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POLYPYRAZOLIC MACROCYCLES—I

A STUDY OF THE POLYCONDENSATION OF 3-CHLOROMETHYL-3′(5′),5-DIMETHYL-5′(3)-PYRAZOLYL-1-PYRAZOLE

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Abstract—The polycondensation of 3 - chloromethyl - 3′(5′),5 - dimethyl - 5′(3′) - pyrazolyl - 1 - pyrazole under neutral or basic conditions yields new macrocyclic compounds. With suitable choice of base it is possible to direct the reaction towards the formation of a species possessing six pyrazole groups.

In previous studies,[1,2] focussed on the behaviour of macrocycles possessing several heterocyclic groups, we have reported the results of the polycondensation of a dipyrazolylmethane. This was notable for the formation of a macrocycle which is an aza analogue of a porphyrinogen. One of the properties of this new compound is its ability to complex alkali metal cations such as sodium or potassium. However the results of these complexations indicate the formation of sandwich complexes, with no selectivity between the two cations Na^+ and K^+.

In order to gain a better understanding of the properties of this new class of complexing agent, we have undertaken the synthesis of a related molecule possessing an internal cavity of a more suitable size to accomodate the alkali cations (Na^+, K^+ or Cs^+). Towards this end we have examined the polycondensation of 3 - chloromethyl - 3′(5′),5 - dimethyl - 5′(3′) - pyrazolyl - 1 - pyrazole (**1**).

Since we have previously shown[3] that the site of alkylation of a pyrazole is dependent on experimental conditions, the results obtained under neutral and basic conditions are now reported separately.

Polycondensation in dimethylformamide in the presence of KI

When the pyrazolyl pyrazole **1** was heated in DMF in the presence of KI only a single reaction product was able to be isolated. The molecular ion peak at *m/e* 348 in the mass spectrum indicated that this product was a macrocycle possessing four pyrazole groups. The ^1H NMR spectrum of this macrocycle in $CDCl_3$ solution is not complex and consists of two methyl signals of which one appears at 2.13 ppm in the form of a doublet ($J = 0.7$ Hz), characteristic of a 5-CH_3 in a pyrazole ring,[4] and the other at 2.33 ppm with no measurable coupling and is thus substituted at position 3 in the pyrazole ring.[4] The C-4 protons show two peaks at 6.18 and 6.23 ppm and the methylene protons a single AB system ($\delta_1 = 4.72$ ppm; $\delta_2 = 5.43$ ppm; $J = 15$ Hz).

This spectrum indicates that the molecule possesses a certain symmetry but that the molecular skeleton is sufficiently rigidly non-planar to account for the non-equivalence of the two methylene protons. Thus of the three possible macrocycles of mass 348, only derivative **2** is consistent with the NMR evidence.

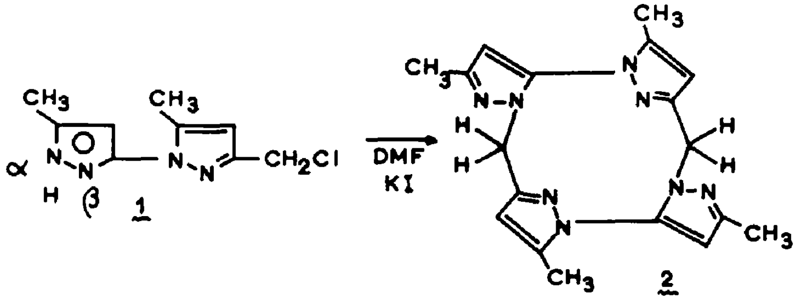
The observed reaction at two β nitrogens is in agreement with previously reported alkylations of pyrazoles, conducted under the same conditions.[3]

Since the aim of this study was to obtain macrocycles possessing sp^2 hybridised nitrogens situated in the interior of the cavity it was necessary to somehow direct the polycondensation reaction towards preferential α-nitrogen attack. With this in mind we examined the technique of phase-transfer catalysis.

Polycondensation of **1** *under basic conditions*

As the results of the polycondensation of **1** under phase transfer catalysis conditions was identical in the presence and absence of catalyst, we reported only the results obtained without any catalyst. Chromatographic separation of the residue obtained by concentrating the benzene phase gave four products **3**, **4**, **5** and **6**.

Compound **3** (yield 4%) mass spectral molecular ion peak at $m/e = 348$ indicates a macrocycle comprised of four pyrazole groups. ^1H NMR ($CDCl_3$): CH_3 2.40 (12H);

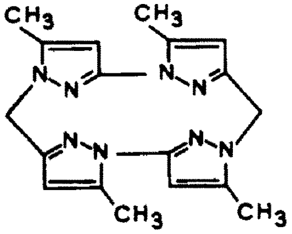


1

2

CH_2 5.12 (4H); CH 5.97 (2H), 6.22 (2H). On addition of several drops of C_6D_6 to the above deuteriochloroform solution, the methyl signal separated into two distinct peaks, each possessing a coupling of approximately 0.7 Hz. The methylene and pyrazolic ring protons showed no such splitting. The observed chemical shifts and coupling constants allow the following conclusions to be drawn. (a) The molecule possesses considerable symmetry (the equivalence of the two CH_2 groups, two signals for the four CH_3 groups and two for the four pyrazole ring protons). (b) Both of the two types of methyl group are located at position −5 in the pyrazole ring (from the characteristic[4] 0.7 Hz coupling to the proton at position-4).

Hence the only structure for compound 3 which is consistent with this data is that shown below.



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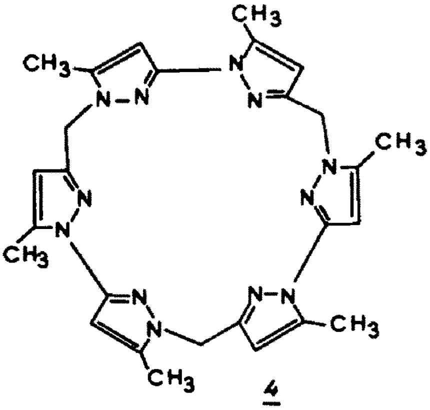
Compound 4 (yield 5%) mass spectrum shows a molecular ion at $m/e = 522$ which indicates that this macrocycle results from the condensation of three monomer molecules. ^1H NMR ($CDCl_3$): CH_3 2.28 (9H), 2.32 (9H); CH_2 5.13 (6H); CH 5.98 (3H), 6.03 (3H). As with 3 the molecule possesses considerable symmetry and, similarly, the addition of several drops of benzene to the deuteriochloroform solution increases the separation of the two types of methyl group without splitting the methylene or pyrazole ring protons. In addition the 0.7 Hz coupling of the methyl groups locate them at position 5 in the pyrazole rings.

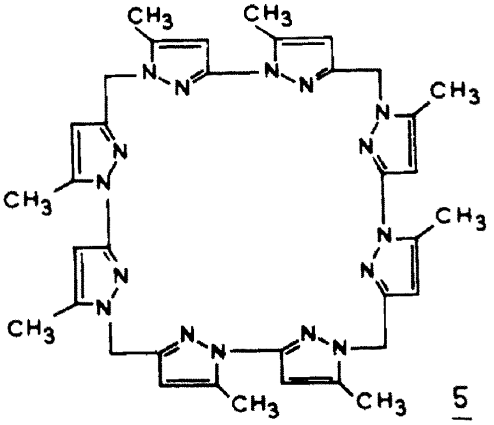
The structure of 4 is therefore unambiguously assigned as that shown below:



4

Compound 5 (yield 7%) mass spectrum indicates a molecular weight of 696 for this product. ^1H NMR ($CDCl_3$): CH_3 2.43 (24H); CH_2 5.17 (8H); CH 6.00 (4H), 6.18 (4H). The addition of several drops of benzene had the same effect as was observed for compounds 3 and 4, namely two signals for the methyl groups, each with $J = 0.7$ Hz.

As with 3 and 4, it follows that compound 5 results from the combination of four pyrazolylpyrazole units as shown below:



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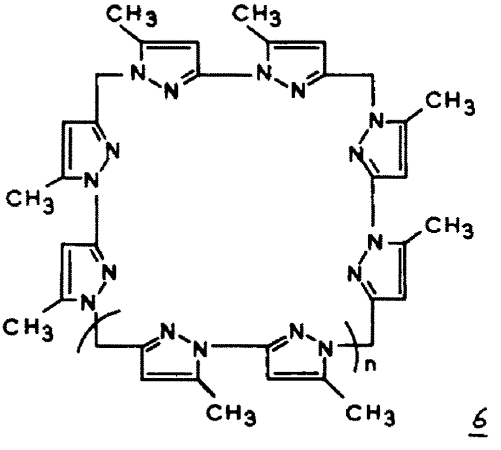
Compound 6 (yield 75%) unlike the three previous products, it has not been possible to detect the molecular ion of compound 6 by mass spectrometry (whether under electron impact, chemical ionisation or field desorption). The reason for this became clearer when an approximate value for the molecular weight of compound 6 was obtained by vapour pressure osmometry. Whilst this technique is not one of high precision it indicated that the molecular weight of 6 was around 2200, which corresponds to a combination of 12 or 13 molecules of the pyrazolypyrazole 1.

In view of the size of this molecule one might expect it to have a very complex NMR spectrum. Nevertheless this is in fact extremely simple. ^1H NMR ($CDCl_3$): CH_3 2.40, 2.48; CH_2 5.37; CH 6.03, 6.27. In order to rule out the possibility of a non-cyclic polymeric structure the ^{13}C NMR spectrum of 6 was recorded, since this technique is more suitable as a probe to molecular skeletal symmetry. As shown below, this spectrum possesses only a limited number of peaks which can be straight forwardly assigned with only minor ambiquities. ^{13}C NMR ($CDCl_3$): CH_3 11.4 (q, J: 130 Hz), 12.7 (q, J: 131 Hz); CH_2 47.7 (q, J: 140 Hz); C_4 99.5 (d, J: 178 Hz), 105.6 (d, J: 176 Hz); C_5 140.3 (complex), 141.2; C_3 147.9 (complex), 148.5. The ^{13}C NMR spectrum again indicates symmetry, and 6 can be represented as shown below:

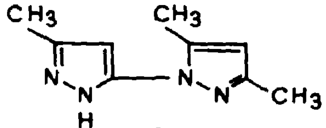


6

n = 9 ou 10

In contrast to the anticipated predominence of products possessing six or eight pyrazole groups in which there is no geometrical strain, the latter product is formed in high yield.

A possible explanation of these results lies in the possibility of the formation, in benzene solution, of reversed micelle type aggregates[6] consisting of an envelope of pyrazolylpyrazole anions whose polar groups, associated to Na^+ cations, are situated in an internal cavity. This is an attractive explanation as a driving force for macrocyclisation, involving alignment of a large number of pyrazolylpyrazoles. It requires that one condition be fulfilled; the reaction must take place in the aprotic medium and not at the interphase. To satisfy this condition it follows that the pyrazolylpyrazole anion when associated with Na^+ has to be soluble in benzene. In order to demonstrate this last point we have studied the properties of a related pyrazolylpyrazole which possesses only the nucleophilic centre whose anion is responsible for the aggregation. When a benzene (C_6D_6) solution of 3′(5′),3,5 - trimethyl - 5′(3′) - pyrazolyl - 1 - pyrazole (7) was mixed with a 50% aqueous sodium hydroxide solution the nature of the solute in the benzene solution underwent considerable change. Table 1 shows the ^1H NMR spectrum of the organic phase; before the addition of the hydroxide solution, and the modification of this spectrum on addition of NaOH.



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The following points should also be noted: (a) The intensity (as determined by integration) of the signals is the same for all the spectra thus indicating that all the pyrazolylpyrazole species has remained in the organic phase. (b) The spectrum of the benzene solution does not change when the aqueous phase is removed, thus implying that the species formed is stable in benzene. (c) When this latter organic solution is washed with water the spectrum of the original pyrazole 7 is regenerated. Thus the observed changes are not due to degradation of the pyrazole system. (d) Titration of the above aqueous washings with 0.1 N hydrochloric acid shows that one molecule of NaOH reacted with one molecule of pyrazolylpyrazole. (e) Finally it should be noted that the N-methylated compound (1′,5′,3,5 - tetramethyl - 3′ - pyrazolyl - 1 - pyrazole), which cannot form an anion, does not exhibit the same phenomenon. Similarly, 3,5-dimethylpyrazole and 3′(5′),3,5 - trimethyl - 5′(3′),1 - dipyrazolylmethane show no significant modification of their NMR spectra under the same conditions. This exemplifies the importance of the pyrazolylpyrazole unit in the polycondensation reaction.

From these facts it was concluded that the polymerisation reaction of the chloromethylpyrazolyl pyrazole 1 does not require a phase-transfer catalyst and that it must be dependent on the alkaline hydroxide used. Indeed the alkali-metal cation on passing into the organic phase should play an important role both in the possibility of aggregate formation and in a template effect in the cyclisation to products 2 and 5.

Table 1. ^1H NMR of 7 in benzene solution with and without added NaOH

	H-4	H-4′	Me-3	Me-5	Me-3′(5′)
7	5.79	6.38	2.28	2.48	1.60
7 + NaOH	5.80	5.58	2.03	2.15	1.87

Table 2. Effect of the alkali hydroxide on the polycondensation of 1

	Yield			
Hydroxide[a]	3	4	5	6
NaOH	4	5	7	75
KOH	5	17	14	53
CsOH	5%	25%	6%	—[b]

[a] The low solubility of LiOH in water prevented its use.

[b] The remainder of the reaction product consists of a complex mixture which was not analysed.

Table 2 shows the yields of products 3–6 obtained under the same experimental conditions for various hydroxides.

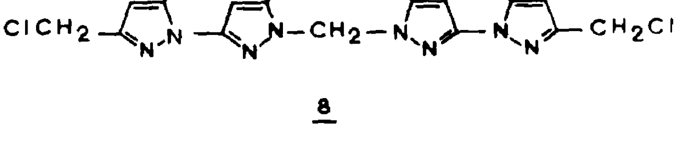
The results in this table confirm the importance of the alkali metal cation in the polymerisation reaction and the existence of a characteristic template effect[5] in the production of 4, in particular. This is consistent with the fact that this system possessing six pyrazole groups is an excellent complexing agent for the Cs^+ cation.

Since the polarity of the organic solvent employed could influence the formation of aggregates the polycondensation of 1 was also carried out in dichloromethane solution. Reaction in this solvent in the presence of 50% NaOH gives a similar result to that in benzene. However, additional competing reactions[7–9] contribute to an extent of approximately 20%. Thus, compounds have been isolated which result from reaction of dichloromethane with the chloromethylpyrazolylpyrazole 1.

The structure of 8 (m.p.: 220–221°) was determined from its mass spectrum (molecular ion at *m/e*: 432, 434) and ^1H NMR spectrum: CH_3 2.48 (d, J: 0.7 Hz), 2.56 (d, J: 0.6 Hz); CH_2Cl 4.60; N–CH_2–N 6.17: CH 6.22, 6.30.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded with Varian T 60 and JEOL PS 100 FT instruments respectively. The chemical shifts are given in ppm downfield from internal TMS for approximately 10% solutions. The mass spectra were recorded with a JEOL JMS D-100 mass spectrometer in the Laboratorie de



8

Mesures Physiques de l'U.S.T.L., by Monsieur L. Guiraud. M.ps were measured in sealed capillaries with a Tottoli apparatus and are uncorrected. Elemental analyses were performed by the central microanalytical service of the CNRS. All compounds for which the word analysis appears, followed by a molecular formula, gave analytical results corresponding to this formula, with a maximum error of 0.3% The following compounds were prepared as described in the literature: Ethyl acetylpyruvate[10]; 3'(5'), 3,5-trimethyl-5' (3')-pyrazolyl - 1 - pyrazole;[3] 3'(5'), 3,5-trimethyl-5', 1-dipyrazolylmethane;[3] 3(5) - methyl - 5(3) - hydrazino pyrazole.[11]

1',5',3,5 - *Tetramethyl - 5' - pyrazolyl - 1 - pyrazole*

Obtained by methylation of 3'(5'), 3,5 - trimethyl - 5' - pyrazolyl - 1 - pyrazole with bromomethane under phase-transfer catalysis conditions using the method previously described.[3] After concentration of the organic phase a white solid was obtained which was recrystallised from petroleum ether, m.p. 43–44°; yield 80%; ^{1}H NMR (C_6D_6) 1.70 (d, J: 0.7 Hz) and 2.52 (d, J: 0.7 Hz), 5–CH_3 and 5'–CH_3; 2.50, 3–CH_3; 3.20, N–CH_3; 5.83 and 6.33, 4–H and 4'–H.

3 - *Carbethoxy* - 3'(5), 5 - *dimethyl* - 5'(3') - *pyrazolyl* - 1 - *pyrazole* **10**

3(5)-methyl-5(3)-hydrazino pyrazole hydrochloride (1.4g) and ethyl acetylpyruvate (1.5 g) were refluxed in ethanol (100 mL) for 3 h. After concentration the residue was taken up in chloroform and neutralised with aqueous sodium bicarbonate solution. The organic phase was concentrated and the residue dissolved in a boiling 1:1 mixture of ether and petroleum ether. **10** was obtained on cooling, m.p. 120–122° (ethyl acetate); yield 65%; ^{1}H NMR ($CDCl_3$) 1.35 (t) and 4.38 (q), Et; 2.2 (d, J: 0.7 Hz), 5'(3')-CH_3; 2.43 (d, J: 0.7 Hz), 5–CH_3; 6.24, 4'–H; 6.67, 4–H. Column chromatography (alumina eluted with 1:1 chloroform: ethyl acetate) of the concentrated filtrate gave the isomeric 5 - carbethoxy - 3'(5'), 3 - dimethyl - 5'(3') - pyrazolyl - 1 - pyrazole, m.p. 113–114° (ether); ^{1}H NMR ($CDCl_3$) 1.22 (t) and 4.22 (q), Et; 2.1, 3'(5')–CH_3; 2.32, 3–CH_3; 6.12, 4'–H; 6.73, 4–H.

3 - *Hydroxymethyl* - 3'(5'), 5 - *dimethyl* - 5'(3') - *pyrazolyl* - 1 - *pyazole* **11**

A soln of **10** (5.5 g) in THF (50 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (1.2 g) in THF (200 ml). After 4 h reflux the excess hydride was destroyed and the solution filtered and concentrated to give **11**, m.p. 107–109° (ether-THF); yield 80%; ^{1}H NMR (d_6-DMSO) 2.13, 3'(5')–CH_3; 2.30, 5–CH_3; 4.43, 3–CH_2; 6.42, 4'–H; 6.75, 4–H.

3 - *Chloromethyl* - 3'(5'), 5 - *dimethyl* - 5'(3') - *pyrazolyl* - 1 - *pyrazole* **1**

11 (1 g) was added in small portions to thionyl chloride (20 ml). After 3 h at room temp the reaction mixture was concentrated to dryness. Ether was added to the residue which was then neutralised with aqueous sodium bicarbonate. The organic phase was concentrated to dryness to give **1**, m.p. 115–120° (ether); yield 60%; ^{1}H NMR ($CDCl_3$) 2.13, 3'(5')–CH_3; 2.40, 5–CH_3; 4.62, 3–CH_3; 6.18 and 6.27, 4–H and 4'–H.

Polycondensation of **1**

Under neutral conditions. A mixture of **1** (0.01 mole) and KI (0.03 mole) in dimethyl formamide was heated at 100° for 4 h. After concentration, the residue was washed with water and the solid product filtered and dissolved in chloroform. This solution was washed with aqueous sodium thiosulphate and the organic phase concentrated to dryness. The residue was disolved in boiling THF (20 mL) which on cooling gave a precipitate of **2**. Chromatography of the filtrate on alumina with 4:1 THF: ethanol gave a second lot of **2**. Yield 30%; m.p. 300°, Analysis: $C_{18}H_{20}N_8$.

Under basic conditions, benzene solution. A mixture of the alkaline hydroxide (50%, 6 ml) and a soln of **1** (0.02 mole) in benzene (300 ml) was heated at 60° for 3 h. Water (100 ml) was then added, the benzene phase separated and the aqueous layer extracted several times with chloroform. The combined organic phases were then concentrated to dryness and the residue taken up in the minimum volume of boiling acetone. A precipitate, consisting principally of **6**, formed after several hours. The residue from the remaining solution was chromatographed on alumina with elution of chloroform containing progressively increasing amounts of ethanol to a maximum of 5%. The following compounds were successively obtained: **3** (m.p. 237–240; Analysis: $C_{18}H_{20}N_8$); **6** (residual unprecipitated product); **5** (m.p. 304–305°, Analysis: $C_{36}H_{40}N_{16}$); **4** (m.p. 300–301°; Analysis: $C_{27}H_{30}N_{12}$). The molecular weight of **6** was determined by VPO using a Hewlett-Packard Model 302 vapour pressure osmometer, in chloroform at 37° with **5** as reference.

Under basic conditions, in CH_2Cl_2. The reaction was carried out at 40° for 2 days using the same method as described above.

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