123.0(2)	123.0(4)
C(4)–C(5)–C(6)	123.3(2)	123.8(5)
N(1)–C(5)–C(6)	113.7(2)	113.1(5)
C(5)–C(6)–O(4)	120.7(2)	109.4(4)
C(5)–C(6)–C(7)	119.6(2)	109.1(4)
O(4)–C(6)–C(7)	119.6(2)	111.1(4)
C(5)–C(6)–O(6)		109.8(4)
C(7)–C(6)–O(6)		110.6(3)
O(4)–C(6)–O(6)		106.9(3)
C(6)–C(7)–N(2)	116.2(2)	114.7(4)
C(6)–C(7)–C(8)	120.2(2)	122.4(4)
N(2)–C(7)–C(8)	123.5(2)	122.8(5)
C(7)–C(8)–C(9)	118.5(2)	117.9(4)
C(8)–C(9)–C(10)	118.9(2)	120.2(5)
C(9)–C(10)–C(11)	118.7(2)	117.3(5)
C(10)–C(11)–N(2)	123.1(2)	124.0(4)
C(10)–C(11)–C(12)	122.3(2)	121.6(4)
N(2)–C(11)–C(12)	114.5(2)	114.3(4)
C(11)–C(12)–O(5)	120.9(2)	108.8(4)
C(11)–C(12)–C(13)	117.9(1)	110.8(3)
O(5)–C(12)–C(13)	121.2(2)	109.9(4)
C(11)–C(12)–O(7)		109.6(4)
O(7)–C(12)–C(13)		111.8(4)
O(5)–C(12)–O(7)		105.7(3)
C(12)–C(13)–N(3)	114.8(2)	113.6(4)
C(12)–C(13)–C(14)	120.8(2)	122.0(5)
N(3)–C(13)–C(14)	124.4(2)	124.3(4)
C(13)–C(14)–C(15)	118.0(2)	117.6(6)
C(14)–C(15)–C(16)	118.5(2)	119.4(6)
C(15)–C(16)–C(17)	118.7(2)	119.0(5)
C(16)–C(17)–N(3)	124.6(2)	123.3(5)
C(16)–C(17)–O(1)	116.5(2)	117.0(4)
N(3)–C(17)–O(1)	118.9(2)	119.7(5)
O(1)–C(18)–C(19)	108.8(2)	111.9(5)
C(18)–C(19)–O(2)	106.9(2)	108.3(4)
O(2)–C(20)–C(21)	107.0(2)	113.3(4)
C(20)–C(21)–O(3)	109.7(2)	106.4(4)
C(6)–O(4)–C(22)		107.6(4)
O(4)–C(22)–C(23)		106.1(5)
C(22)–C(23)–O(6)		106.3(5)
C(23)–O(6)–C(6)		107.8(3)
C(12)–O(5)–C(24)		107.8(3)
O(5)–C(24)–C(25)		106.1(4)
C(24)–C(25)–O(7)		103.9(5)
C(25)–O(7)–C(12)		105.3(4)

the molecule may usefully be thought of as that of a tennis ball; the large 24-atom ring formed by the carbon backbone of the pyridine rings and the polyether chain trace out a shape similar to the seam of a tennis ball, wrapping around the central cavity. The polyether oxygen atoms all point *outwards* from this cavity.

TABLE 6

Selected torsion angles (°) for diacetal (1) and diketone (2)

Atoms	Diacetal (1)	Diketone (2)
N(2)–C(11)–C(12)–C(13)	−57.1	14.4
N(2)–C(7)–C(6)–C(5)	51.8	3.1
N(3)–C(13)–C(12)–C(11)	−51.3	56.4
N(1)–C(5)–C(6)–C(7)	76.3	−134.1
N(3)–C(17)–O(1)–C(18)	10.1	−0.4
N(1)–C(1)–O(3)–C(21)	−8.6	26.4

Bond distances in the diacetal molecule are listed in Table 4 and important angles are given in Table 5. The numbering scheme employed in these *X*-ray studies is shown in Figure 1. Distances for each of the bond types represented vary somewhat, but are chemically reasonable. Average distances for important bond types are: 1.335(7) for C–N, 1.379(5) for aromatic C–C, 1.504(7) for aliphatic C–C, and 1.359(6) Å for O–C (aromatic) bonds. Table 6 lists selected torsion angles for the diacetal (1). Of particular interest are the torsion angles about the chemically equivalent bonds C(6)–C(7) and C(11)–C(12), as well as the chemically equivalent bonds C(5)–C(6) and C(12)–C(13). Examination of these angles reveals that the main carbon backbone forms a large angle (averaging *ca.* 60°) with the plane of the pyridine ring in all four cases. Other important torsion angles given in Table 6 are those about the chemically equivalent bonds O(1)–C(17) and O(3)–C(1). The two angles are similar, and their absolute values average *ca.* 9°. Stated simply, the linkage of the polyether chain to the pyridine ring is approximately in the plane of the ring and *cis* to the nitrogen atom. This conformation has also been noted in similar structures,[3-5] and appears to be a rigid constraint upon the flexibility of such molecules. The packing of molecules of (1) in the crystal is illustrated in Figure 3; no unusually close intermolecular contacts exist.

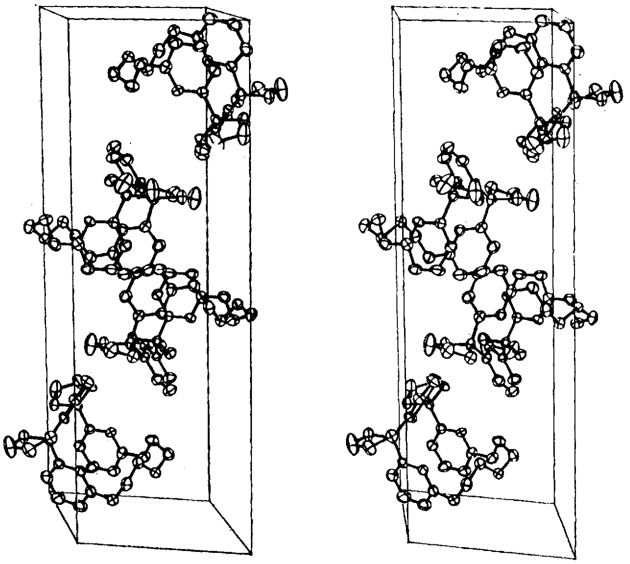

FIGURE 3 Crystal packing for diacetal (1)

In order to further delineate the precise stereochemistry of (2) and to obtain insight into the structural differences between (1) and (2), the *X*-ray crystal structure of (2) was undertaken. Refined non-hydrogen atom co-ordinates for (2) are listed in Table 3; anisotropic thermal parameters and hydrogen atom parameters are given in SUP 23036. This molecule is also seen (Figure 4) to exist in the crystal in a conformation such that the nitrogen lone pairs of the pyridine groups do not point inwards towards a central cavity. The nitrogen lone pairs of the asymmetrically disubstituted pyridine rings are approximately parallel and separated by *ca.* 4.4 Å. The direction of the nitrogen lone pair of the central pyridine ring deviates from antiparallelism with the other two by *ca.* 60°. The overall conformation of the molecule is suggestive of the shape of a wheelchair, with the ' back ' of the chair (the central pyridine ring) tilted distinctly away from the interior of the molecule.

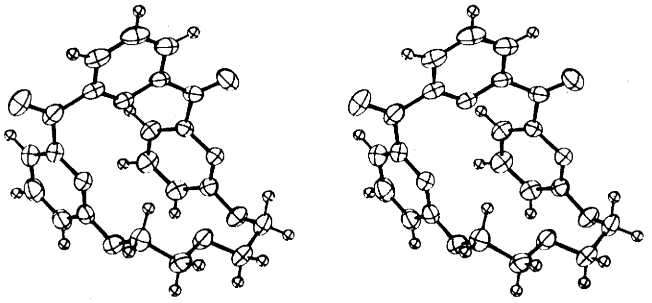

FIGURE 4 Stereopair for the diketone molecule (2). Atoms are represented by 30% probability contours, and hydrogen atoms are drawn arbitrarily small

Bond distances and angles in the diketone (2) are listed in Tables 4 and 5, respectively, with the numbering scheme shown on Figure 1. All are chemically reasonable. Average values for important bond types are 1.337(5) for C–N, 1.379(3) for aromatic C–C, 1.502(7) for aliphatic C–C, 1.361(3) for O–C (aromatic), and 1.214(4) Å for C=O bonds. These averages are in excellent agreement with corresponding averages found in the diacetal (1), and with accepted values.

Torsion angles of interest (Table 6) reveal several notable features of the conformation. It is obvious that most of the distortion from a possible conformation in which all three pyridine rings are coplanar and nitrogen lone pairs converge is accomplished *via* rotation about the bonds C(5)–C(6) and C(12)–C(13), leaving the carbonyl groups close to the plane of the central pyridine ring, as in dipicolinic acid.[6]

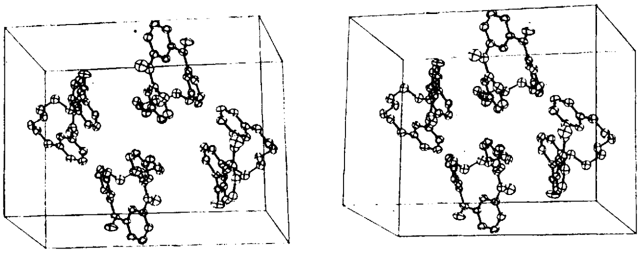

FIGURE 5 Molecules of diketone (2) associated with one lattice point

The torsion angles about O(1)–C(17) and O(3)–C(1) average 13.4° in absolute value, indicating that as in the diacetal (1), the linkage of the polyether chain to the pyridine ring is essentially *cis* to the nitrogen atom. The packing of molecules of (2) in the crystal is illustrated in Figure 5; no unusually close intermolecular contacts exist.

DISCUSSION

The primary question to be resolved is: why do all the diacetals undergo smooth hydrolysis to give the corresponding diketones, except for (3) which undergoes ring fragmentation under similar hydrolytic conditions? Initial protonation of (3) will be directed to the most basic available site(s); thus, the central pyridine nitrogen is of the 2,6-lutidine type (pK_a *ca.* 6.7) and should be the most favoured site for protonation. The remaining two nitrogen atoms are *ca.* 10^3 less basic [7] and are also hindered from direct approach by an electrophile due to the orientation of the α-methylene group as (a) suggested by MINDO-3 calculations [8] and (b) demonstrated in the crystal structure of (1) as well as related macrocycles.[3,4,9]

From these *X*-ray data, the $-N=C-O-CH_2$ dihedral angle has been shown to be *ca.* ±10°. The ease of protonation, and thus ease of acid hydrolysis of these macrocycles is therefore expected to depend upon the steric environment of the central pyridine nitrogen atom N(2). Protonation at N(2) would be plausible if the cavity is of sufficient size to permit approach of a protonated solvent molecule. Subsequent easy transfer of the proton from nitrogen to the juxtaposed acetal oxygen atoms would accelerate the rate of hydrolysis, as has been noted for glycosyl cleavage in nucleosides.[10-12]

If a proton is placed in a calculated position bonded to N(2) of the diacetal molecule, it forms intramolecular contacts at or very slightly longer than sums of van der Waal's radii. The closest such contact is to an acetal oxygen atom, at 2.64 Å. It is clear that compound (3), with its shortened ether chain, would possess a much smaller cavity. This steric crowding of the central cavity by the noncentral pyridine rings precludes initial protonation of the central pyridine ring. Related molecules with longer polyether chains would not be expected to possess this steric problem, and indeed they hydrolyse readily to the corresponding ketones.

The fact that the sulphur analogue (4) is hydrolysed normally while (3) is not may also be rationalized on the grounds of steric differences involving the protonation site. C–S Bond distances are expected to be *ca.* 0.4 Å longer than corresponding C–O distances, and C–S–C angles are expected to be *ca.* 15° smaller than the corresponding C–O–C bond angles. These structural differences should affect the conformation of the molecule, and the sulphur analogue (4) should have a quite different central cavity from the narrow and hindered one which (3) cannot avoid. Space-filling (CPK) models of (4) indicate that its central cavity is much more comparable to that of (1) than that of (3). Additionally, the crystal structure of the diketone derivative of (4) has recently been determined,[13] and it is found to have little steric hindrance at the protonation site. The details of that structure determination will be the subject of a later paper.

Lastly, assuming that the crystal structures of (1) and (2) are typical representatives of the acetal and ketone series, comparison of these structures can afford insight into the structural alterations which occur upon hydrolysis. The major structural difference is a tilting of the central pyridine ring away from the centre of the molecule resulting in a ' tennis ball ' [in (1)] to ' wheelchair ' [in (2)] conformational change. The fact that ketone (2) is much less spherical is apparently brought about by the tendency for the carbonyl group(s) to be coplanar with the *central* pyridine ring. This opening of the molecular wrapping upon hydrolysis is also accomplished by a conformational change in the polyether linkage. In the polyethereal chain of (1), all three of its oxygen atoms are on its exterior, whereas in (2) the central oxygen atom O(4) faces *towards* the middle of the molecule. Except for changes ($sp^3 \longrightarrow sp^2$) associated with C(6) and C(12) none of the bond distances (Table 4) or angles (Table 5) are dramatically changed.

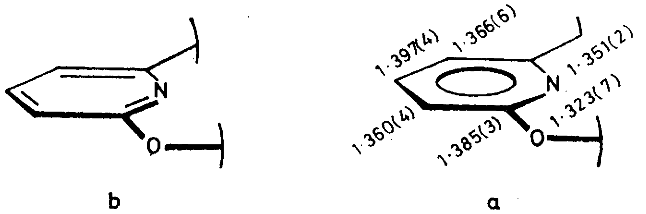

FIGURE 6 a, Average bond distances for the asymmetrically disubstituted pyridine rings of both molecules. b, Bonding representation for the asymmetrically disubstituted pyridine rings

Scrutiny of bond distances within the pyridine rings reveals a trend which is surprising and certainly worth further comment. For the central symmetrically disubstituted pyridine ring of both (1) and (2), all C–N bonds are equal within experimental error and all C–C bond lengths are likewise equal, as anticipated. However, the asymmetrically disubstituted pyridine rings are shown to possess significant and systematic differences. Choosing any of these four such pyridine rings, the C–N bond, which involves the polyether linkage, is *shorter* than the other C–N distance. Discrepancies also exist in the C–C bond lengths, in which the overall pattern is one of alternation of long and short bonds around the pyridine nucleus. This effect is more clearly presented in Figure 6a, which illustrates the average distances for the asymmetrically disubstituted subrings. These differences between ' long ' and ' short ' bonds are statistically significant and can be better represented by the partial localization of double bond character as envisioned in Figure 6b. Although this effect is presently not well understood, it does emphasize the imidate ester characteristics in these macrocycles and offers a rationale for the low –N=C–O–CH_2 dihedral bond angle. The literature affords little insight; even though numerous structures of substituted pyridines are known, few are asymmetrically 2,6-disubstituted. The most similar compound for which crystal data are known appears to be 6-chloro-2-hydroxypyridine;[14] however it does not exhibit partial localization of double bonds.

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