Articles

A Proton-Ionizable Ester Crown of 3,5-Disubstituted 1*H*-Pyrazole Able To Form Stable Dinuclear Complexes with Lipophilic Phenethylamines

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A convenient synthesis of the proton-ionizable crown **3** is reported that uses dibutyltin oxide. In acetonitrile, the reaction of **3** (LH_2) with phenethylamine and homoveratrylamine (molar ratio 1:2) affords solid dinuclear complexes $[LH_2]2RNH_2$ (**4a**,**b**), which spectroscopic (FAB-MS, IR, ^1H and ^{13}C NMR) data point toward a strong participation of the pyrazole nitrogens in the amine complexation. In DMSO-d_6 solution, a ^{13}C NMR study demonstrates the formation *in situ* of analogous neutral **4a**−**d**$[LH_2]2RNH_2$ or charged **5a**−**d**$[L^{2-}]2RNH_3^+$ dinuclear complexes by reaction of **3** $[LH_2]$ or **3′**$[L^{2-}]2Na^+$ with RNH_2 (phenethylamine, homoveratrylamine, dopamine, and norepinephrine) or their $RNH_3^+Cl^-$ salts, respectively. Differences between the structure of complexes **4** and **5** have been evaluated by taking the homoveratrylamine derivatives **4b** and **5b** as models. An ^1H and ^{13}C NMR study (by raising the temperature) and measurements of intermolecular NOE effects (from NOESY and ROESY spectra) demonstrate that both complexes behave as prototropic isomers showing different conformations. By increasing the ionic strength, the **4b** isomer structure becomes similar to that of **5b**. The molecular modeling (GenMol software) of **4a**−**d** and **5a**−**d** shows that the assemblage in which both amine molecules are on the same side of the crown is the more stable. Lipophilic amines afford more stable complexes than hydrophilic ones and charged species are much more stable than the neutral ones.

Introduction

The structure of neurotransmitter catecholamines (dopamine and norepinephrine) involved in the normal emotional and autonomic control of humans, is characterized by a common hydrophilic 3,4-dihydroxyphenethylamine nucleus. In contrast, 3,4-dimethoxyphenethylamine (homoveratrylamine) and other lipophilic amines of related structure such as mescaline (3,4,5-trimetoxyphenethylamine) are psychedelic drugs showing hallucinogen effects.[1]

Polyoxa and polyaza macrocycles containing a trigonal symmetrical arrangement of HN binding sites are able to complex catecholamines by interaction with their primary ammonium ions.[2] In this way, we previously reported dinuclear ether and ester crowns of 3,5-disubstituted pyrazoles **1** and **2** (Scheme 1) of similar size to that of valinomycin (36-membered ring), which are able to facilitate the passive transport of NH_4^+ and RNH_3^+ ions of catecholamines.[3−5] Furthermore, it has been demonstrated that polyether crowns **1** (R = CH_3, H) form ammonium dinuclear complexes in which two sp^2 pyrazole nitrogens and four oxygen atoms belonging to the poly(ethyleneglycol) chains are involved in two $[NO_2]-NH_4^+$ centers.[6]

In this way, we have previously obtained a smaller 26-membered proton-ionizable ester crown of 1*H*-pyrazole **3**$[LH_2]$, which was isolated and identified as free ligand and as disodium dipyrazolate salt **3′**$[L^{2-}]2Na^+$.[7] This receptor, in neutral or in basic medium, is able to form mono- and dinuclear complexes with transition metals of the general structure $M^{2+}[LH_2]2X^-$ and $2M^{2+}[L^{2-}]2X^-$, respectively.

Now, taking into account that crown **3** contains four nitrogens and two oxygens in an optimal double trigonal symmetrical arrangement of NH binding sites, we have studied the behavior of both the free ligand **3** and its dipyrazolate salt **3′** as complexing agents of phenethylamine derivatives.

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⊗ Abstract published in *Advance ACS Abstracts,* April 15, 1997.

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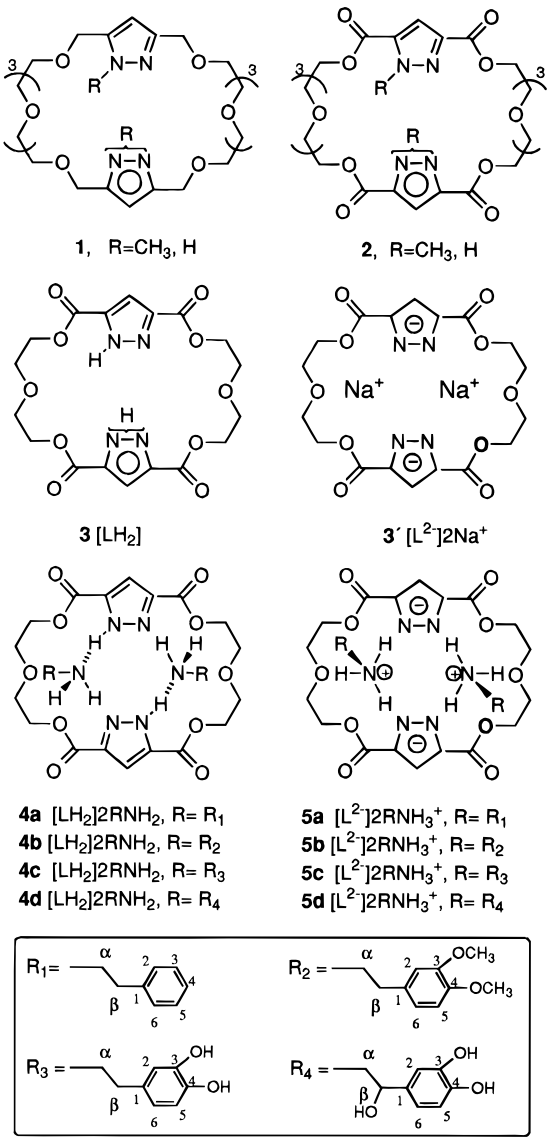
Scheme 1



In fact, this is the full paper corresponding to a previous short communication[8] in which we announced the excellent complexing properties of crown **3** toward homoveratrylamine. Firstly, we report that when acetonitrile is used as solvent, crown **3** strongly interacts with lipophilic phenethylamines leading to neutral dinuclear complexes of structure **4a**,**b** (see Scheme 1), which were isolated as stable solid compounds. Both structures have been clearly established on the basis of their analytical and spectroscopic FAB MS, IR, and ^{1}H and ^{13}C NMR data. In addition, by means of a ^{13}C NMR study carried out in DMSO-d_6 as solvent, we have confirmed the formation *in situ* of neutral dinuclear complexes of structure **4a**−**d**[LH_2] $2RNH_2$ by treatment of crown **3**[LH_2] with not only phenethylamine and homoveratrylamine but also with dopamine and norepinephrine. Taking into account the great interest of getting synthetic ligands able to selectively complex psychedelic drugs as ammonium salts, we have also carried out a similar ^{13}C NMR study on the formation *in situ* of charged **5a**−**d**[L^{2-}]-$2RNH_3^+$ dinuclear complexes by treatment of the disodium dipyrazolate salt **3′** with the ammonium salts of the four phenethylamine derivatives mentioned above.

Structural differences between complexes of general structure **4** and **5** have been studied, taking as models the homoveratrylamine derivatives **4b** and **5b** by means of different NMR experiments (e.g., by raising the temperature, evaluation of intermolecular NOE effects, influence of increased ionic strength).

On the other hand, using molecular modeling based on molecular mechanics calculations (GenMol software), a theoretical approach of the stability of both uncharged **4a**−**d**[LH_2]$2RNH_2$ and charged **5a**−**d**[L^{2-}]$2RNH_3^+$ dinuclear complexes has been performed.

Finally, regarding the great interest of this versatile ligand **3**, we have carried out an additional effort in order to improve its synthesis, which had previously been reported by us following more complicated procedures.

Results and Discussion

Improved Synthesis of Crown 3[LH_2]. In general, the synthesis of proton-ionizable tetraester-polyether crowns derived from 1*H*-pyrazole by direct cyclization of 1*H*-pyrazole-3,5-dicarbonyl dichloride and poly(ethylene glycol)s is very difficult and occurs in low yield, which dramatically diminishes as the length of the polyethylene chain is shortened. On the other hand, the obtention of the precursor 1*H*-pyrazole-3,5-dicarbonyl dichloride by heating pyrazole-3,5-dicarboxylic acid with thionyl chloride occurred in very low yield due to the simultaneous formation of undesirable amounts of diketopiperazine derivatives as reaction byproducts. In fact, the first synthesis of crown **3** was performed in 2% overall yield following a troublesome procedure that involved the previous cyclization of 1-benzylpyrazole-3,5-dicarbonyl dichloride with diethylene glycol (DEG) followed by Lewis acid-catalyzed debenzylation of the corresponding [2 + 2] cyclization adduct.[9]

On the other hand, we later obtained optimal reaction conditions leading to 1*H*-pyrazole-3,5-dicarbonyl dichloride as a pure solid in 92% yield, and on the basis of the above result, we carried out an alternative and selective synthesis of **3** in 5% overall yield that included the following reaction steps: (a) obtention of the acyclic diol 5′-hydroxy-3′-oxapentyl-1*H*-pyrazole-3,5-dicarboxylate by deprotection of its 6′-(2″-tetrahydropyranyl)-3′,6′-dioxahexylpyrazole-3,5-dicarboxylate precursor and (b) cyclization reaction of the acyclic diol mentioned above with 1*H*-pyrazole-3,5-dicarbonyl dichloride.[7]

Now, when dibutyltin oxide and 1*H*-pyrazole-3,5-dicarbonyl dichloride were used as the starting materials the synthesis of crown **3** was directly achieved in 15% yield as depicted in Scheme 2.

Diethylene glycol was heated to reflux in toluene with dibutyltin oxide to give the corresponding cyclic stannoxane,[10] which was treated with 1*H*-pyrazole-3,5-dicarbonyl dichloride to afford crown **3** [mp 258−260 °C; FAB 453 (100% abundance) MH^+] in a one-step reaction.

Synthesis and Structure of Solid Dinuclear Complexes 4a,b. The complexing ability of crown **3** [LH_2] was tested by stirring for 15 min with phenethylamine or homoveratrylamine in a 1:2 molar ratio using acetonitrile as the solvent. In both cases, white pure solids were isolated, which after crystallization from EtOAc

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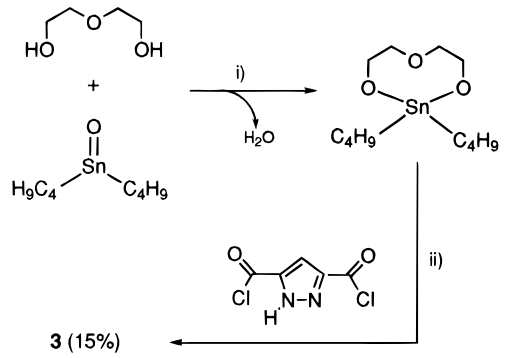
Scheme 2[a]



[a] Key: (i) toluene, N_2, reflux 2 h; (ii) high dilution; N_2; toluene−DME (5:1 v/v); 60 °C, 24 h.

showed analytical and spectroscopic data consistent with neutral dinuclear complexes **4a** [mp 262−264 °C, FAB 695 $(M + 1)^+$] and **4b** [mp 156−157 °C, FAB 815 $(M + 1)^+$] obtained in 74% and 95% yield, respectively (Scheme 1).

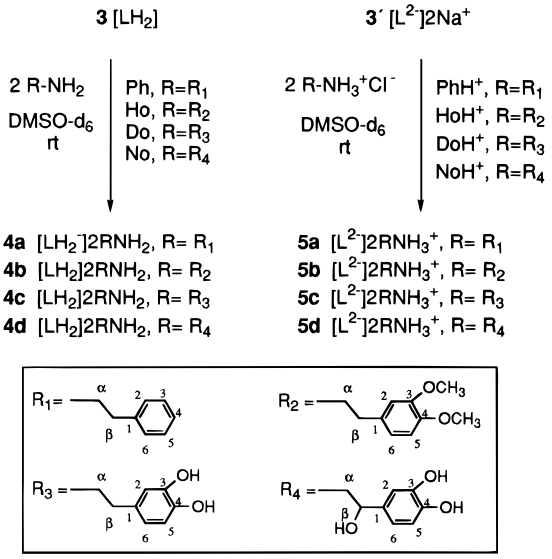
It is interesting to point that the IR(KBr) spectra of **4a** and **4b** show weak ammonium ion bands between 2750 and 2000 cm^{-1} of similar type to those observed in the IR spectra of hydrochlorides of phenethylamine and homoveratrylamine. This fact could be indicative of a strong interaction of the basic amino group of phenethylamine derivatives with the pyrazole nitrogens. Besides, as could be expected in the formation of two different N·· HN hydrogen bonds,[11] in the ^1H NMR spectra of both complexes, the complexation strongly affects the NH signals of the primary amines (deshielded 4−5 ppm in relation to the free phenethylamine derivatives) and those belonging to the pyrazole ring (shielded −8 ppm in relation to the free crown **3**).

In the complexed host moiety of **4a** and **4b**, the signals corresponding to PzH(4) and those of the COO*CH*$_2$ methylene groups show intermediate values between those observed in the free ligand (**3**) and those of its dipyrazolate salt (**3′**). In relation to the guest moiety, the α-C*H*$_2$ and *β*-*CH*$_2$ methylenes that are nearer to both complexation centers experiment chemical shifts to lower field (0.2 ppm) very close to those observed when the same methylenes of free phenethylamine and homoveratrylamine are compared with those of their corresponding hydrochlorides.

The ^{13}C NMR spectral data also afford relevant structural information. First, the pyrazole carbons C(3,5), which in **3** appeared as a very broad signal due to the pyrazole prototropic equilibrium, collapse after complexation to a sharp singlet, confirming that in **4a** and **4b** the above-mentioned equilibrium has disappeared. Furthermore, the above carbons C(3,5) undergo in both complexes chemical shifts to downfield that are smaller but of identical sign to those observed when crown **3** is fully deprotonated leading to its dipyrazolate salt (**3′**).[7]

On the other hand, after complexation, the two methylene carbons belonging to the guest amines as well as the *ipso* aromatic carbon experience considerable upfield shifts that are larger for the C_β (**4a**, −3.65 ppm; **4b**, −2.73 ppm) than for the C_α (**4a**, −2.3 ppm; **4b**, −1.72 ppm) and C_1Ar (**4a**, −1.62 ppm; **4b**, −1.36 ppm) carbons. This

Scheme 3



behavior agrees with a reduction of electronic density at the sp^3 nitrogen that takes place when the complex is formed.[12]

In agreement with the above IR, ^1H NMR, and ^{13}C NMR data, the FAB mass spectrum of the phenethylamine dinuclear complex (**4a**) shows a pattern in which characteristic C_2H_7O, C_4H_8O, $C_4H_8O_2$, and $C_5H_8O_3$ fragments belonging to the host flexible side chain, as well as C_7H_7 and C_8H_9 aromatic fragments belonging to the amine guest, are successively or simultaneously lost, giving up a series of peaks of *m*/*z* 647 $(M^+ - C_2H_7O)$ (1.0); 607 $[(M + 1)^+ - C_4H_8O_2]$ (9.9); 603 $(M^+ - C_7H_7)$ (2.0); 579 $[(M + 1)^+ - C_5H_8O_3]$ (4.6); 550 $[M^+ - 2(C_4H_8O)]$ (2.0); 460 $\{(M + 1)^+ - [C_7H_7 + 2(C_4H_8O)]\}$ (2.2); and 340 $[M^+ - [2(C_4H_8O) + 2(C_8H_9)]$ (1.7). All of them are clearly demonstrating the strong interaction of the two amino groups with both pyrazole rings.

In a similar way, the FAB mass spectrum of the homoveratrylamine dinuclear complex (**4b**) shows a pattern in which a host side-chain fragment (C_4H_8O) as well as a complete series of aromatic fragments belonging to the amine guest ($C_8H_9O_2$, $C_9H_{11}O_2$, $C_{10}H_{13}O_2$, and $C_{10}H_{15}O_2$) are also successively or simultaneously lost, affording characteristic peaks: 677 $(M^+ - C_8H_9O_2)$ (1.0); 663 $(M^+ - C_9H_{11}O_2)$ (1.3); 649 $(M^+ - C_{10}H_{13}O_2$) (1.1); 647 $(M^+ - C_{10}H_{15}O_2$) (1.8); 607 [$(M + 2)^+ - (C_8H_9O_2 + C_4H_8O)$] (9.6); 606 $[(M + 1)^+ - (C_8H_9O_2 + C_4H_8O)]$ (2.3); 579 $[(M + 1)^+ - (C_{10}H_{11}O_2 + C_4H_8O)]$ (4.9); 577 $[(M + 1)^+ - (C_{10}H_{13}O_2 + C_4H_8O)]$ (1.8); 485 $[(M + 1)^+ - 2(C_{10}H_{13}O_2)]$ (1.0); 369 $\{(M + 1)^+ - [2(C_9H_{11}O_2) + 2(C_4H_8O)]\}$ (2.0); and 341 $\{(M + 1)^+ - [2(C_{10}H_{13}O_2) + 2(C_4H_8O)]\}$ (29). Furthermore, in the **4a** mass spectrum, the C_8H_9 phenethylamine fragment is giving up a intense peak of *m*/*z* 105 (32.4) while, in that of **4b**, the homoveratrylamine aromatic fragments $C_8H_9O_2$, $C_9H_{11}O_2$, and $C_{10}H_{13}O_2$ are directly responsible of three peaks of *m*/*z* 137 (77), 151 (7.5), and 165 (19.5), respectively.

All of this points again toward a strong participation of both pyrazole nitrogens in the amine complexation, so that two pairs of NH···N═ and N···HN hydrogen bonds could be polarizing the nitrogens involved in both complexation centers in such a way that a partial positive charge at the guest amine and a negative one at the

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Table 1. ^{13}C NMR Spectral Data (50 MHz, DMSO-d_6, δ) of Neutral (4a−d) and Charged (5a−d) Complexes Compared with Those of the Free Host (3), Its Disodium Dipyrazolate Salt (3′), the Free Guests Phenethylamine (Ph), Homoveratrylamine (Ho), Dopamine (Do), Norepinephrine (No), and Their Corresponding Ammonium Chlorides (PhH^+), (HoH^+), (DoH^+), and (NoH^+)

compd	**3**	**4a**	**5a**	**3′**
C(3,5)	138.40[a]	140.33[b]	141.20[c]	143.20[b]
C(4)	110.60	110.83	110.71	110.10
CO	159.60	160.81	160.20	161.60
*C*OCO	63.30	62.75	63.17	62.20
*C*O	67.80	68.30	67.97	68.00
compd	**Ph**	**4a**	**5a**	PhH^+
Cα	43.77	41.64	40.53	39.91
Cβ	40.02	36.77	34.22	32.83
C_1-Ar	140.39	138.94	137.99	137.51
compd	**3**	**4b**	**5b**	**3′**
C(3,5)	138.40[a]	140.40[b]	142.00[c]	143.20[b]
C(4)	110.60	110.79	110.10	110.10
CO	159.60	160.86	161.10	161.60
COCO	63.30	62.68	62.46	62.20
CO	67.80	68.31	67.78	68.00
compd	**Ho**	**4b**	**5b**	HoH^+
Cα	43.77	41.69	40.69	40.06
Cβ	39.50	36.27	33.84	32.51
C_1-Ar	132.96	131.36	130.44	129.80
compd	**3**	**4c**	**5c**	**3′**
C(3,5)	138.40[a]	142.17[b]	141.17[c]	143.20[b]
C(4)	110.60	110.99	110.35	110.10
CO	159.60	161.86	160.91	161.60
*C*OCO	63.30	62.99	62.59	62.20
*C*O	67.80	68.37	67.94	68.00
compd	Do	**4c**	**5c**	DoH^+
Cα	43.50	41.25	41.10	40.38
Cβ	38.50	34.02	33.65	32.37
C_1-Ar	130.79	129.12	128.53	128.04
compd	**3**	**4d**	**5d**	**3′**
C(3,5)	138.40[a]	139.29[b]	141.03[c]	143.20[b]
C(4)	110.60	110.81	110.35	110.10
CO	159.60	160.07	160.96	161.60
COCO	63.30	63.35	62.62	62.20
CO	67.80	67.98	67.93	68.00
compd	No	**4d**	**5d**	NoH^+
Cα	47.77	46.52	46.93	46.01
Cβ	71.60	69.81	70.21	68.87
C_1-Ar	134.27	133.31	133.34	132.79

[a] Very broad signal. [b] Sharp singlet. [c] Broad signal.

pyrazole ring could be responsible of many of the above FAB^+, IR, and ^{1}H and ^{13}C NMR spectroscopic data.

^{13}C NMR study on the Formation of Uncharged and Charged Dinuclear Complexes in Organic Solution. The formation *in situ* of uncharged dinuclear complexes of structure **4a**−**d** has been performed by comparison of the ^{13}C NMR spectrum of **3** (LH_2) in DMSO-d_6 solution with those obtained after addition of the free amines (phenethylamine, homoveratrylamine, dopamine, or norepinephrine) in a molar ratio of 1:2 (see Scheme 3). In a similar way, the formation of charged dinuclear complexes of general structure **5a**−**d** was studied by comparison of the DMSO-d_6 spectrum of **3′**$[L^{2-}]2Na^+$ with those obtained after addition of the corresponding ammonium chlorides (molar ratio 1:2) and filtration of the NaCl formed in the reaction mixture.

In Table 1, the carbons belonging to the host moiety of uncharged complexes **4a**−**d** are compared with those of the macrocyclic cavity of the free crown **3** and carbons belonging to the host moiety of charged complexes **5a**−**d** with those of the macrocyclic cavity of the dipyrazolate salt **3′**. On the other hand, the chemical shifts of carbons belonging to the guest moiety of **4a**−**d** are compared with those of the corresponding free phenethylamine derivative and carbons belonging to the guest moiety of **5a**−**d** with those corresponding to the hydrochlorides of phenethylamine, homoveratrylamine, dopamine, and norepinephrine.

As we have previously observed for isolated complexes **4a**,**b**, when the uncharged **4a**−**d** complexes are formed *in situ*, the C(3,5) pyrazole carbons appear as sharp singlets that are shifted to lower field in relation to the free ligand **3**. Besides, the Cα, Cβ and C_1-Ar phenethylamine carbons experience in the four complexes significant chemical shifts to higher field which in **4**(**a**, **b**) are of similar absolute values to those previously observed. In constrast with the above behavior, the C(3,5) pyrazole carbons, which in the dipyrazolate salt **3′** appear as a singlet, in the four charged complexes **5a**−**d** experience a clear broadening indicating that the protons belonging to the RNH_3^+ ions may be in fast equilibrium among the ammonium and the pyrazole nitrogens. On the other hand, taking the dipyrazolate salt **3′** as reference, the chemical shifts induced by the formation *in situ* of charged complexes **5a**−**d** show opposite sign to those observed in the formation of **4a**−**d** by complexation of **3** with free amines as can be clearly observed in Table 1.

The above behavior suggests that electrostatic interactions with permanent charges may be mainly involved in complexes **5**, while a molecular association through hydrogen bonds may play an important role in the structure of complexes **4**. Since compounds that have identical molecular formulas but differ in the nature of bonding of their atoms or in the arrangement of their atoms in space are termed isomers,[13] it could be considered that complexes of general structure **4** are prototropic isomers of charged complexes of type **5**.

^{1}H and ^{13}C NMR Spectroscopic Behavior of Homoveratrylamine Isomers 4b and 5b by Increasing the Temperature. In order to obtain more clear information about the structural differences between both types of complexes, taking as models those corresponding to homoveratrylamine (**4b** and **5b**), we have carried out additional ^{1}H and ^{13}C NMR experiments by gradually raising the temperature.

The ^{13}C NMR chemical shift changes experimented by **4b** at 30, 50, 70, and 90 °C suggest that as the temperature is gradually increased the guest amine C_α, C_β, and C_1-Ar carbons are shifted to higher field in such a manner that at 90 °C their values are very close to those of free homoveratrylamine. In a similar way, the host C(3,5) pyrazole carbons neighboring both complexation centers are shifted to lower field. As a result, at 90 °C their values are very close to those of the free host **3**. On the other hand, we have verified that the ^{13}C NMR spectrum of **4b** initially registered at 30 °C is identical to that of a sample previously heated at 90 °C and then cooled again to 30 °C. The above behavior clearly indicates that **4b** is a very stable complex. However, after being heated at 90 °C, their host−guest interactions are strongly weakened.

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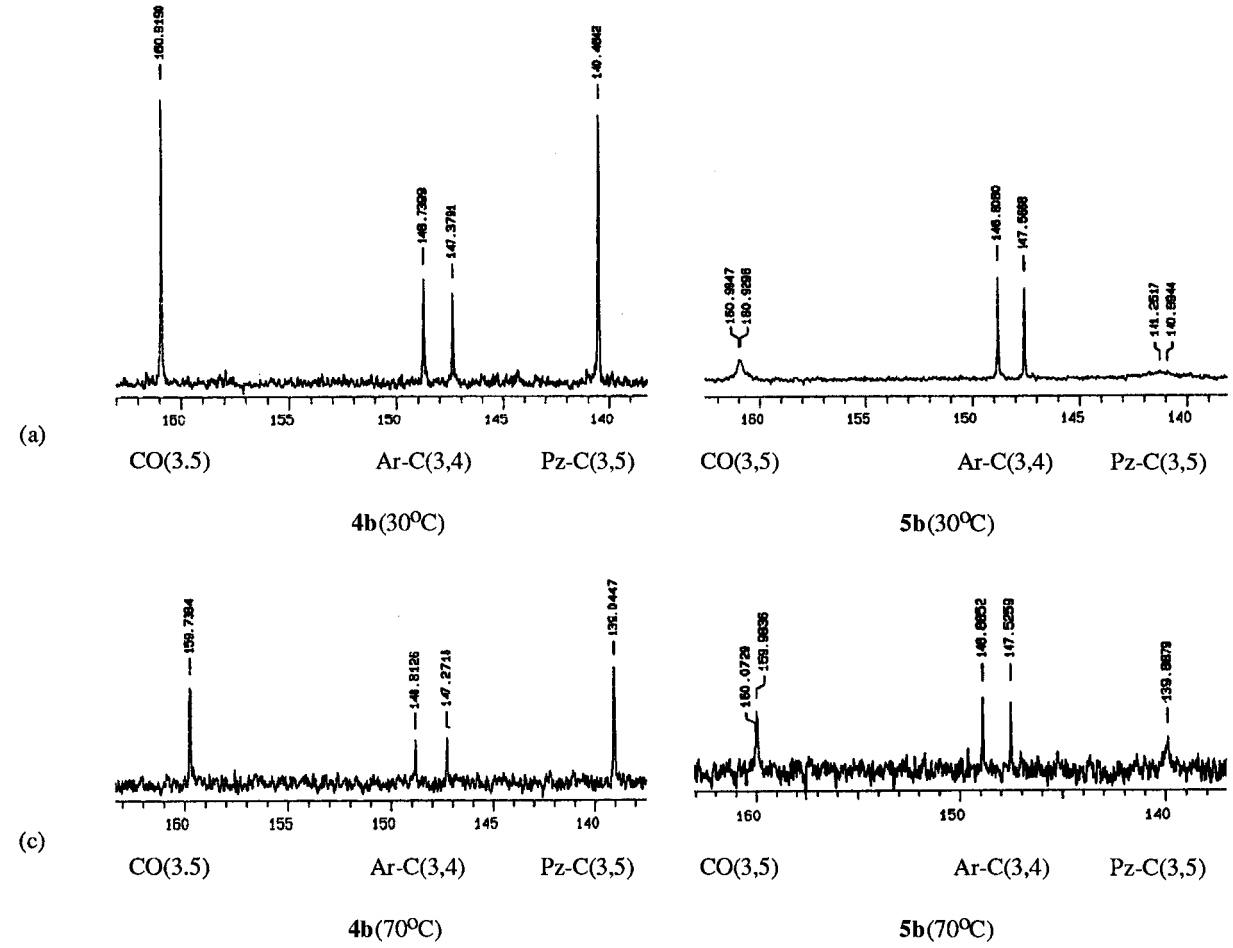

Figure 1.

In relation to **5b**, the ^{13}C NMR chemical shift changes experienced as the temperature is similarly increased demostrate that after heating to 90 °C, the chemical shifts of the guest homoveratrylammonium C_α, C_β, and C_1-Ar carbons are close to those exhibited by the complexed homoveratrylamine of **4b** at 30 °C. In a similar way, the host C(3,5) pyrazole carbons as well as the CO carbonyl ones experience strong chemical shifts to lower field in such a manner that at 90 °C the corresponding values are very close to those found for **4b** at 70 °C. Consequently, it can be concluded that when **5b** is heated to 90 °C its structure is very close to that of **4b**.

Figure 1 graphically shows the clear differences between both the C(3,5) pyrazole carbons and the neighbor CO carbonyl carbons of **4b** and **5b** at 30 °C (a) and 70 °C (b).

In the spectrum of **5b** registered at 30 °C the C(3,5) pyrazole carbons display a very broad signal at 147.01 ppm and the CO carbonyl ones a broad singlet at 160.96 ppm. By increasing the temperature to 70 °C, the broad signal corresponding to the C(3,5) pyrazole carbons is not significantly modified. Only at 90 °C does it appear as a singlet. The above behavior confirms that in the ammonium dipyrazolate complex **5b** the N*H* pyrazole protons are "smeared" among the guest and the host nitrogens. Then, it seems reasonable to think that electrostatic (coulombic) interactions with permanent charges may be mainly involved in complexes of **5** type.

In contrast with the above behavior, at 30 and 70 °C the C(3,5) pyrazole carbons and the neighbor CO carbonyl carbons belonging to the neutral complex **4b** appear as sharp singlets. This behavior confirms that after complexation with free homoveratrylamine the prototropic equilibrium of **3** has disappeared, and the N*H* pyrazole protons are not ambiguously located but fastened to the guest amine. The above situation agrees with a molecular association in which polarized hydrogen bonds may be involved.

We have also studied the differences between the ^1H NMR signals of the methylene groups belonging to the host flexible side chains in the free ligand **3** and its dipyrazolate sodium salt (**3′**) as well as in their corresponding dinuclear complexes **4b** and **5b** when their spectra are registered at 30 and 90 °C. From the above data, the following have been clearly demonstrated: (1) Either at 30 or at 90 °C, the conformation of the macrocyclic cavity belonging to the free host (**3**) is different from that of its disodium dipyrazolate salt (**3′**). (2) At 30 °C, there are small differences between the host methylenes $COOCH_2$ and CH_2O of **4b** and **5b** that indicate that the conformation of both macrocyclic cavities are different. (3) After the temperature increases to 90 °C, the macrocyclic cavity conformations of both **4b** and **5b** complexes are similar to that of the free host **3** at the same temperature.

Study of Intermolecular NOE Effects from Both the NOESY and ROESY Spectra of 4b and 5b. In order to obtain more clear information about the different geometries involved in both complexes, we have performed a series of NOE measurements. In Table 2 are gathered the interproton NOEs found for both molecular

Table 2. Interproton NOEs in the NOESY and ROESY Spectra of the Complexes 4b and 5b by Inversion of the Host Protons

inverted proton	obsd NOE **4b**	obsd ROE **4b**	inverted proton	obsd NOE **5b**	obsd ROE **5b**
Pz-H(4)			Pz-H(4)	CH_2-(α) (inter) 0.2% CH_2-(β) (inter) 0.2%	CH_2-β (inter) 0.7%
	OMe (inter) 2.0% Ar-H (inter) ($H_6 > H_2 > H_5$)) 0.4% $COOCH_2$ (intra) 0.1% OCH_2(intra) 0.1%	OMe (inter) 1.6% $COOCH_2$ (intra) 0.8% OCH_2(intra) 0.1%		OMe (inter) 2.0% Ar-H(inter) ($H_6 > H_5$) 0.5% $COOCH_2$ (intra) 0.2%	OMe (inter) 3.0% $COOCH_2$ (intra) 0.5%
COO-CH_2			COO-CH_2		CH_2-(β) (inter) 3.0%
	Ar-H (inter) ($H_2 > H_5 > H_6$) 0.1%			Ar-H (inter) (H_2, $H_5 > H_6$) 0.4%	Ar-H (inter) ($H_2 > H_5 \gg H_6$) 1.0%
	OCH_2 (intra) 5.0% Pz-H(4) (intra) 0.1%	OMe (inter) 2% OCH_2 (intra) 23.0% Pz-H(4) (intra) 3.0%		OMe (inter) 0.6% OCH_2 (intra) 1.5% Pz-H(4) (intra) 0.5%	OMe (inter) 2% OCH_2 (intra) 10.0% Pz-H(4) (intra) 5.0%
OCH_2			OCH_2		CH_2(α) (inter) 2.2%
	Ar-H (inter) ($H_2 \gg H_5$) 0.4% $COOCH_2$ (intra) 4% Pz-H(4) (intra) 0.3%	Ar-H (inter) ($H_2 \gg H_5$) 0.8% $COOCH_2$ (intra) 9.0% Pz-H(4) (intra) 1.4%		Ar-H (inter) ($H_2 \gg H_5$, H_6) 1.0% $COOCH_2$ (intra) 5.0% Pz-H(4) (intra) 0.2%	Ar-H (inter) ($H_2 > H_5 \gg H_6$) 2.0% $COOCH_2$ (intra) 12% Pz-H(4) (intra) 2.0%

complexes (**4b** and **5b**) in their NOESY and ROESY spectra by inversion of the host protons.

In particular, pyrazole/aromatic interactions are evident in both systems from which a different orientation of the guest aromatic rings in relation to the host pyrazole rings can be deduced from the NOESY spectra of **4b** and **5b**. Thus, in **4b** the Pz-H(4) interact with the Ar-H(2, 5, 6) aromatic guest protons in the following order Ar-H (6) > Ar-H (2) > Ar-H (5). However, in **5b** the Pz-H(4) only interact with the Ar-H(5, 6) protons in the following order: Ar-H (6) > Ar-H (5).

Different intermolecular cross peaks are also observed between the OMe groups and the Ar-H (2, 5, 6) protons of the guest aromatic moiety and the methylene protons of the host in both complexes.

Finally, major differences between **4b** and **5b** are found in contacts involving the CH_2-(α) and CH_2-(β) groups of the guest. Thus, the NOESY and ROESY spectra of **5b** show CH_2-(β) intermolecular contacts with both the Pz-H(4) and the COO-CH_2 host protons. However, the CH_2-(α) guest protons mainly interact with the CH_2O host protons. In contrast with the above behavior, in the NOESY and ROESY spectra of **4b** any of the above-mentioned contacts are observed.

In conclusion, all the host/guest intermolecular interactions observed in the NOESY and ROESY spectra of **4b** and **5b** indicate that the guest amine in **4b** adopts a different orientation in relation to the host macrocycle than that found for the guest amine in **5b**.

On the basis of the spectroscopical data previously commented it can be deduced that the conformation of **4b** is different from that of **5b**.

Influence of Salt Effects on Solutions Containing the 4b Isomer. It has been reported that, in spite of hydrogen-bonded association involving the participation of at least three interaction mechanisms [electrostatic (coulombic), dispersive, and charge transfer], the predominant role of the coulombic forces has become increasingly apparent trough quantum-chemical calculations utilizing larger basis sets. Besides, it is supported by experimental evidence of a stability dependence for appropriate complexation systems on the acidity of the donor XH and the basicity of the acceptor. For this reason, structure and energies of such complexes are most often calculated on the basis of Coulomb potentials.[14]

On the hypothesis that electrostatic (coulombic) forces could be a common factor in both type of complexes, the main differences between both isomers should arise from the major or minor participation of such electrostatic forces in **5b** and **4b**, respectively.

In this way, it is important to point out that in the *in situ* obtention of **5b** 2 equiv of NaCl are simultaneously formed. However, the formation *in situ* of **4b** occurs in the absence of NaCl.

Taking into account that in molecular associations involving electrostatic interactions salt effects—by way of the ionic strength—are able to induce ΔG_{HG} changes,[15] we have studied the effect of an excess of NaCl on the last mentioned complex (**4b**). Comparison of the ^{1}H NMR signals corresponding to the guest amine in **4b**, **5b**, and (**4b** + NaCl) has demonstrated that at 30 °C marked differences exist between the complexed homoveratrylamine in **4b** and the complexed homoveratrylammonium in **5b**. However, in (**4b** + NaCl) all the guest signals are much more similar to those of **5b** than those of **4b**.

(14) Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1417–1436.

(15) Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, V. *J. Am. Chem. Soc.* **1988**, *110*, 6442 and references cited therein.

Consequently, the above spectroscopical data seem to confirm that, starting from **4b**, when the ionic strength is strongly increased the structural differences between both complexes **4b** and **5b** disappear.

On the other hand, considering that the filtered solution of **5b** could contain traces of NaCl (most of the formed NaCl is filtered off), we have registered the ^{1}H and ^{13}C NMR spectra of a 1:1 mixture of both isomers. The resulting (**4b** + **5b**) ^{13}C NMR spectrum registered at 30 °C clearly demostrates the following: (1) There are only a series of carbon signals that show intermediate values between those previously registered for **4b** and **5b**. (2) The chemical shift differences $\Delta\delta_1$ [(**4b** + **5b**) − **4b**] and $\Delta\delta_2$ [(**4b** + **5b**) − **5b**] corresponding to the guest amine [Cα, Cβ, and C_1-Ar carbons] show similar absolute values of opposite sign. Therefore, in the 1:1 mixture solution of **4b** and **5b** both isomers may be in equilibrium. (3) The C(3,5) pyrazole signals of the 1:1 mixture of **4b** and **5b** registered at 30 °C are much more similar to those of **5b** than to those of **4b**. This last result confirms that in the presence of NaCl traces the N*H*-pyrazole protons belonging to **4b** are not fastened to the guest amine but "smeared" between the host and the guest nitrogens as occurs in **5b**.

On the basis of both experiments, it is obvious that the presence of NaCl traces in **5b** solution may increase the stability of the isomer **5b** but never favor the formation of the isomer of **4b**. Besides, the behavior previously demonstrated for both homoveratrylamine-derived isomers could be extended to the rest of complexes of general structures **4** and **5** shown in Scheme 1.

Finally, the small structural differences found between both type of complexes demostrate that, in agreement with the previous report of Schneider,[14] one of the main advantages of synthetic host−guest chemistry is that it permits targeted construction of supramolecular complexes with infinitely variable noncovalent interactions arranged in conformationally defined ways.

Theoretical Approach of the Stability of Dinuclear Complexes 4a−d and 5a−d. In order to better understand the formation of dinuclear complex structure, we calculated their relative stability in a theoretical approach. The main question to answer is as follows: are the two guest molecules on the same or on different faces of the macrocycle?

The stability of the complexes was evaluated using molecular modeling through GenMol sofware.[16] This program based on molecular mechanics calculations is designed to build molecules and to find their preferred conformations.[17] It also allows us to model molecular interactions and to find the minimum energy of complex molecular systems.[18−20]

The strategy used is summarized below. In the first step, among the set of possible conformations for the host molecule (bipyrazole crown), we selected two conformations able to lead to both desired complexes, i.e., with amines on the same side or on the opposite sides of the mean plane of the crown. These conformations (C1 and C2, respectively) are reported in Figure 2. The first one,

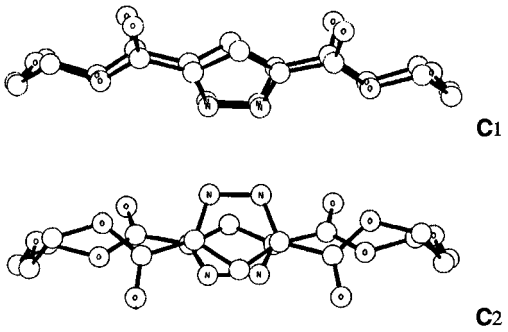

Figure 2. Conformation of **3** allowing the building of *syn* complexes (C1) or *anti* complexes (C2).

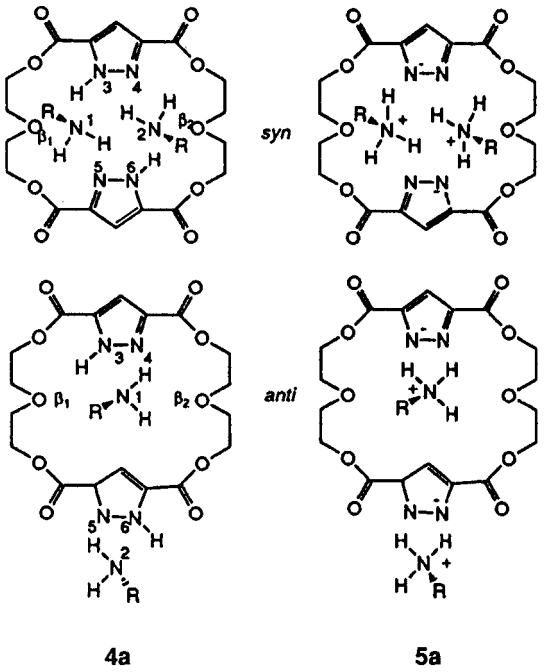

Figure 3. *Syn* and *anti* structures of uncharged (**4a**) and charged (**5a**) dinuclear complexes of bipyrazole crown (**3**) and phenethylamine.

with the aza parts of the two pyrazole nuclei in the *syn* position, is more stable (total constrain energy, $E_{TC} = 83$ kcal) than the second one with the aza parts in the *anti* position ($E_{TC} = 91.4$ kcal).

The corresponding dinuclear uncharged (**4a**) and charged (**5a**) complexes with the phenethyalamine were modeled starting from C1 and C2 (Figure 3).

The building was realized automatically according to the docking technique. Each molecule of amine is approached along a perpendicular axis to the mean plane of the ester crown. The relative position of the molecules (the geometry of which is fixed) in the complex is found by minimizing the intermolecular energy (sum of van der Waals, coulombic, and eventually hydrogen bond energies). Then, the geometry of the complex is optimized by complete force field calculation and the corresponding energy E_{TC} calculated, with or without some structural constrains. Three cases were simulated with different fixed distances between nonbonded atoms (amino and pyrazolic nitrogens, ether oxygens).

The results of the refinement of the complexes **4a** and **5a** are reported in Table 3.

Entries 1 and 4 of Table 3 concern the model of complex in which we strained the distance between the phen-

(16) Pèpe, G.; Siri, D. *Stud. Phys. Theor. Chem.* **1990**, *71*, 93−101.
(17) Cavelier-Frontin, F.; Pèpe, G.; Verducci, J.; Siri, D.; Jacquier, R. *J. Am. Chem. Soc.* **1992**, *114*, 8885−8890.
(18) Pèpe, G.; Siri, D.; Samat, A.; Pottier, E.; Guglielmetti, R. *Mol. Cryst. Liq. Cryst.* **1994,** *246*, 247−250.
(19) Vila, F.; Tordo, P.; Siri, D.; Pèpe, G. *Free Rad. Res. Commun.* **1993**, *19*, 517−522.
(20) Cavelier-Frontin, F.; Sadijah, A.; Pèpe, G.; Verducci, J.; Jacquier, R. *THEOCHEM* **1993**, *286*, 125−130.

Table 3. Relative Stability of the Different Modeled Dinuclear Complexes of Bipyrazole from Crown 3 and Phenethylamine[a]

		syn		anti	
entry	compd	E_{TC}	E_H	E_{TC}	E_H
1	**4a**[b]	77.1	−3.8	91.5	−2.0
2	**4a**[c]	89.3	−6.1	130.0	−4.9
3	**4a**[d]	78.2	−1.5	94.1	−1.1
4	**5a**[b]	−14.3	−5.3	10.0	−3.4
5	**5a**[c]	−8.6	−8.3	29.1	−9.3
6	**5a**[d]	−9.8	−4.5	22.7	−2.2

[a] E_{TC} (kcal) is the constrain energy (from GenMol). E_{TC} is the sum of nonbonded energies (van der Waals, coulombic, hydrogen) and the bonded energies (stretching, bending, torsion). E_H (kcal) is the value of hydrogen bond energy. [b] Constraints on distances: for the *syn* complexes, N_1-N_3, N_1-N_5, N_2-N_4, N_2-N_6 = 2.7 Å; for the anti complexes, N_1-N_3, N_1-N_4, N_2-N_5, N_2-N_6 = 2.7 Å. [c] Constraints on N−N distances as described in footnote b and $N_1-O_{\beta 1}$, $N_2-O_{\beta 2}$ = 2.7 Å. [d] Without constrain.

ethyl-N and the pyrazolic-N to 2.7 Å (distance for which there is a possibility of a strong hydrogen bond, H^+ being shared between both nitrogen atoms).

In the case of the *syn* complexes the concerned atoms are N_1-N_3, N_1-N_5, N_2-N_4, and N_2-N_6 (Figure 3). For the *anti* complexes, they are N_1-N_3, N_1-N_4, N_2-N_5, and N_2-N_6, respectively.

Entries 2 and 5 of Table 3 are related to complexes for which, the distances between the phenethyl-N and the ether-O are also strained to a value of 2.7 Å, in additional to the previous set.

Entries 3 and 6 of Table 3 correspond to a conformation obtained from the last structure, optimized without any constrain.

The main observation is that whatever the nature of the complexes charged or uncharged and whatever the strains about distances between nonbonded heteroatoms the *syn* complex is always the most stable.

Thus, considering the uncharged complex **4a**, the structures corresponding to the forced hydrogen bonds between the amine-N and the ether-O are the less stable: the gain of energy by the hydrogen bond is lost by the increase of the nonbonded interactions. The models optimized without structural constrain and those in which N−N distances are forced to 2.7 Å have very similar total strain energies of 78.2 and 77.1 kcal, respectively. In fact, in the structure corresponding to the former models, the distance between the amine-nitrogen and the pyrazole-nitrogen lightly increases, which explains the weaker energy of H-bonding.

It is interesting to note that the preferred complex obtained when the refinement is performed with forced N−N distances is more stable than the free macrocycle.

In the most stable conformation, the aromatic ring would be bent toward the macrocycle mean plane, in a quite parallel direction, leading to attractive interactions with the oxygen atoms (Figure 4).

Finally, calculations performed on charged complexes **5**[21] indicate that the latest would be always more stable than the parent one, with negative values for the constrain energies, due to high dipole−dipole interactions. In such calculations, the coulombic energy is probably overestimated. Thus, the best stability of the dinuclear complex is obtained when the distance between the amine-N and the pyrazole-N allows hydrogen bonding.

(21) The geometries of the charged complexes have been obtained from the corresponding uncharged complexes by adding the charges (proton transfer from the pyrazole-N to the amine) and by optimizing the energy.

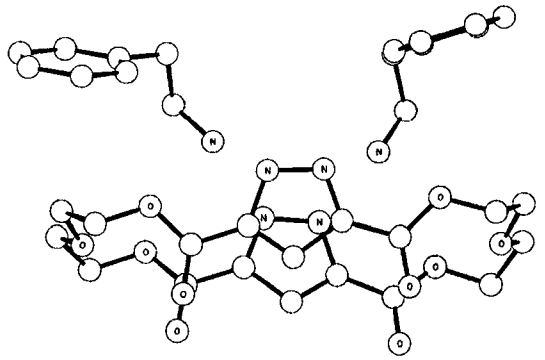

Figure 4.

Table 4. Relative Stability of the Different Modeled Dinuclear Complexes of Bipyrazole Crown 3 and Phenethylamine (a), Homoveratrylamine (b), Dopamine (c), and Norepinephrine (d)[a]

	syn		anti	
compd	E_{TC}	E_H	E_{TC}	E_H
4a	77.1	−3.8	91.5	−2.0
4b	89.3	−4.1	106.0	−2.7
4c	109.0	−4.0	134.0	−2.2
4d	102.0	−4.6	120.0	−3.3
5a	−14.3	−5.3	10.0	−3.4
5b	−4.8	−6.2	23.8	−4.0
5c	17.5	−5.4	47.7	−3.4
5d	−3.2	−6.3	26.7	−4.7

[a] E_{TC} and E_H are, respectively, the constrain energy and the hydrogen bond energy (kcal). Calculations have been performed from the structure with forced distances between N-(amine) and N-(pyrazole) to 2.7 Å (see text).

This kind of constraints were chosen to calculate complexes obtained with homoveratrylamine, dopamine and norepinephrine (Table 4).

From a general point of view, the substitution of the aromatic ring seems to increase the total energy of uncharged and charged complexes, and much more when it bears hydroxy group (dopamine and norepinephrine) instead of methoxy groups (homoveratrylamine).

Conclusions

An improved synthesis of the proton-ionizable ester crown **3** has been performed in 15% yield by direct cyclization of 1*H*-pyrazole-3,5-dicarbonyl dichloride and 2,2-dibutyl-6-oxa-1,3-dioxa-2-stannocyclooctane.

Using acetonitrile as solvent, the reaction of crown **3** with phenethylamine and homoveratrylamine [molar ratio 1:2] affords solid dinuclear complexes **4a** and **4b**, respectively, whose structures have been identified by analytical and spectroscopic data (FAB MS, IR, ^{1}H NMR, and ^{13}C NMR).

Following a similar procedure and using **3** and **3′** as starting ligands, a ^{13}C NMR study in DMSO-d_6 has been carried out by *in situ* formation of uncharged **4a**−**d** and charged **5a**−**d** dinuclear complexes of phenethylamine, homoveratrylamine, dopamine, and norepinephrine.

The ^{13}C NMR spectra of complexes **4a**−**d** demonstrate that the N*H* pyrazole protons are not ambiguously located but fastened to the guest amine. However, in **5a**−**d** the N*H* pyrazole protons are "smeared" among the guest and the host nitrogens.

The above behavior suggests that electrostatic interactions with permanent charges may be mainly involved in complexes of general structure **5** while in complexes of general structure **4** a molecular association through hydrogen bonds may play an important role.

In order to demonstrate if complexes of general structure **4** and **5** behave as prototropic isomers, taking as models the homoveratrylamine derivatives **4b** and **5b**, additional ^{1}H and ^{13}C NMR studies by raising the temperature have been performed. Furthermore, the intermolecular NOE effects have been measured from both their NOESY and ROESY spectra. From them the following can be deduced:

(a) In agreement with our earlier hypothesis, the ^{13}C NMR spectra of **4b** and **5b** confirm that at 30 °C the N*H*-pyrazole protons of **5b** are cleary "smeared" among the guest and the host nitrogens while those of **4b** are fastened to the guest amine. The above differences gradually diminish as the temperature increases to 50, 70, and 90 °C.

(b) The **4b** isomer is a very stable complex in which host−guest interactions are strongly weakened at 90 °C.

(c) By raising the temperature to 90 °C, the structure of **5b** became similar to that of **4b**.

(d) The ^{1}H NMR spectra of both the free host **3** and its dipirazolate sodium salt **3′** show conformational differences that are more clearly demostrated by raising the temperature to 90 °C.

(e) The ^{1}H NMR signals corresponding to both the guest amine and the host macrocyclic cavity of **4b** and **5b** also show marked conformational differences at 30 °C that disappear by raising the temperature to 90 °C.

(f) Intermolecular NOE effects from the NOESY and ROESY spectra of **4b** and **5b** confirm that the conformation of **4b** is different to that of **5b**.

(g) By increasing the ionic strength, the **4b** isomer structure becomes similar to that of **5b**.

(h) In a 1:1 mixture solution, both **4b** and **5b** isomers are in equilibrium.

The molecular modeling approach shows that the assemblage in which both amine molecules are on the same side of the crown is more stable than the structure in which the amines are on opposite sides.

Hydrogen bonds between the amine and the pyrazole nitrogens are stabilizing the complexes. These complexes are more stable with the charged species.

The theoretical calculations show that the hypothesis of other hydrogen bonds with the ethers-O is not probable because of the too high values of the bending energies in the complex. Furthermore, from a general point of view, the *o*-dihydroxy substitution of the phenethylamine aromatic ring increases the total energy of uncharged and charged complexes in relation to *o*-dimethoxy derivatives.

Experimental Section

Analytical TLC and flash column chromatography were performed using silica gel 60 PF_{254} (Merck) and silica gel (Merck) 200−400 mesh, respectively.

All reagents were of commercial quality from freshly opened containers. Thionyl chloride (Scharlau) was freshly distilled prior use. Pyrazole-3,5-dicarboxylic acid (Aldrich), diethylene glycol (Aldrich), dibutyltin oxide (Merck), phenethylamine (Aldrich), homoveratrylamine (Aldrich), phenethylamine hydrochloride (Aldrich), dopamine hydrochloride (Aldrich), norepinephrine hydrochloride (Aldrich), and reagent quality solvents were used without further purification. Anhydrous acetonitrile free of acetic acid was prepared following the method of Perrin and co-workers.[22] Homoveratrylamine hydrochloride was prepared from an anhydrous solution of homoveratrylamine (Aldrich) in ether followed by treatment with HCl (gas).

1*H*-Pyrazole-3,5-dicarbonyl Dichloride. A suspension of 1*H*-pyrazole-3,5-dicarboxylic acid (2.0 g, 12.81 mmol) in freshly distilled thionyl chloride (350 mL) was heated at 140 °C over 2 h. The hot reaction mixture was filtered and the resulting solution evaporated to dryness to give the title compound (2.27 g, 11.78 mmol) as a white solid (mp 72−74 °C) in 92% yield.

2,2-Dibutyl-1,3,6-trioxa-2-stannocyclooctane. To a solution of diethylene glycol (1.21 g, 11.40 mmol) in toluene (200 mL) was slowly added solid dibutyltin oxide (2.84 g, 11.40 mmol). The reaction mixture was refluxed for 2 h, and the water formed in the cyclocondensation was removed by azeotropic distillation. The resulting suspension was diluted with dry toluene (260 mL) and collected to be used in the following step.

Preparation of Tetraester Crown 3. The suspension obtained above was stirred and heated to 60 °C under nitrogen. Then, a solution of 1*H*-pyrazole-3,5-dicarbonyl chloride (2.20 g, 11.40 mmol) in dry dimethoxyethane (80 mL) was added dropwise over a period of 2.5 h. When the addition was complete, the reaction mixture was allowed to proceed for 24 h at the same temperature (60 °C) and then cooled to rt. The residual tin salts were filtered off and the filtrate evaporated to dryness to give an oil that when treated with dry acetone afforded a white solid (236 mg) that was identified as crown **3**. Then, the filtrate was evaporated *in vacuo* and the residue purified by flash column chromatography, eluting with an acetone/chloroform (4:1 v/v) mixture. From the fraction of R_f = 0.50, an additional amount of pure crown **3** (150 mg) was obtained: mp 258−259 °C (acetonitrile); overall yield 15%; MS (FAB) 453 (MH^+, 100). Anal. Calcd for $C_{18}H_{20}N_4O_{10}$: C, 47.78; H, 4.42; N, 12.38. Found: C, 47.76; H, 4.53; N, 12.38.

Disodium Dipyrazolate Salt 3′. A vigorously stirred suspension of **3** (0.1 g, 0.22 mmol) in anhydrous acetonitrile (60 mL) was heated at 75 °C until a clear solution was obtained. The resulting mixture was slowly cooled to room temperature, and a solution of sodium hydroxide (0.018 g, 0.45 mmol) dissolved in anhydrous ethanol (10 mL) was slowly added. When the addition was complete, a fine solid was formed, which was isolated by filtration and dried *in vacuo* to give compound **3′** as a white crystalline solid: mp 338 °C dec (0.108 g, 99% yield); IR (KBr, cm^{-1}) 1710; MS (FAB) 497 (MH^+, 2), 475 [$MH^+ - (Na^+ + 1)$, 4], 453 [$MH^+ - (2Na^+ + 2)$, 17], 451 [$MH^+ - 2Na^+$, 2]. Anal. Calcd for $C_{18}H_{18}N_4O_{10}Na_2$: C, 43.55; H, 3.62; N, 11.29. Found: C, 43.61; H, 3.80; N, 11.28.

Synthesis of Solid Dinuclear Complexes 4a,b. General Procedure. A suspension of crown **3** (0.025 g, 0.055 mmol) in anhydrous acetonitrile (5 mL) was heated at 75 °C until a clear solution was obtained. The resulting mixture was slowly cooled to room temperature. Then, a solution of the corresponding phenethylamine derivative (0.11 mmol) in acetonitrile (1 mL) was added dropwise under stirring. After concentration of the solvent, a white solid was formed, filtered off and dried *in vacuo*.

Complex **4a**. Following the above procedure, **4a** was obtained in 74% yield: mp 262−64 °C dec. Anal. Calcd for $C_{34}H_{42}N_6O_{10}\cdot 0.5H_2O$: C, 58.03; H, 6.11; N, 11.94. Found: C, 58.04; H, 6.07; N, 11.91.

Complex **4b.** Following the general procedure**, 4b** was obtained in 95% yield: mp 156−157 °C (EtOAc); Anal. Calcd for $C_{38}H_{50}N_6O_{14}\cdot H_2O$: C, 54.80; H, 6.29; N, 10.09. Found: C, 54.80; H, 6.58; N, 10.00.

Formation *in Situ* of Uncharged Dinuclear Complexes 4a−d from Crown 3. Complexes 4a,b. To a solution of the free host **3** (0.02 g, 0.044 mmol) in DMSO-d_6 (300 μL) was added a solution of phenethylamine or homoveratrylamine (0.088 mmol) in DMSO-d_6 (200 μL) and the resulting solution shaken under sonication at rt. After 2 h, the 50-MHz ^{13}C NMR spectra showed that the very broad signal corresponding to

(22) Perrin, D. D.; Armarego, W. L. F.; Perrin D. R. In *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1980; p 79.

both pyrazole C(3,5) carbons had changed to a sharp singlet, indicating that the corresponding dinuclear complexes had been completely formed.

Complexes 4c,d. Dopamine hydrochloride (or norepinephrine hydrochloride) (0.088 mmol) dissolved in DMSO-d_6 (150 μL) under argon was treated with NaOH (3.45 mg, 0.088 mmol) dissolved in D_2O (50 μL). The NaCl formed was filtered off and the clear solution containing the free amine added to the host **3** (0.044 mmol) previously dissolved in DMSO-d_6 (300 μL) under argon. After the solution was shaken for 2 h under sonication at rt, the 50-MHz ^{13}C NMR spectra indicated the complete formation of the corresponding dinuclear complexes.

Formation *in Situ* of Charged Dinuclear Complexes 5a−d from 3′. General procedure. The hydrochloride (0.08 mmol) of the corresponding amine (phenethylamine, homoveratrylamine, dopamine, and norepinephrine) previously dissolved in DMSO-d_6 (150 μL) under argon was added to a solution of disodium dipyrazolate salt **3′** (0.02 g, 0.04 mmol) in DMSO-d_6 (350 μL), and the NaCl formed was filtered off. The filtrate was shaken under sonication as indicated before. After 2 h, the corresponding 50-MHz ^{13}C NMR spectra showed that the sharp singlet corresponding to the pyrazole carbons C(3,5) had changed to a characteristic broad signal indicating the formation of charged dinuclear complexes.

NMR Experiments. NMR spectra were recorded on a Varian Unity 500 spectrometer, using millimolar solutions in DMSO-d_6. Selective inversion 1D experiments were performed by using a DANTE-Z module[23] during 80 ms. In particular, 1D-NOESY and 1D-ROESY experiments were carried out. NOESY experiments were recorded using mixing times of 600 ms. The rf carrier frequency for ROESY was set at δ 6.0 ppm, and the spin locking field was 2.5 KHz. The experiments were carried out at 303 K. Estimated errors are better than 10%.

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Supporting Information Available: IR and ^{1}H and ^{13}C NMR data of the free host **3**, its dipyrazolate salt **3′**, the solid complexes **4a** and **4b**, the free amines [phenethylamine (**Ph**) and homoveratrylamine (**Ho**], and their corresponding hydrochlorides (**PhH**$^+$ and **HoH**$^+$). ^{13}C NMR data of charged and neutral complexes **5b** and **4b** registered at 30, 50, 70, and 90 °C compared with those of **3**, **3′**, **Ho**, and **HoH**$^+$. ^{13}C NMR data registered at 30 °C of a 1:1 mixture of **4b** + **5b** compared with those of **4b** and **5b**. Graphical differences between both the C(3,5) pyrazole carbons and the CO carbonyl carbons of **4b** and **5b** at 30, 50, 70, and 90 °C. Graphical differences between the ^{1}H NMR signals of the methylene groups of the host flexible side chains in **3**, **3′**, **4b**, and **5b** when their spectra are registered at 30 and 90 °C. Comparison of ^{1}H NMR graphical data (at 30 °C) corresponding to homoveratrylamine in **4b**, **5b**, and (**4b** + NaCl). Comparison of ^{13}C NMR graphical data (at 30 °C) corresponding to a 1:1 mixture of **4b** and **5b** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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