New Syntheses of Polyaza Derivatives.
Crystal Structure of Pyridazine-3,6-dicarboxylic Acid

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A new route allowing the synthesis of pyridazine-3,6-dicarboxylic acid in preparative quantities is described. The crystal structure of this compound is reported. Several polyaza derivatives were prepared and their structures determined by specroscopic methods (ir, ¹H and ¹³C nmr).
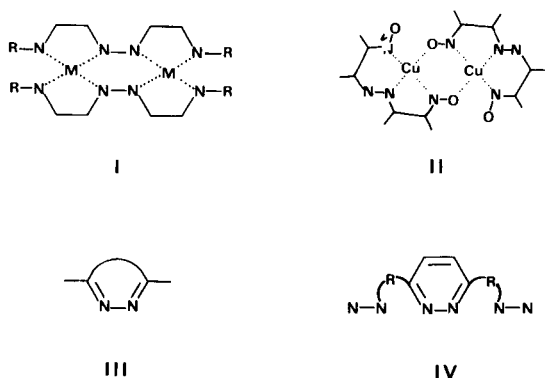
Introduction.

Dinucleating macrocyclic ligands are attractive systems to control in a systematic manner the disposition and the separation of metal ions in homo and heterodinuclear complexes [2-4]. Such complexes form a field of increasing interest, especially with regard to electrical conductivity and the magnetic exchange process.

Unfortunately, the difficulties encountered in the synthesis of compartmental ligands able to maintain in close proximity three or more metal centres is the main limit to their application to polynuclear complexations.

The aim of our research is to synthesize acyclic polyaza ligands having similar properties which could be used as polynucleating agents able to secure metal centres in a linear structure (I) (Scheme 1). The next step will be to introduce terminal reactive functions able to link together several structures.

about the azine group commonly observed in ketazine polymetallic compounds [6] does not permit any further linkage: this steric effect can be avoided if the azine group is included in a ring system III. For this purpose, we have synthesized new polyaza ligands derived from a 3,6-disubstituted pyridazine IV.

Precursors of such compounds must contain electron withdrawing functions like carbonyl and carboxylic groups. Unfortunately, very little is known about the synthesis of these products in preparative quantities.

The title diacid has been prepared in low yield by degradation of 3,6-distyrylpyridazine [7] and its dimethyl ester

Scheme 1

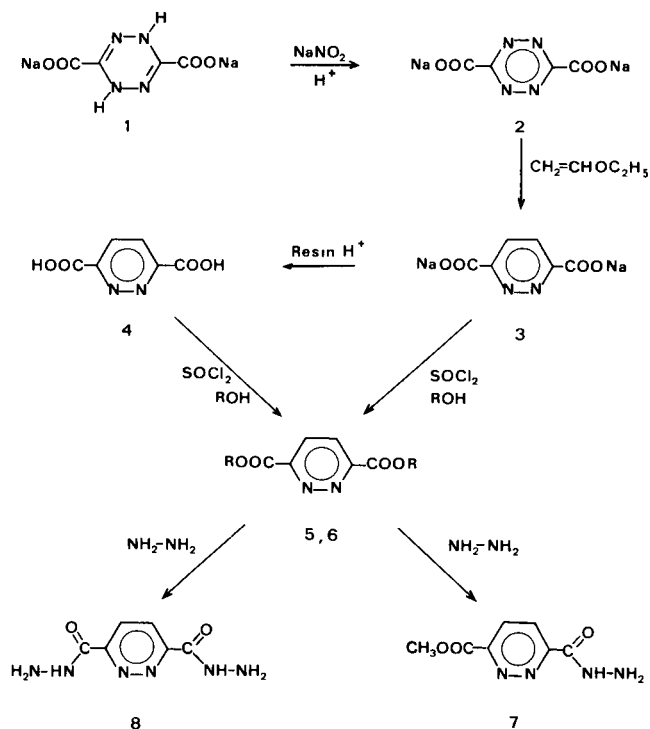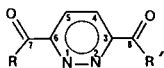

Scheme 2

Results.

We have recently reported the structural study and spectroscopy of a binuclear Cu(II) polyaza-complex derived from diacetylazine dioxime II [5]. The expected binuclear structure I was not observed, since free rotation

Table 1

3,6-Disubstituted Pyridazines

Compound No.	R (R') [d]	% Yield	Mp °C	Formula	Elementary Analysis % Calcd./(Found)			
					C	H	N	O
4 [a]	Hydroxy	75	230	$C_6H_4N_2O_4$	42.86 (43.02)	2.38 (2.27)	16.67 (16.52)	38.09 (38.15)
5 [b] [c]	Methoxy	77 69	202	$C_8H_8N_2O_4$	48.98 (48.90)	4.08 (4.05)	14.29 (14.43)	32.65 (32.47)
6 [b] [c]	Ethoxy	72 65	114	$C_{10}H_{12}N_2O_4$	53.57 (53.92)	5.36 (5.31)	12.50 (12.39)	28.57 (28.81)
7	Hydrazino Methoxy	52	242	$C_7H_8N_4O_3$	42.86 (42.69)	4.08 (4.06)	28.57 (28.35)	24.49 (24.80)
8	Hydrazino	93	>290(d)	$C_6H_8N_6O_2$	36.73 (36.89)	4.08 (4.10)	42.86 (42.52)	16.33 (16.62)

[a] Compound 4 crystallizes from water as a dihydrate which loses its water molecules slowly even at room temperature. This analysis has been carried out on a carefully dried sample. [b] Prepared from compound 4. [c]Prepared from compound 3. [d] Compounds 4, 5, 6, 8: R = R'; Compound 7: R = hydrazino, R' = methoxy.

Table 2

Spectroscopic Data of Pyridazines 4 to 8 [d]

No.	Infrared spectrum KBr cm⁻¹		Mass Spectrum M/e	¹H₁NMR spectrum			¹³C NMR spectrum			
	OH, N-H	C=O		H₄ H₅	CH₂ CH₃	C₇ C₈	C₃ C₆	C₄ C₅	CH₂ CH₃
4 [b]	3460	1700	168	8.4 (s)		165	153.5	129.5	
5 [a]	see Ref [7]		196	8.35 (s)	4.10 (s)	164	152.7	128.3	53.6
6 [a]		1735	224	8.30 (s)	4.55 (q) 1.45 (t)	163.6	153.0	128.1	62.9 14.2
7 [b]	3310	1658 1725	196	8.35 (s)	4.05 (s)	160.3 163.7	154.1 152.2	126.4 129.1	53.1
8 [c]	3380 3320	1695	196	8.30 (s)		160.8	153.9	126.5	

[a] Deuteriochloroform, ppm. [b] DMSO-d₆, ppm. [c] DMSO-d₆ (80°), ppm. [d] Compounds 4, 5, 6, 8: R = R'; Compound 7: R = hydrazino, R' = methoxy.

by reaction of s-tetrazine esters with a variety of unsaturated compounds [8-9].

We have modified this last route in order to obtain more readily the sodium 3,6-pyridazinedicarboxylate in good yield according to Scheme 2.

Compound 1 was prepared according to the literature [9-11]. Preparations of 2 and 3 were carried out in water without isolation of the free acid species. This avoids easy decarboxylation of diacid intermediates and offers higher yields. Recovering of pure diacid 4 is effected by treating

3 with a cationic exchange resin (all attempts to recover 4 using protic acids led to systematic decarboxylation). Thermal analysis confirms the presence of two molecules of water of hydration per molecule in the crystals. These water molecules are slowly released even at room temperature. The preparation of diesters 5 and 6 from compounds 3 and 4 in the corresponding alcohols requires the formation in situ at low temperature of the acid chloride and its subsequent reaction with the solvent.

Compounds 7 and 8 were obtained by reaction of hydra-

zine hydrate on **5**. If one molecule of hydrazine hydrate per molecule of **5** is used, compound **7** was selectively recovered. If more than two molecules of hydrazine hydrate were used, compound **8** was obtained.

Analytical and spectral data for compounds **4** to **8** are summarized in Tables 1 and 2. Chemical shift values fall in the field of those reported in the literature for ¹H and ¹³C nmr studies [12-13].

EXPERIMENTAL

General Methods.

Melting points were determined on a Kofler hot stage apparatus (and are uncorrected). Infrared Spectra were recorded on a Perkin Elmer infrared spectrophotometer 1310 as potassium bromide pellets. The ¹H nmr spectra were measured on a Perkin Elmer R24B 60Hz spectrometer. Chemical shifts are expressed in parts per million with respect to TMS: s, singlet; t, triplet; q, quadruplet. The ¹³C nmr spectra were measured on a Brücker WP 80MHz. Chemical shifts are expressed in parts per million using methanol as the internal reference. Mass spectra were determined on a Ribermag 10-10 spectrometer. Thermal analyses were performed on a Dupont 951 Thermogravimetric Analyzer. Microanalyses for C, H, N and O were performed by the Service Central d'Analyses du C.N.R.S. (Vernaison, France).

Preparations.

Sodium s-Tetrazine-3,6-dicarboxylate (2).

Fifty g (0.23 mole) of sodium s-dihydrotetrazine-3,6-dicarboxylate **1** were introduced into 200 ml of water together with 56 g (0.81 mole) of sodium nitrite. The mixture was cooled to 0° and 50 g (0.83 mole) of acetic acid added dropwise. The mixture turned from yellow to deep red color during the addition. The tetrazine **2** was separated upon addition of 1 liter of methanol. It was washed several times with cold methanol and dried *in vacuo* to give 35 g (71%) of a red powder.

Sodium 3,6-pyridazinedicarboxylate (3).

To a solution of 35 g (0.16 mole) of tetrazine **2** in 400 ml of water were added portionwise 30 g (0.42 mole) of ethyl vinyl ether under vigorous stirring. After each addition, a slightly exothermic reaction occurred with evolution of nitrogen and disappearance of the characteristic tetrazine color. After the end of the reaction, the solution was concentrated and cooled. A yield of 90% (31 g) of pyridazine **3** was obtained.

Pyridazine-3,6-dicarboxylic Acid (4).

To a solution of 30 g (0.14 mole) of the sodium salt **3** in a minimum amount of water were added 100 g of wet Amberlite IRN 77. After half an hour of stirring all the diacid had separated. Methanol was added to the mixture until complete dissolution of the crystals. The resin was separated and the solution was concentrated under vacuum. On cooling a crop (20 g, 75%) of pale yellow crystals separated.

3,6-Dicarbomethoxypyridazine (5).

a) Five g (0.03 mole) of dehydrated diacid **4** were dissolved in 250 ml of methanol and the solution was cooled to −30°. Thionyl chloride (8.6 ml, 0.12 mole) were then added slowly and the mixture allowed to come back to room temperature. After concentration and cooling, a crop (4.5 g, 77%) of yellow crystals was collected.

b) Compound **3** (10.6 g, 0.05 mole) was suspended into 250 ml of methanol and the suspension was cooled to −30°. Thionyl chloride (15 ml, 0.21 mole) was added slowly and the mixture allowed to come to room temperature. After elimination of the solvent, the resulting crystalline mixture was washed with cold water to eliminate sodium chloride. Compound **5** was recrystallized from methanol (6.8 g, 69%).

3,6-Dicarboethoxypyridazine (6).

The procedures reported for compound **5** were repeated except that absolute ethanol was used in place of methanol.

Procedure (a) gave 4.8 g of yellow crystals (72%). Procedure (b) gave 7.3 g of yellow crystals (65%).

6-Carbomethoxy-3-pyridazinecarboxylic Acid Hydrazide (7).

To 2 g (0.01 mole) of **5** dissolved in 250 ml of methanol was added 0.5 ml (0.01 mole) of 99% hydrazine hydrate. On standing overnight at room temperature, yellow cotton-like crystals separated, 1.04 g (52%).

Pyridazine-3,6-dicarboxylic Acid Bishydrazide (8).

The procedure reported for **7** was repeated except that 2 ml (0.04 mole) of hydrazine hydrate were introduced; 1.86 g (93%) of yellow crystals separated.

X-ray Analysis of Compound 4.

A diamond-shaped single crystal measuring 0.50 mm and 0.22 mm diagonally and 0.13 mm in thickness was chosen for the X-ray study. All crystallographic measurements were performed on a Philips PW 1100 four-circle diffractometer using graphite monochromated Mo Kα radiation (λ = 0.7107 Å). The title compound was found to crystallize in the monoclinic space group Cc or C2/c. The lattice parameters were obtained using a least-squares refinement of 25 centered 2θ values. These parameters, along with the other crystal data, are listed in Table 3. Single crystal data were collected using a θ-2θ technique in a quarter of reciprocal space defined by k ≥ 0 and l ≥ 0. Three standard reflections measured every 120 minutes showed regular decrease of their intensity, probably due to a slow dehydration of the crystal. The experimental intensities were corrected for this decomposition using a factor function of the time of measurement.

Table 3

Crystal and Physical Data

Space group		C2/c (C_{2h}^6, No15)
a	=	9.052(3) Å
b	=	10.820(6) Å
c	=	9.551(4) Å
β	=	111.78(3)°
Z	=	4
D_m	=	1.54(3) g.cm⁻³
D_c	=	1.56 g.cm⁻³
F (0 0 0)	=	424
μ (MoK)	=	1.52 cm⁻¹

A total of 1501 reflections were collected of which 662 independent data were considered as observed having I > 3σ(I) (σ based on counting statistics). They were corrected for Lorentz and polarization effects.

Determination and Description of the Structure.

The structure was solved by MULTAN [14] in space group C2/c. The E-map showed all non-hydrogen atoms except the water oxygen, which was located after subsequent refinement and difference synthesis. All the heavy atoms were refined anisotropically. The refinement was carried out using the SFLS-5 program [15], by full-matrix least squares (atomic scattering factors were taken from [16]). A difference map calculated at this stage of refinement clearly indicated the positions of the hydrogen atoms, and in the last cycles their coordinates and isotropic thermal parameters were refined. A weight of unity was attributed to all reflections. When refinement was terminated the conventional R was 0.054 and the weighted R was 0.050. The final difference map did not show the presence of any other atom.

The fractional coordinates and equivalent isotropic temperature factors are listed in Table 4. The list of anisotropic temperature factors and the table of observed and calculated structure factors are available on request. An ORTEP [17] view of the molecule is presented in Figure 1.
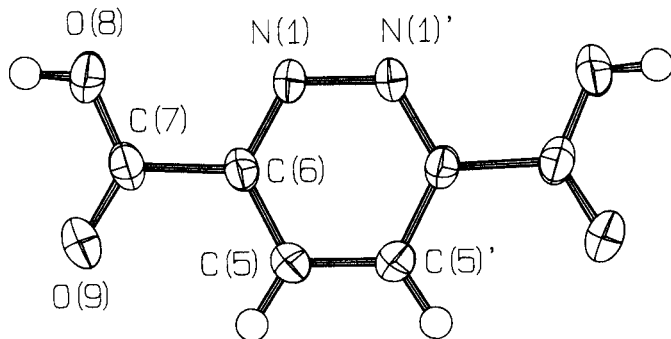

Figure 1. The molecule of pyridazine-3,6-dicarboxylic acid.

Table 4

Fractional coordinates ($\times 10^4$ for non-H atoms and $\times 10^3$ for H atoms) and Thermal Parameters (with estimated standard deviation)

$$B_{eq} = 4/3 \; \Sigma_{ij}\beta_{ij}a_i a_j$$

Atom	x	y	z	B_{eq}
N(1)	4435(3)	3727(2)	7794(3)	2.7(1)
C(5)	4414(4)	5947(3)	7797(4)	2.8(1)
C(6)	3883(4)	4800(3)	8074(4)	2.5(1)
C(7)	2637(4)	4739(3)	8776(4)	2.8(1)
O(8)	2066(3)	3649(3)	8803(4)	4.3(1)
O(9)	2295(3)	5674(2)	9283(3)	4.1(1)
O_w	4504(4)	1492(3)	9485(4)	5.3(1)
HC(5)	397(4)	670(3)	802(4)	1.5(7)
HO(8)	152(7)	359(5)	937(6)	4.8(1.1)
HO_w	434(6)	212(5)	889(5)	4.0(1.0)
HO'_w	525(6)	123(5)	951(6)	4.2(1.1)

The symmetry of the space group requires that the molecule possesses a two fold axis of symmetry. The bond lengths and angles are listed in Tables 5 and 6. It is interesting to compare the results of this study to the structures of gaseous pyridazine itself and dichloropyridazine determined by electron diffraction [18]. The bond lengths and angles involving ring atoms are close in the three compounds. The C-N-N bond angle is

Table 5

Interatomic Distances (Å) for Non-hydrogen Atoms with e.s.d's in Parentheses

C(6)-N(1)	1.330(4)
C(5)-C(6)	1.391(5)
N(1)-N(1)'	1.337(6)
C(5)-C(5)'	1.376(9)
C(6)-C(7)	1.512(6)
C(7)-O(8)	1.292(5)
C(7)-O(9)	1.210(4)

119.2(5)° and is close to the values found in pyridazine ring non protonated at the nitrogen atoms. Conversely, when a nitrogen atom is protonated, as in pyridazine hydrochloride [19], the C-N-N angles are significantly modified (115.8(3) and 125.8(3)°). The pyridazine ring is quite planar, but the C(7) atom is 0.042(4) Å out of the mean plane.

Table 6

Interatomic Angles (°) with e.s.d's in Parentheses

N(1)'-N(1)-C(6)	119.2(5)
N(1)-C(6)-C(5)	123.9(6)
C(6)-C(5)-C(5)'	116.9(8)
N(1)-C(6)-C(7)	116.7(6)
C(5)-C(6)-C(7)	119.4(7)
C(6)-C(7)-O(8)	114.7(6)
C(6)-C(7)-O(9)	119.0(7)
O(8)-C(7)-O(9)	126.3(7)

The most characteristic feature of the molecular structure is the high dihedral angle between the planes of the pyridazine ring and the carboxylic groups (10.7°). This value is larger than the values reported for picolinic acid (4.8°) [20] and for terephtalic acid (5.25°) [21]. This high torsion angle about C(6)-C(7) leads to a poor π orbital overlap and thus explains the rather long C(6)-C(7) distance (1.512(6) Å).

It must also be pointed out that angle N(1)-C(6)-C(7) is quite compressed vs. C(5)-C(6)-C(7), a similar situation exists about C(7): it seems fairly obvious that O(9) is trying to avoid the C(5) proton sterically.

In a very great number of carboxylic acids, the molecules are linked together by two hydrogen bonds involving two carboxylic groups. In the present case, there is no direct hydrogen bond between the diacids but only through the water molecules. Each water molecule bridges three different pyridazines via hydrogen bonds (Figure 2):
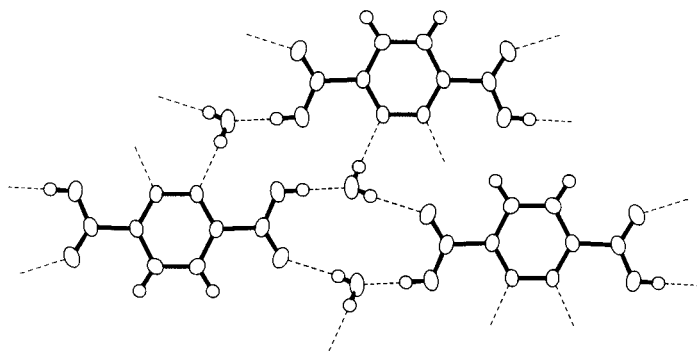

Figure 2. Hydrogen bonds between water and pyridazine-3,6-dicarboxylic acid molecules.

- two involving water hydrogens and
  - N(1) atom:

O_w---N(1)	= 2.896(4) Å	O_w-HO_w	= 0.86(5) Å
HO_w---N(1)	= 2.05(5) Å	O_w-H_w---N(1)	= 167°

  - or O(9) atom:

O_w---O(9)	= 2.750(5) Å	O_w-HO'_w	= 0.73(6) Å
HO'_w---O(9)	= 2.03(6) Å	O_w-H_w---O(9)	= 171°

- One, stronger, involving the hydrogen of the carboxylic group:

O_w---O(8)	= 2.538(6) Å	O(8)-HO(8)	= 0.86(7) Å
HO(8)---O_w	= 1.68(7) Å	O_w---H-O(8)	= 178°

Consequently each pyridazine is connected to six water molecules to form an intricate infinite three dimensional network visualized on the
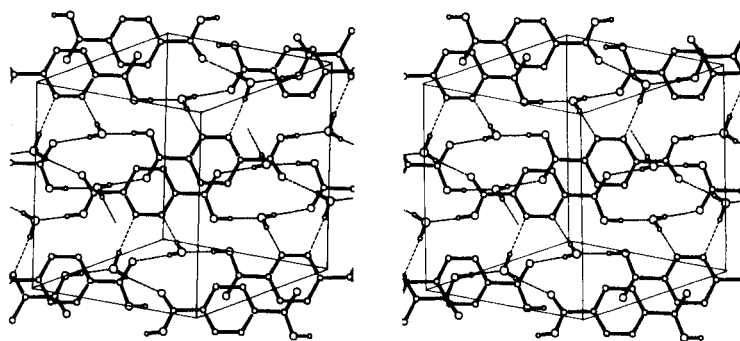
Figure 3. A stereo ORTEP packing diagram.

stereo ORTEP packing diagram of Figure 3. It is quite evident that the torsion of the carbonyl groups is at least partially due to the hydrogen bonds scheme. It should be interesting to crystallize and establish the structure of the anhydrous pyridazine-3,6-dicarboxylic acid.

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