acetone (1.0 mL) to give 8 (76 mg, 45%): mp 168–170 °C dec; ^{1}H NMR (DMSO) δ 4.35 (s, 4 H), 7.27–7.36 (m, 10 H), 12.60 (s, 2 H); MS (CI) 345 (M + 1)$^+$, 327 (100), 301, 299, 283, 271, 257, 198, 99; IR (KBr) 1680, 680 cm^{-1}. Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.74; H, 4.65. Found: C, 76.46; H, 4.85. ^{1}H NMR of methyl ester of 8 (MeOH/cat. CH_3SO_3H/reflux/6 h) ($CDCl_3$) δ 3.48 (s, 6 H, 4.48 (s, 4 H), 7.21 (m, 6 H), 7.36 (m, 4 H). From the acetone solution was obtained 62 mg of benzoic acid.

When a solution of 7 (240 mg, 0.5 mmol) in a 0.06 M solution of dimethyldioxirane[17] in wet acetone (100 mL, 6.0 mmol) was stirred at room temperature for 12 h, the yield of 8 was only 25%.

X-ray Crystallographic Determination of 7. Rectangular-shaped crystals were obtained from methylene chloride/hexane solution. A 0.25 × 0.3 × 0.4 mm crystal was used for X-ray data measurements with Mo Kα radiation (λ = 0.710 69 Å; incident beam graphite monochromator) on an Enraf-Nonius CAD-4 diffractometer. Monoclinic space group, $P2_1/n$; a = 9.641 (2) Å, b = 15.900 (5) Å, c = 10.864 (2) Å, β = 117.92 (1)°; Z = 2.; ρ_{calcd} = 1.03 g cm^{-3}. A total of 3322 reflections measured to $2\theta_{max}$ = 50°; 2648 unique data; 1348 with $I > 3\sigma(I)$. Crystallographic calculations were done on a Digital Equipment Corp. MicroVax II computer with the TEXSAN system of programs.[18a] Structure solution by the MITHRIL direct methods[18b] subroutine of TEXSAN. Structure refinement by full-matrix least-squares method with anisotropic temperature factors for C and N, and isotropic terms of H; minimization of $\sum w(F_o - F_c)^2$, $w = 1/\sigma^2(F_o)$. Final R, R_w, and goodness-of-fit values of 0.054, 0.060, and 2.0, respectively. Tables of atomic coordinates and temperature factors and bond lengths and angles are available as supplementary material.

Acknowledgment. Special thanks to Professor H. Hart, Dr. G. Doyle, and Dr. D. Stec for their helpful contributions and to Dr. Ted Axenrod, CUNY, for his insightful interpretation of the NMR spectra. Support by the National Science Foundation (Grant CHE-84-02155) for purchase of the X-ray diffractometer/computer system and the National Institute of Health (Grant SIO RR03354) for purchase of a computer graphics system at the University of Maryland, and financial support provided by ARDEC under Contract DAAA21-86-C-0101 to GEO-CENTERS, INC., is gratefully acknowledged.

Registry No. 1, 116531-75-0; 2, 94161-36-1; 5, 116531-78-3; 6, 123776-36-3; 7, 123776-37-4; 8, 123776-38-5; 8 (dimethyl ester), 123776-39-6; PhBr, 108-86-1; benzoic acid, 65-85-0.

Supplementary Material Available: Full table of crystallographic data, bond distances and angles, anisotropic thermal parameters, and hydrogen coordinates for 7 (6 pages). Ordering information is given on any current masthead page.

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New Tetraheterocyclic Macrocycles Containing Triazole, Pyrazole, Pyridine, and/or Furan Subunits. Synthesis and Cation Binding Properties

Georges Tarrago,* Claude Marzin, Ouafa Najimi, and Valdo Pellegrin

Laboratoire de Synthèse et d'Etudes Physicochimiques de Macrocycles, Université des Sciences et Techniques du Languedoc, 34060 Montpellier Cedex, France

Received April 3, 1989

Ten new tetraheterocyclic macrocyclic ligands **2–4** in the porphyrinogen series were prepared. Their structures differ from **1** in (1) the type of junction between hetrocycles (NCH_2C or CCH_2C), (2) the donor nature of the complexation sites, (3) the five- or six-membered geometry of the included heterocycles, and (4) their symmetry. The capabilities of **2–4** for extraction and transport of alkali metal and NH_4^+ cations were less than those of **1**. The rigid dipyrazole ditriazole macrocycles **3** extract Na^+ selectively, whereas the more flexible dipyrazole monotriazole monopyridine macrocycles **2** have the best transport selectivity for Na^+.

Introduction

Synthetic polydentate macrocyclic receptors containing oxygen donor atoms, such as crown ethers,[1,2] cryptands,[2,3] and spherands,[2,4] are well known for their ability to complex alkali and alkaline earth cations. Recently a new class of polydentate sp^2 hybrid nitrogen donor macrocycles that includes polypyridine[5,6] and mixed pyridine–imine[7,8] ligands has been shown to form complexes with these ions. These complexes are so stable that it is often difficult to obtain the free macrocycles from them. For some years we have investigated polypyrazole macrocycles, which have the unusual property of being able not only to extract, transport, and release alkali cations[9–11] like crown ethers but also to form stable complexes with transition metal cations.[12] For instance, the tetrazaporphyrinogen mac-

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(2) (a) Izatt, R. M.; Christensen, J. J. *Synthetic Multidentate Macrocyclic Compounds*; Academic Press: New York, 1978. (b) Izatt, R. M.; Christensen, J. J. *Progress in Macrocyclic Chemistry*; Wiley Interscience: New York, 1979; Vol 1. (c) Izatt, R. M.; Christensen, J. J. *Progress in Macrocyclic Chemistry*; Wiley Interscience: New York, 1981; Vol. 2. (d) Vögtle, F. *Topics in Current Chemistry*; Springer Verlag: West Berlin, 1981; Vol. 98. (e) Melson, G. A. *Coordination Chemistry of Macrocyclic Compounds*; Plenum Press: New York, 1979.
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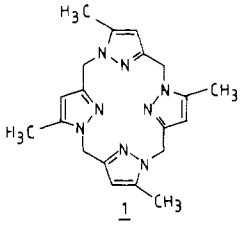
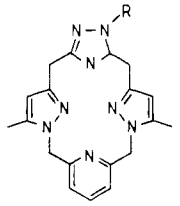
0022-3263/90/1955-0420$02.50/0

rocycle 1 extracts and transports Na^+ and K^+ efficiently and forms stable complexes with Ru(II).

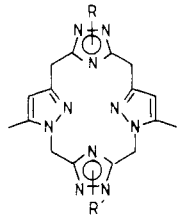
In the present paper we describe the synthesis of a series of new macrocycles **2–4**, whose structure is close to that of 1, and their behavior toward alkali and ammonium cations. The study of their complexation with transition metal cations will be reported elsewhere. The following abbreviations are used in the text: Py = pyridine, Pz = pyrazole, Tz = triazole, and Fur = furan.



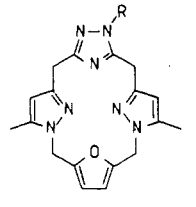
1



2a R = H
2b R = CH_3
2c R = $CH_2C_6H_5$



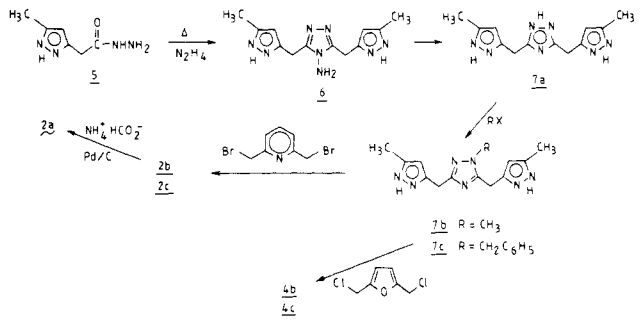
3aa R = R′ = H
3ac R = H, R′ = $CH_2C_6H_5$
3bb R = R′ = CH_3
3cc R = R′ = $CH_2C_6H_5$
3bc R = CH_3, R′ = $CH_2C_6H_5$



4b R = CH_3
4c R = $CH_2C_6H_5$

In order to get a better understanding of the complexing abilities of 1, and possibly increase it, we changed its structure in three ways. First, we replaced one pyrazole ring with a triazole ring and a second pyrazole with another triazole (series **3**), a pyridine (series **2**), or a furan (series **4**) ring. These changes not only perturb the geometry of 1 because of different ring sizes but also introduce triazole or pyridine sp^2 nitrogen or furan oxygen atoms that do not have the same donor characteristics as pyrazole sp^2 nitrogen. Crown ethers bearing these coordination sites have been shown to complex alkali ions: triazole,[13] pyridine,[2c,d] and furan.[2d] Second, in these replacements, we changed the nature of the bonds between heterocycles. In 1, the four pyrazole rings are linked by C(Het)–CH_2–N(Het) junctions; in series **2**, **3**, and **4**, only two junctions are of this type, and the two others are C(Het)–CH_2–C(Het). This change alters the rigidity of the macrocycles because of the different number of CH_2–N(Pz) bonds. Despite the aromaticity of the pyrazole ring, this CH_2–N(Pz) bond is not in the ring plane and undergoes a wagging of small amplitude that makes the macrocycle more flexible. The third change is in macrocycle symmetry: 1 is centrosymmetric, and its four complexation sites are of the same type, whereas **2–4** are not centrosymmetric. This change,

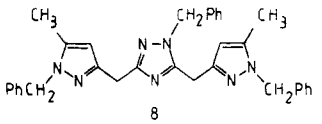
Scheme I. Preparation of Macrocycles 2 and 4



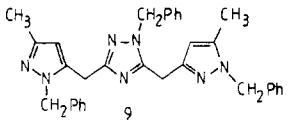
together with the different donor characteristics, creates an electronic density dissymmetry in the cavity. Spherical alkali cations cannot fit perfectly inside such a macrocyclic cavity, thus decreasing complex stability as has been observed for other macrocycles of low symmetry containing both sp^2 nitrogen and oxygen complexation sites.[14]

Results and Discussion

Syntheses. Macrocycles **2–4** were prepared as shown in Schemes I and II. 3(5)-(Hydrazidomethyl)-5(3)-methylpyrazole (**5**) was obtained by the action of hydrazine on 2-hydroxy-6-methyl-4-pyrone.[15] Heating **5** with hydrazine led to the triheterocycle **6**, which was deaminated to give the NH triazole derivative **7a**. As cyclization to **2–4** must occur on pyrazole nitrogen atoms only, we protected the NH triazole group with methyl or benzyl groups, depending on whether or not a leaving group was desired. The problem was to substitute the triazole nitrogen exclusively without affecting the four pyrazole nucleophilic centers. Several experimental conditions for benzylating the triazolic ring were investigated. Under neutral conditions (benzyl bromide in DMF in the presence of KI) a mixture of products mono- and disubstituted on the pyrazolic rings was obtained. Because azoles are more readily alkylated in the anionic form and because pyrazole has a higher pK_a than triazole,[16] we explored alkylation under basic conditions. In both heterogeneous (benzyl bromide in THF with crushed KOH and a small amount of 18-crown-6) and homogeneous reactions (benzyl bromide in methanol in the presence of KOH), the same result was obtained: trisubstituted derivatives **8** (60%), **9** (15%), and **10** (15%).



8



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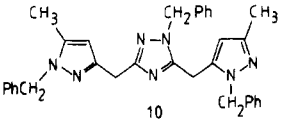

10

The desired tricycles **7b** and **7c** were finally obtained by alkylation with methyl iodide or benzyl bromide in CH_3OH in the presence of CH_3ONa. The pyridino macrocycles **2b** and **2c** were obtained by treating **7b** and **7c** with 2,6-bis(bromomethyl)pyridine[17] (Scheme I). This

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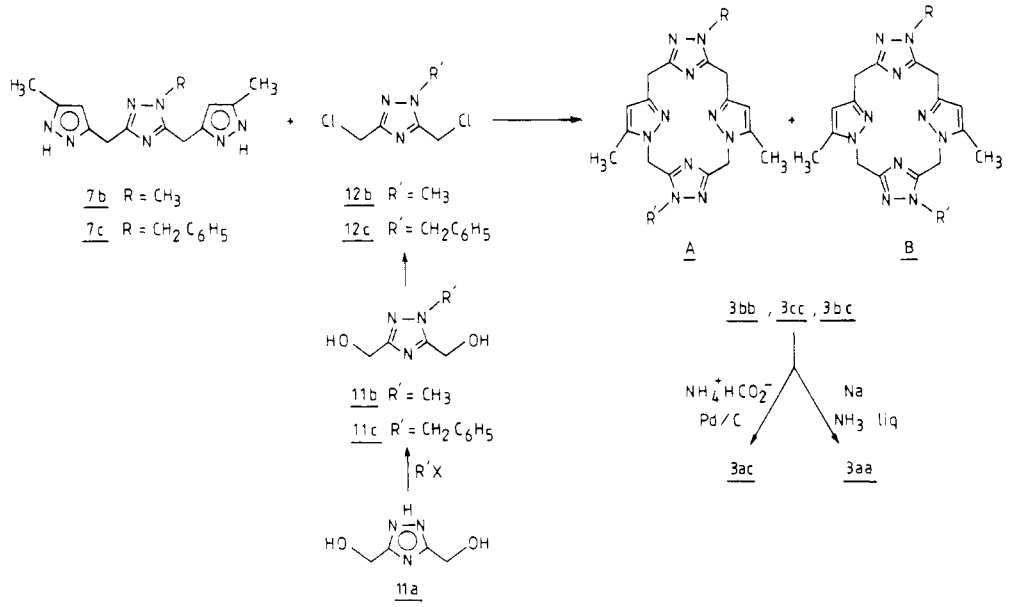
Scheme II. Preparation of Macrocycles 3



cyclization was carried out in a heterogeneous reaction in THF with crushed KOH and a catalytic amount of 18-crown-6.

Several methods were tried to obtain the NH macrocycle **2a**,[18] but debenzylation of **2c** occurred in good yield only with ammonium formate in CH_3OH in presence of 10% Pd/C.[19]

The macrocycles of the bitriazole series **3** were obtained by condensation of **7b** or **7c** with a 1-substituted 3,5-bis(chloromethyl)-1,2,4-triazole **12b** (R′ = CH_3) or **12c** (R′ = CH_2Ph). These last two compounds were prepared from the N-substituted 3,5-bis(hydroxymethyl)-1,2,4-triazoles **11b** and **11c**. The latter were obtained by alkylation of **11a**[20] in methanolic KOH, which gave better yields than $NaOCH_3$. In the synthesis of **3bb** (R = R′ = CH_3), **3cc** (R = R′ = CH_2Ph), and **3bc** (R = CH_3, R′ = CH_2Ph), we obtained each of them as a mixture of two isomers A and B, which could not be separated. The formation of the isomers depends on the way the N-substituted triazole **12** reacts with **7** (Scheme II). The yields of macrocycles **3** were lower than those obtained in the pyridinic series **2**, probably because the asymmetry of triazoles **12** gives different reactivities to the two CH_2Cl groups for electronic as well as steric reasons.

Debenzylation of **3cc** under the same conditions used for **2c** afforded only the monodebenzylated macrocycle **3ac**. The di-NH macrocycle **3aa** was obtained under the more drastic conditions of Na in liquid ammonia;[18c] however, the compound obtained was totally insoluble in organic solvents, preventing further studies.

The synthesis of **4** was carried out as described in Scheme I. In the cyclizing step we used 2,5-bis(chloromethyl)furan[21] that we prepared from 2,5-bis(hydroxymethyl)furan by reaction with $SOCl_2$ and pyridine in $CHCl_3$ at −10 °C. The product was used as such (chromatographic purification induces decomposition) in the condensation with **7b** and **7c** in a heterogeneous reaction as described for **2**.

Table I. Cation Extracted Percentages

	cations, %				
macrocycles	Li^+	Na^+	K^+	Cs^+	NH_4^+
1	3	35	35	13	11
2b	3	21	20	3	11
2c	5	22	23	5	14
3bb	2	15	2	2	2
3cc	3	16	3	3	2
3bc	2	16	3	2	2
4b	2	7	4	2	2
4c	2	8	3	2	2

Liquid–Liquid Extraction of Alkali and Ammonium Cations. We used this method in order to compare the relative capabilities of **2–4** in extracting Li^+, Na^+, K^+, Cs^+, and NH_4^+ cations. Metal and ammonium picrates were extracted into the organic phase by complex formation with the macrocycle; the decrease in absorbance of the picrate in the aqueous phase was followed by UV spectroscopy. The percentage limits of extraction are given in Table I together with those for **1** for comparison.

It is apparent that **2–4** are less effective than **1** in extracting alkali cations, and that **2–4** lack affinity for Li^+ and Cs^+. The three bitriazole macrocycles **3bb**, **3cc**, and **3bc** have the same good selective affinity for Na^+ regardless of the nature of the N-substituent. In this respect they differ from **1**, which shows high extracted percentages for K^+ as well as for Na^+. Two structural differences between **1** and **3** may explain the different behavior. The lower σ-donor character of the sp^2 triazole nitrogen atoms in **3** compared to the pyrazole nitrogens in **1**[22] explains the decrease in extraction power for **3**. Moreover, the four C–N junctions linking the heterocycles in **1**, compared with two in **3**, gives to **1** a higher degree of flexibility, which allows accommodation of both Na^+ and K^+; the size and rigidity of **3** make them perfectly fitted for Na^+.

The results in Table I indicate that **2** shows lower extracted percentages than **1** but higher than **3**; the different nature of the coordination sites and their asymmetric location may explain the lower extraction capacity in **2**. Moreover, like **1**, **2** shows no selectivity between Na^+ and K^+, although it might have been expected because both

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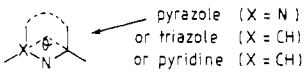
2 and 3 have the same intercyclic junctions. Another factor makes 2 and 3 different: the presence in the former of a six-membered ring in the macrocycle. From the angle values known for pyridine, pyrazole, and triazole rings,[23] it is possible to calculate the angle θ between the extracyclic bonds α to the coordination site:



For a pyridine ring this angle is close to 124°, but for a five-membered ring (pyrazole or triazole) it is calculated as 144°. Molecular models indicate that such an increase of the angle θ in 3 leads to considerable strain in the macrocycle, which prevents any conformational reorganization to accommodate a substrate not exactly fitted. Such a result is an example of the balance between flexibility and rigidity which is primordial in binding interactions.

Both furan macrocycles **4b** and **4c** show a lack of extraction capacity for any of the alkali cations. As all the macrocycles described here have the identical triheterocyclic part, $PzCH_2TzCH_2Pz$, the behavior of 4 must reflect the presence of the furan ring. First, it is known that the furan oxygen atom has a lower donor character than an alkyl ether oxygen atom.[2d] Second, the complexation sites inside the cavity (three sp^2 nitrogen atoms and an oxygen) must create a strong dissymmetry in the cavity.

Macrocycle **2a** is the only compound unsubstituted on the triazole ring we have studied. It has a tautomerizable NH proton, which may be localized on any of the three triazole nitrogen atoms, thus leading to a special complexing behavior of the macrocycle. The NH 1,2,4-triazole derivatives have been shown to exist predominantly in the unsymmetrical form N-1 or N-2. Furthermore, this NH proton is ionizable and is part of the macrocycle ring. Several polyether macrocycles with such an NH triazole group have been studied.[13] If the macrocycle is relatively rigid near the triazole ring, the triazole NH proton is located inside the cavity, linked to a water molecule.[13a] If the macrocycle is more flexible, it is outside the cavity.[13b,d] In the latter case, preliminary reports show a good transport ability for K^+ if the macrocycle contains a lipophilic group.[13d]

In **2a**, the triazole ring is included in a nearly planar part of the macrocycle in which the pyrazole nitrogen atoms of the cavity may stabilize the NH proton inside the cavity. We have observed that **2a** does not extract any alkali cation; this is understandable if the triazole NH proton is located inside the macrocyclic cavity, linked or not to a water molecule.

As far as NH_4^+ extractibility is concerned, if cation size were the only factor, the results should be close to those for K^+. However, 1 and 2 have quite different extracting abilities for these two cations (Table I), which probably reflects their differences in charge distribution (spherical for K^+ and tetrahedral for NH_4^+) and in their interactions (electrostatic for K^+, and stabilization by hydrogen bonding for NH_4^+).[25] The complexation of a NH_4^+ cation with a macrocycle involves interaction of a tripod of three $^+NH\cdots X$ hydrogen bonds[2d] with sp^2 nitrogen atoms in the cavity. The weak extraction percentages observed for the bitriazole 3 and furan 4 (~2%) indicate that the $PzCH_2TzCH_2Pz$ arrangement is less effective than $PzCH_2PzCH_2Pz$ in complexing with NH_4^+.

The extraction percentages for NH_4^+ by 1 and 2 are equivalent, which suggests that the $PzCH_2PyCH_2Pz$ part of 2 is involved in the complexation. The different behavior of the $PzCH_2TzCH_2Pz$ (3) arrangement toward NH_4^+ compared to $PzCH_2PzCH_2Pz$ (1) or $PzCH_2PyCH_2Pz$ (2) ones may arise from two factors. First, pyrazole and pyridine sp^2 nitrogen atoms may have a greater tendency to complex with NH_4^+ than a triazole nitrogen. Second, the greater rigidity of 3 compared with 1 or 2 may prevent the triazole nitrogen lone pair from being well disposed to bind the NH_4^+ cation.

Table II. Transport Rate Values in 10^{-6} mol/h

	cations				
macrocycles	Li^+	Na^+	K^+	Cs^+	NH_4^+
1	0.15	0.7	0.2	0.3	0.6
2b	0.1	0.6	0.2	0.1	0.3
2c	0.1	0.6	0.2	0.1	0.3
3bb	0.1	0.2	0.1	0.1	0.1
3cc	0.1	0.2	0.1	0.1	0.1
3bc	0.1	0.2	0.1	0.1	0.1
4b	0.1	0.1	0.1	0.1	0.1
4c	0.1	0.1	0.1	0.1	0.1

Transport of Alkali and Ammonium Cations through a Bulk Liquid Membrane. For transport experiments we used artificial liquid membranes to allow comparisons with previous work.[9-11,14] We studied the carrier abilities of 1–4 toward Li^+, Na^+, K^+, Cs^+, and NH_4^+ cations. The transport was carried out through a CH_2Cl_2 membrane separating two aqueous solutions as previously described.[9] Transport rates are given in Table II.

One may observe very low transport rates for the macrocycles that have low extraction aptitude: **4b** and **4c** with all the cations, 2 with Li^+ and Cs^+, and 3 with Li^+, K^+, Cs^+, and NH_4^+. However, macrocycles that show high extraction percentages do not all show high transport rates. For instance, although macrocycles 2 all have the same extraction ability (~20%) toward Na^+ and K^+, they have transport rates for Na^+ three times higher than for K^+. This result may be explained by differences in decomplexation rates for these two cations, arising because complexes with K^+ are more stable than those with Na^+. This same explanation holds when one compares the transport rates of NH_4^+ with 1 and 2 (the rate for 2 is half that for 1). The NH_4^+ cation is better retained by 2, as indicated by extraction results and confirming the good binding ability of the $PzCH_2PyCH_2Pz$ arrangement for NH_4^+.

Macrocycles 3 have low transport rates for Na^+, similar to those of the three other alkali cations. This result was unexpected because Na^+ cation is selectively extracted by 3, and apparently reflects the good affinity of 3 for Na^+, which is better retained than K^+ and thus has a relatively low transport rate.

Experimental Section

General. ^1H NMR spectra were recorded with Varian EM 390, HA 100, or Bruker AC 250 spectrometers. ^{13}C NMR spectra were obtained with a Bruker WP 200 spectrometer at 50.327 MHz. Chemical shifts are reported in ppm (δ) downfield from internal Me_4Si. Mass spectra were obtained with a JEOL JMS DX-333 mass spectrometer. Melting points are uncorrected. Elemental analyses were performed by the Central Microanalytical Service of the CNRS.

Extraction Experiments. A cylindrical reaction cell (50 mm in diameter) contained a spectroscopic grade CH_2Cl_2 solution (30

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mL) of the ligand (7×10^{-5} M) and an aqueous solution (30 mL) of metal picrates (7×10^{-5} M) and hydroxide (0.1 M). The organic phase was magnetically stirred (a 25 mm long magnetic bar, 5 mm in diameter, was rotated at 1 turn/s); the complexation was followed by measuring the picrate anion concentration in the aqueous phase by UV spectroscopy at 355 nm.

Transport Experiments. The apparatus described in a previous paper[9] was used with the following experimental conditions. Source phase: aqueous solution (10 mL) of metal picrate (10^{-3} M) and nitrate (10^{-1} M). Membrane phase: 50 mL of a CH_2Cl_2 solution of the macrocycle (7×10^{-5} M). Receiving phase: bidistilled water (20 mL). The appearance of picrate anion in the third phase was followed by UV spectroscopy.

Syntheses. 1-Amino-3,5-bis[3′(5′)-methyl-5′(3′)-pyrazolyl]-1,2,4-triazole (6). A mixture of the hydrazidopyrazole **5**[15] (0.25 mol) and monohydrated hydrazine (0.5 mol) was refluxed at 120 °C for 3 h and then between 120 and 160 °C for 6 h after the low-boiling products had been distilled. Compound **6** was obtained as a white solid (95%) which was washed with water and then used as such in the following reaction: mp 209–211 °C; ^{1}H NMR (DMSO-d_6) δ 2.11 [s, 6 H, CH_3-3′(5′)], 4.00 (s, 4 H, CH_2), 5.88 (s, 2 H, H-4′); MS m/z 272. Anal. Calcd for $C_{12}H_{16}N_8$: C, 52.99; H, 5.93; N, 41.20. Found: C, 53.08; H, 5.84; N, 41.12.

3,5-Bis[3′(5′)-methyl-5′(3′)-pyrazolyl]-1,2,4-triazole (7a). The *N*-amino compound **6** (0.06 mol) was dissolved in a mixture of HCl (0.6 mL)/H_2O (7.5 mL); a solution of $NaNO_2$ (0.12 mol) in water (100 mL) was slowly added at 8 °C. The mixture was then stirred for 3 h and neutralized with Na_2CO_3. The precipitate formed was filtered and purified by chromatography on alumina (eluant: CH_2Cl_2/C_2H_5OH, 40/60) (88% yield): mp 127–130 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 [s, 6 H, CH_3-3′(5′)], 3.93 (s, 4 H, CH_2), 5.90 (s, 2 H, H-4′); MS m/z 257. Anal. Calcd for $C_{12}H_{15}N_7$: C, 56.01; H, 5.88; N, 38.11. Found: C, 55.82; H, 5.80; N, 38.22.

1-Methyl-3,5-bis[3′(5′)-methyl-5′(3′)-pyrazolyl]-1,2,4-triazole (7b). The tricycle **7a** (7.78 mmol) dissolved in CH_3OH (10 mL) was added to a solution of CH_3ONa (7.78 mmol) in CH_3OH (75 mL). The mixture was stirred for 1 h; methyl iodide (7.78 mmol) was slowly added. The solution was heated at 60 °C for 18 h, evaporated to dryness, and the residue was extracted three times with CH_2Cl_2. The organic phase was concentrated, and the residue was chromatographed on alumina using a mixture of CH_2Cl_2/C_2H_5OH, 90/10, as eluant (90% yield): mp 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 [s, 6 H, CH_3-3′(5′)], 3.68 (s, 3 H, CH_3-1), 4.03 and 4.10 (2 s, 4 H, CH_2), 5.90 and 6.00 (2 s, 2 H, H-4′); ^{13}C NMR ($CDCl_3$) δ 11.3 and 12.1 [CH_3(pz)], 35.2 (N-CH_3), 25.0 and 26.35 (PzCH_2Tz), 103.9 and 104.2 [C-4′(pz)], 142.4 and 144.4 [C-5′(3′)(Pz)], 142.5 [*C*-CH_3 (Pz)], 153.1 [C-5(Tz)], 160.1 [C-3(Tz)]; MS m/z 271. Anal. Calcd for $C_{13}H_{17}N_7$: C, 57.54; H, 6.32; N, 36.14. Found: C, 57.68; H, 6.25; N, 36.28.

1-Benzyl-3,5-bis[3′(5′)-methyl-5′(3′)-pyrazolyl]-1,2,4-triazole (7c). The same process as described for **7b** was used with benzyl bromide (50% yield): mp 112–114 °C; ^{1}H NMR ($CDCl_3$) δ 2.06 and 2.13 [2 s, 6 H, CH_3-3′(5′)], 4.03 (br s, 4 H, CH_2), 5.18 (s, 2 H, CH_2Ph), 5.70 and 5.93 (2 s, 2 H, H-4′), 7.21 (br s, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 11.3 and 11.9 [CH_3(Pz)], 25.1 and 26.1 (PzCH_2Pz), 52.2 (N-CH_2Ph), 104.2 and 104.7 [C-4′(Pz)], 142.6 [*C*-CH_3 (Pz)], 144.3 and 144.7 [*C*-5′(3′)(Pz)], 154.0 [*C*-5(Tz)], 159.8 [*C*-3(Tz)]; MS m/z 347. Anal. Calcd for $C_{19}H_{21}N_7$: C, 65.68; H, 6.09; N, 28.22. Found: C, 65.41; H, 6.22; N, 27.98.

Tribenzylated Derivatives 8, 9, and 10. Benzyl bromide (7.5 mmol) and 18-crown-6 (100 mg) were added to a suspension of crushed KOH (45 mmol) in anhydrous THF. The mixture was refluxed for 6 h. THF was evaporated, and the residue was chromatographed on alumina (eluant: CH_2Cl_2/C_2H_5OH, 98/2). The three derivatives were obtained as oils with respective yields of 30, 6, and 6%: ^{1}H NMR ($CDCl_3$) δ (**8**) 2.03 [s, 6 H, CH_3-3′(5′)], 4.06 (s, 4 H, CH_2), 5.11, 5.18, and 5.19 (3 s, 6 H, CH_2Ph), 5.83 and 5.98 (2 s, 2 H, H-4′), 7.16 (br s, 15 H, Ph); (**9**) 2.26 [s, 6 H, CH_3-3′(5′)], 4.45 (s, 4 H, PzCH_2Tz), 5.40 (br, 6 H, CH_2Ph), 5.88 and 5.98 (2 s, 2 H, H-4′), 7.20 (br, 15 H, Ph); (**10**) 2.13 and 2.26 [2 s, 6 H, CH_3-3′(5′)], 3.96 and 4.08 (2 s, 4 H, PzCH_2Tz), 5.25 and 5.40 (2 s, 6 H, CH_2Ph), 5.91 and 6.10 (2 s, 2 H, H-4′), 7.26 (br, 15 H, Ph); MS m/z 527 for **8**, **9**, and **10**.

Macrocycle 2b. The 2,6-bis(bromomethyl)pyridine[17] (12 mmol) and a catalytic amount of 18-crown-6 were added to a solution of the tris heterocycle **7b** (12 mmol) in THF (500 mL) in the presence of crushed potassium hydroxide (70 mmol). The mixture was refluxed for 6 h, filtered, and evaporated to dryness. The residue was taken up with water (100 mL) and extracted twice with CH_2Cl_2. The organic phase was washed with water, filtered, and evaporated to dryness. The residue was purified by chromatography on alumina (eluant: CH_2Cl_2/C_2H_5OH, 95/5) to give **2b** (40% yield): mp 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 [s, 6 H, CH_3(Pz)], 3.69 [s, 3 H, CH_3(Tz)], 3.83 (s, 4 H, TzCH_2Pz), 5.12 (s, 4 H, PyCH_2Pz), 5.89 [s, 2 H, H-4′(Pz)], 7.06 [d, 2 H, H-β(Py)], 7.55 [t, 1 H, H-γ(Py)]; MS m/z 374. Anal. Calcd for $C_{20}H_{22}N_8$: C, 64.15; H, 5.92; N, 29.93. Found: C, 63.94; H, 5.98; N, 30.04.

Macrocycle 2c. The same method as described for **2b** was used from the triheterocycle **7c** (30% yield): mp 153–155 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 [s, 6 H, CH_3(Pz)], 3.72 and 3.78 (2 s, 4 H, TzCH_2Pz), 4.95 and 5.00 (2 s, 4 H, PzCH_2Py), 5.07 (s, 2 H, CH_2Ph), 5.68 and 5.78 [2 s, 2 H, H-4′(Pz)], 7.13 [br s, 7 H, Ph and H-β(Py)], 7.50 [t, 1 H, H-γ(Py)]; MS m/z 450. Anal. Calcd for $C_{26}H_{26}N_8$: C, 69.40; H, 5.82; N, 24.90. Found: C, 69.28; H, 5.93; N, 24.78.

Macrocycle 2a. Macrocycle **2c** (0.28 mmol) was added to a suspension of Pd/C, 10% (130 mg), in anhydrous methanol; then, ammonium formate (0.28 mmol) was added portionwise. The reaction was followed by TLC until total disappearance of **2c**. The mixture was filtered on Celite, methanol was evaporated, and the residue was extracted with CH_2Cl_2 and purified by chromatography on alumina (eluant: CH_2Cl_2/C_2H_5OH, 98/2) (70% yield): mp 224–225 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 [s, 6 H, CH_3(Pz)], 3.95 (s, 4 H, PzCH_2Tz), 5.13 (s, 4 H, PzCH_2Py), 5.83 [s, 2 H, H-4′(Pz)], 7.19 [d, 2 H, H-β(Py)], 7.68 [t, 1 H, H-γ(Py)]; MS m/z 360. Anal. Calcd for $C_{19}H_{20}N_8$: C, 63.39; H, 5.60; N, 31.13. Found C, 63.45; H, 5.67; N, 30.94.

***N*-Alkyl-3,5-bis(hydroxymethyl)-1,2,4-triazole (11b and 11c).** The 3,5-bis(hydroxymethyl)-1,2,4-triazole **11a**[19] (31 mmol) was added to a solution of potassium hydroxide (31 mmol) in CH_3OH; the mixture was stirred for 1 h, and methyl iodide or benzyl bromide (34 mmol) was added. The solution was heated at 60 °C for 18 h, and methanol was evaporated. Two purification methods were used depending on the nature of the N-substitution:

11b. The residue was dissolved in the minimum amount of an aqueous sodium thiosulfate solution and continuously extracted with CH_2Cl_2 for 24 h. After evaporation of the dichloromethane, the oil obtained was treated with ether to give a solid (78% yield): mp 117–118 °C; ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3 H, N-CH_3), 4.38 and 4.55 (2 d, 4 H, CH_2OH), 5.18 and 5.60 (2 t, 2 H, OH); MS m/z 143. Anal. Calcd for $C_5H_9N_3O_2$: C, 41.95; H, 6.34; N, 29.36. Found: C, 41.73; H, 6.40; N, 29.25.

11c. The residue was taken up in water (150 mL) and extracted three times with CH_2Cl_2; the organic phase was evaporated to dryness, and the residue chromatographed on alumina (eluant: CH_2Cl_2/ether, 70/30) to give an oil (80% yield): ^{1}H NMR (DMSO-d_6) δ 4.60 (br s, 4 H, CH_2OH), 5.35 (s, 2 H, CH_2Ph), 5.57 (br, 2 H, OH), 7.30 (s, 5 H, Ph); MS m/z 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.42; H, 5.86; N, 19.12.

***N*-Alkyl-3,5-bis(chloromethyl)-1,2,4-triazole (12b and 12c).** Compound **11b** or **11c** (20 mmol) was added portionwise to $SOCl_2$ (200 mL), and the mixture was refluxed for 4 h; $SOCl_2$ was evaporated, and the residue was suspended in ether; the solution was neutralized with a saturated solution of Na_2CO_3 and extracted; the ether was evaporated to give an oil, which was chromatographed on alumina (eluant: CH_2Cl_2).

12b (48% yield): mp 78 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3 H, N-CH_3), 4.61 and 4.73 (2 s, 4 H, CH_2Cl); MS m/z 180. Anal. Calcd for $C_5H_7Cl_2N_3$: C, 33.36; H, 3.92; N, 23.34. Found: C, 33.19; H, 3.87; N, 23.27.

12c (53% yield): oil; ^{1}H NMR ($CDCl_3$) δ 4.50 and 4.55 (2 s, 4 H, CH_2Cl), 5.37 (s, 2 H, CH_2Ph), 7.31 (s, 5 H, Ph); MS m/z 256. Anal. Calcd for $C_{11}H_{11}Cl_2N_3$: C, 51.61; H, 4.33; N, 16.41. Found: C, 51.82; H, 4.38; N, 16.28.

Macrocycle 3bb. A solution of **7b** (4.3 mmol) and **12b** (4.3 mmol) in CH_2Cl_2 (300 mL) was added to a solution of 50% NaOH (5 mL); a catalytic amount of tetrabutylammonium bromide was also added. The mixture was refluxed for 6 h, taken up in water (200 mL), and extracted three times with CH_2Cl_2. The CH_2Cl_2 phase was washed with water and evaporated. The residue was chromatographed on alumina (eluant: CH_2Cl_2/C_2H_5OH, 98/2) (28% yield): mp 238–240 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 and 2.23

[2 s, 6 H, CH_3(Pz)], 3.80 and 3.83 [2 s, 4 H, (Pz)CCH_2C(Tz)], 3.70 [br s, 6 H, N-CH_3(Tz)], 5.03 and 5.10 [2 s, 4 H, (Pz)NCH_2C(Tz)], 5.86 and 5.93 [2 s, 2 H, CH(Pz)]; MS m/z 378. Anal. Calcd for $C_{18}H_{22}N_{10}$: C, 57.20; H, 5.87; N, 37.05. Found: C, 57.29; H, 5.90; N, 36.88.

Macrocycle 3cc. The same method described for **3bb** was used for condensation of **7c** and **12c**. The residue obtained was purified by chromatography on alumina (eluant: CH_2Cl_2/C_2H_5OH, 96/4) (25% yield): mp 110-112 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 and 2.13 [2 s, 6 H, CH_3(Pz)], 3.66 and 3.70 [2 s, 4 H, (Pz)CCH_2C(Tz)], 4.90 and 5.00 [2 s, 4 H, (Pz)NCH_2C(Tz)], 5.16 and 5.21 (2 s, 4 H, CH_2Ph), 5.73 and 5.83 [2 s, 2 H, CH(Pz)], 7.15 (br, 10 H, Ph); MS m/z 530. Anal. Calcd for $C_{30}H_{30}N_{10}$: C, 67.99; H, 5.71; N, 26.43. Found: C, 67.82; H, 5.80; N, 26.32.

Macrocycle 3bc. This macrocycle was obtained as described for **3bb** or **3cc** by condensation of **7b** and **12c**. Purification of the crude product was done by chromatography on alumina (eluant: CH_2Cl_2/C_2H_5OH, 96/4) (25% yield): mp 152-154 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 and 2.25 [2 s, 6 H, CH_3(Pz)], 3.70 [s, 3 H, CH_3(Tz)], 3.76 and 3.80 [2 s, 4 H, (Pz)CCH_2C(Tz)], 4.93 and 5.03 [2 s, 4 H, (Pz)NCH_2C(Tz)], 5.30 (s, 2 H, CH_2Ph), 5.88 [br s, 2 H, CH(Pz)], 7.26 (br, 5 H, Ph); MS m/z 454. Anal. Calcd for $C_{24}H_{26}N_{10}$: C, 63.50; H, 5.77; N, 30.85. Found: C, 63.71; H, 5.68; N, 30.78.

Macrocycle 3ac. Macrocycle **3cc** (0.33 mmol) was added to a suspension of 10% Pd/C (186 mg) in anhydrous methanol under nitrogen. The ammonium formate was added portionwise. The mixture was refluxed for 72 h. After total disappearance of macrocycle **3cc**, the mixture was filtered on Celite, and the methanol was evaporated to give an oil (23% yield), which is the monobenzylated macrocycle **3ac** or **3ca**: ^{1}H NMR ($CDCl_3$) δ 2.20 [s, 6 H, CH_3(Pz)], 4.07 [br, 4 H, (Pz)CCH_2C(Tz)], 5.30 [br, 6 H, (Pz)NCH_2C(Tz) and CH_2Ph], 5.93 [br s, 2 H, CH(Pz)], 7.26 (br, 5 H, Ph); MS m/z 440. Anal. Calcd for $C_{23}H_{24}N_{10}$: C, 62.79; H, 5.50; N, 31.83. Found: C, 62.88; H, 5.48; N, 31.72.

Macrocycle 3aa. Macrocycle **3cc** (0.1 mmol) was added to liquid ammonia. Small pieces of Na (0.44 mmol) were added until the blue color did not disappear anymore. Ammonium chloride (0.72 mmol) was added, and the ammonia was allowed to evaporate. The residue obtained was totally insoluble in organic solvents.

2,5-Bis(chloromethyl)furan. A solution of $SOCl_2$ (6.1 mL) in $CHCl_3$ (4 mL) was added to a mixture of 2,5-(hydroxymethyl)furan (0.04 mol) and pyridine (7.7 mL) in $CHCl_3$ (12 mL) between -10 and 0 °C under nitrogen. The solution was stirred for 2 h at -10 °C and poured into a mixture HCl/H_2O (1/10) at 0 °C. The solution was decanted, the chloroform phase was washed twice with an aqueous solution of HCl (1/10) and once with a solution of 3% NaOH on cooling with ice. The organic phase was dried over KOH and evaporated to dryness without heating in order to avoid any oxidation of the furan derivative. An oil was obtained (lit. mp 63-67 °C)[21] (45% yield): ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 4 H, CH_2Cl), 6.06 [s, 2 H, H(Fur)].

Macrocycles 4. Macrocycles **4b** and **4c** were obtained by condensation of 2,5-bis(chloromethyl)furan with the triheterocycles **7b** and **7c**, respectively, following the same procedure as for the synthesis of macrocycles **2** in heterogeneous phase under nitrogen. The products were purified by chromatography on alumina (eluant CH_2Cl_2/C_2H_5OH, 95/5).

4b (20% yield): mp 178-180 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 [s, 6 H, CH_3(Pz)], 3.86 [s, 3 H, CH_3(Tz)], 3.90 (s, 4 H, $PzCH_2Tz$), 5.03 and 5.06 (2 s, 4 H, $PzCH_2$Fur), 5.90 [s, 2 H, CH(Pz)], 6.16 [s, 2 H, H(Fur)]; MS m/z 363. Anal. Calcd for $C_{19}H_{21}N_7O$: C, 62.87; H, 5.83; N, 27.01. Found: C, 62.73; H, 5.91; N, 27.19.

4c (22% yield): mp 143-145 °C; ^{1}H NMR ($CDCl_3$) δ 2.06 [s, 6 H, CH_3(Pz)], 3.73 and 3.83 (2 s, 4 H, $PzCH_2Tz$), 4.90 and 4.95 (2 s, 4 H, $PzCH_2$Fur), 5.26 (s, 2 H, CH_2Ph), 5.66 and 5.76 [2 s, 2 H, CH(Pz)], 6.03 [s, 2 H, CH(Fur)], 7.15 (br s, 5 H, Ph); MS m/z 439. Anal. Calcd for $C_{25}H_{25}N_7O$: C, 68.40; H, 5.74; N, 22.39. Found: C, 68.62; H, 5.79; N, 22.18.

^{17}O NMR Studies on Alkyl-Substituted 1-Tetralones: Effect of Torsion Angle Change and Repulsive van der Waals Interactions

David W. Boykin*

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

Brahmadeo Dewprashad and Edmund J. Eisenbraun*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078

Received July 28, 1989

Natural abundance ^{17}O NMR spectroscopic data, in acetonitrile at 75 °C, were obtained for 24 substituted 1-tetralones. Substituent effect additivity was observed for the ^{17}O NMR chemical shifts for these compounds. Substituents ortho to the carbonyl group produced large (~40 ppm) downfield shifts. The downfield shifts could be quantitatively predicted based upon a combination of molecular mechanics estimated torsion angle twist of the carbonyl group and repulsive van der Waals interactions. A general method of analysis of carbonyl ^{17}O NMR chemical shifts in semiflexible systems is presented and applied to previously published chromanone results.

^{17}O NMR spectroscopy continues to be exploited as a probe for a range of structural problems of interest to organic chemistry.[1] Recent investigations have demonstrated a relationship between downfield shift of ^{17}O NMR data and torsion angles for a variety of function groups[1] including aryl ketones.[2,3] In these systems torsion angle rotation results in local repulsive van der Waals energies being near zero. Large downfield shifts of ^{17}O NMR data have also been observed for aromatic carbonyl groups, located near bulky groups in rigid planar systems, for which torsion angle change is not thought to be possible.[1,4-6] In these rigid planar systems, bond angle defor-

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