A new diaza heteroaromatic crown of 3,5-disubstituted 1*H*-pyrazole which forms solid dinuclear complexes with lipophilic phenethylamines

Ana M. Sanz, Pilar Navarro, Fernando Gomez-Contreras, Mercedes Pardo, Gèrard Pèpe, and André Samat

Abstract: The cyclic stannoxane obtained from *N*-methyldiethanolamine and dibutyltin oxide reacts with 1*H*-pyrazole-3,5-dicarbonyl dichloride to afford the new 26-membered diaza tetraester crown **3**. In neutral medium, the above crown forms 1:2 solid dinuclear complexes with phenethylamine (**3a**) and homoveratrylamine (**3b**), which, after crystallization from acetonitrile, were isolated in high yield (90% and 85%, respectively). The **3**, **3a**, and **3b** structures were identified from their analytical and spectroscopic (^{1}H, ^{13}C NMR, and MS (FAB)) data. The spectroscopic properties of **3a** and **3b** are demonstrating that, in each complexation centre, simultaneously to the strong participation of the four pyrazole nitrogens, an additional weaker interaction between the aliphatic nitrogen of the side chain and the amine is involved. Comparison of the total interaction energies calculated (GenMol software) for phenethylamine-derived complex (**3a**) and homoveratrylamine-derived one (**3b**) suggests that the *o*-dimethoxy substitution of the guest aromatic ring could be improving the stability of **3b** in relation to **3a**.

Key words: diazacrown, 1*H*-pyrazole, dinuclear, complexes, phenethylamines.

Résumé : Le stannoxane cyclique obtenu à partir du *N*-méthyldiéthanolamine et de l'oxyde de dibutylétain réagit avec le dichlorure de 1*H*-pyrazole-3,5-dicarbonyle pour conduire à un nouvel éther diazacouronne tétraester à 26 chaînons (**3**). En milieu neutre, cette couronne forme des complexes dinucléaires solide 1:2 avec la phénéthylamine (**3a**) et l'homovératrylamine (**3b**) qui ont été isolés avec d'excellents rendements (90 et 85% respectivement) après cristallisation dans l'acétonitrile. On a identifié les structures **3**, **3a** et **3b** à partir de leurs données analytiques et spectroscopiques (RMN du ^{1}H et du ^{13}C et SM (FAB)). Les propriétés spectroscopiques des composés **3a** et **3b** démontrent que, pour chaque centre de complexation, en plus de la forte participation des quatre azotes des pyrazoles, il existe une faible interaction entre l'azote aliphatique de la chaîne latérale et celui de l'amine. Une comparaison des énergies totales d'interaction (calculées à l'aide du programme GenMol) des complexes dérivés de la phénéthylamine (**3a**) et de l'homovératrylamine (**3b**) suggère que le substituant *o*-diméthoxy du noyau aromatique de l'invité améliore la stabilité du composé **3b** par rapport à **3a**.

Mots clés : diazacouronne, 1*H*-pyrazole, dinucléaire, complexes, phénéthylamines.

[Traduit par la Rédaction]

Introduction

One of the two main categories of psychedelic drugs that produce perceptual distortions (hallucinations, illusions, and disorders of thinking such as paranoia) are hallucinogen phenethylamines methoxy and (or) methylenedioxy substituted at the aromatic ring (1).

The selective complexation of such hallucinogen substrates by adequately arranged synthetic receptors, in relation to neurotransmitter catecholamines, is an important but difficult target due to the similarity of their structures. Thus, dopamine and norepinephrine, involved in the normal emotional and autonomic control of humans, have in common a hydrophilic 3,4-dihydroxyphenethylamine nucleus, while its 3,4-dimethoxy substituted analogue (homoveratrylamine) of higher lipophilic character shows hallucinogen effects (2).

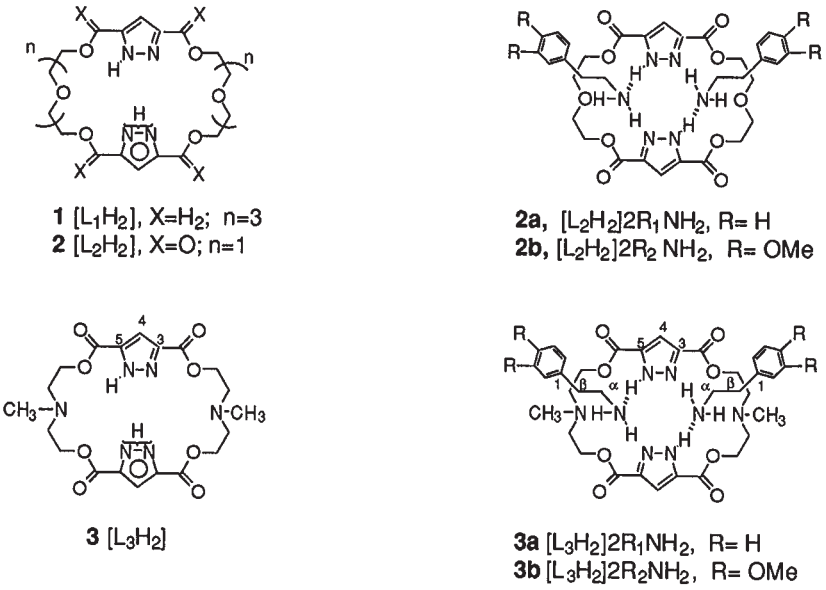
It is well known that synthetic oxaaza and polyaza macrocycles containing a trigonal symmetrical arrangement of NH binding sites are able to selectively complex ammonium and catecholammonium ions (3). In this way, we have previously synthesized and studied the transport properties of different series of synthetic heteroaromatic receptors

Received January 28, 1998.

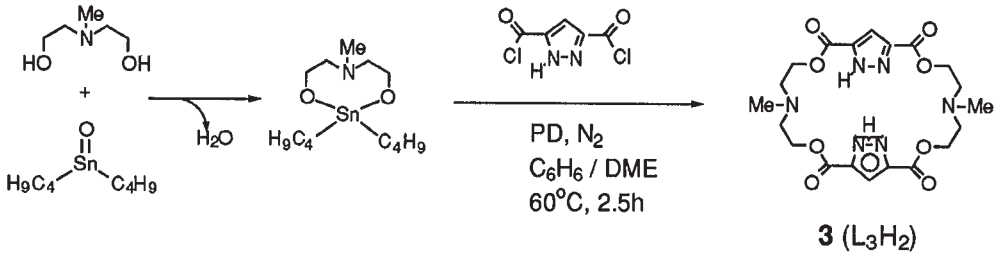
A.M. Sanz and P. Navarro.[1] Instituto de Química Médica, Centro Nacional de Química Orgánica, Manuel Lora Tamayo, C.S.I.C., c/ Juan de la Cierva 3, 28006 Madrid, Spain.
F. Gomez-Contreras and M. Pardo. Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain.
G. Pèpe and A. Samat. UERS CNRS 158, Faculté des Sciences de Luminy, Université de la Méditerranée, Case 901, Cedex 9, 13288 Marseille, France.

[1]Author to whom correspondence may be addressed. Telephone: 34 91 5622900. Fax: 34 91 5644853. E-mail: iqmnt38@fresno.csic.es

Fig. 1.



Scheme 1.



containing one to three 1,3,5- or 3,5-substituted pyrazole units (4). As the result of the above studies, we discovered a dinuclear receptor of 1*H*- pyrazole of similar size to that of valinomycin (36-membered) **1** [L_1H_2] (X = H_2; *n* = 3) (Fig. 1), which behaves as an effective and selective carrier of NH_4^+ (5). Furthermore, it has been recently discovered that such crown is able to form dinuclear complexes with lipophilic phenethylamine R-NH_3^+ ions of higher stability than those formed with those of hydrophilic phenethylamines.[2]

On the other side, we have also synthesized an analogous dinuclear receptor of 1*H*- pyrazole **2** [L_2H_2] of smaller size (26-membered), which strongly interacts with neutral lipophilic R-NH_2 phenethylamines, affording dinuclear complexes **2a** R = H; phenethylamine) and **2b** R = OMe;

homoveratrylamine), which were isolated in the solid state (6). Besides, the theoretical calculations (GenMol software) together with a careful ^{1}H and ^{13}C NMR study has recently demonstrated that in both complexes, the two sp^2 pyrazole nitrogens and the two N*H* pyrazole protons are involved in the complexation of the two guest amine molecules, affording a molecular association mainly stabilized by symmetrical hydrogen bonds (7), while other hydrogen bonds with ether oxygens belonging to the receptor side chains were discarded.

Considering the strong insoluble character of the above dioxa substituted coronand **2**, and taking into account that N···HN hydrogen bonds are more effective than O···HN ones, in this paper we have synthesized a more convenient diazatetraester crown of 1*H*-pyrazole **3**, [L_3H_2], which is soluble in common lipophilic organic solvents. This new diazacoronand is containing a double trigonal symmetrical arrangement of NH binding sites in which the two basic nitrogens incorporated to the side chains are improving the complexing properties of **3** toward phenethylamine and homoveratrylamine.

Results and discussion

The synthesis of the **3** has been achieved as depicted in Scheme 1.

N-Methyldiethanolamine was heated to reflux in benzene with dibutyltin oxide to give the corresponding cyclic stannoxane (8), which was reacted with 1*H*-pyrazole-3,5-dicarbonyl dichloride to afford crown **3** (mp 190–192°C; $C_{20}H_{26}N_6O_8 \cdot 2H_2O$; MH^+ 479) in a 10% overall yield.

In the FAB mass spectrum of the diaza tetraester crown **3**, the expected molecular ion MH^+ corresponds to the base peak (*m/z* 479, 100%). From MH^+, the fragmentation is mainly governed by usual ruptures of amine and ester bonds,

[2] M.I. Rodriguez-Franco, B. Gonzalez, A. Sanz, P. Navarro, C. Ochoa, A. Doménech, and E. García-España. 1998. Unpublished results.

Table 1. The ^{13}C NMR spectral data (75 MHz, Cl_3CD, δ) of complexes **3a** and **3b** compared with those of the free guests (phenethylamine(Ph), homoveratrylamine (Ho)) and host (**3**).

Compd.	Ph	**3a**	$\Delta\delta_{\mathbf{3a}\text{-Ph}}$	Ho	**3b**	$\Delta\delta_{\mathbf{3b}\text{-Ho}}$
Cα	43.35	42.95	–0.40	43.33	42.73	–0.60
Cβ	39.93	39.38	–0.55	39.20	38.06	–1.14
C_1-Ar	139.62	139.40	–0.22	132.07	131,48	–0.59

Compd.	**3**	**3a**	$\Delta\delta_{\mathbf{3a}\text{-}\mathbf{3}}$	**3**	**3b**	$\Delta\delta_{\mathbf{3b}\text{-}\mathbf{3}}$
C(3,5)	139.36	139.56	+0.20	139.36	139.93	+0.57
C(4)	111.70	111.52	–0.18	111.70	111.59	–0.11
CO	159.60	159.57	–0.03	159.60	160.07	+0.47
CH_2O	59.74	59.41	–0.33	59.74	59.37	–0.37
CH_2N	55.91	55.79	–0.12	55.91	56.07	+0.16
NMe	40.01	39.74	–0.27	40.01	39.82	–0.19

responsible for sequential losses of a = C_3H_7N (57) and b = C_5H_9N (83) fragments belonging to the host flexible chain, as well as c = $C_5H_2N_2O_2$ (122) and d = $C_5H_2N_2O_3$ (138) fragments corresponding to the losses of one of the two diceto pyrazolo moieties. Furthermore, as usually occurs with tetraester and polyether crowns of dimmer structure (5), from M^+ other important decompositions give rise to the characteristic $(M/2 + H)^+$ species (m/z 240, 7%).

The complexing ability of crown **3** [L_3H_2] was tested by stirring for 15 min with phenethylamine or homoveratrylamine in a 1:2 molar ratio using chloroform as solvent. In both cases, after concentration, the diaza substituted complexes were isolated as white solids and crystallized from acetonitrile. Their analytical and spectroscopic data were consistent with neutral dinuclear complexes **3a** (mp 140–142°C; $C_{36}H_{48}N_8O_8 \cdot 3H_2O$; $MH^+ - C_3H_7N$ 664) and **3b** (mp 170–172°C; $C_{40}H_{56}N_8O_{12} \cdot H_2O$; $MH^+ - C_3H_7N$ 684), which were obtained in 90% and 85% yield, respectively (Fig. 1).

The FAB mass spectra of both dinuclear complexes are clearly demonstrating the strong interaction of the two amino groups with both pyrazole rings. The phenethylamine complex **3a** shows a pattern in which two a = C_3H_7N (57), b = C_4H_9N (71), or c = $C_5H_{11}N$ (85) fragments belonging to the host flexible side chain, as well as two d = C_6H_5 (77) aromatic fragments belonging to the amine guest, are simultaneously lost giving up a series of peaks of m/z: 606 ($M^+ - 2(C_3H_7N)$) (0.1); 578 ($M^+ - 2(C_4H_9N)$) (1.9); 567 ($MH^+ - 2(C_6H_5)$) (0.6); 551 ($MH^+ - 2(C_5H_{11}N)$) (11.0); 550 ($M^+ - 2(C_5H_{11}N)$) (26.3). In a similar way, the homoveratrylamine complex **3b** show a pattern in which one or two host flexible side chain fragments (a = C_3H_7N (57); b = C_4H_9N (71); c = $C_5H_{10}N$ (84); and d = $C_5H_{11}NO_2$ (117)) and one or two homoveratrylamine fragments (e = $C_8H_9O_2$ (137) and f = $C_8H_9O_2$ (138)) are successively or simultaneously lost from the $MH^+(H_2O)$, $M^+(H_2O)$, MH^+, and M^+ molecular ions, affording different series of peaks of m/z: 801 ($M^+(H_2O) - C_3H_7N$) (0.2); 744 ($M^+(H_2O) - 2(C_3H_7N)$) (0.2); 788 ($MH^+(H_2O) - C_4H_9N$) (0.2); 716 ($MH^+(H_2O) - 2(C_4H_9N)$) (0.1); 703 ($M^+ - C_8H_9O_2$) (0.5); 566 ($M^+ - 2(C_8H_9O_2)$) (0.5); 606 ($M^+ - 2(C_5H_{11}NO_2)$) (0.1); 565 ($M^+ - (C_8H_9O_2) - (C_8H_{10}O_2)$) (0.46); 373 ($MH^+ - 2\ (C_5H_{10}N) - 2(C_9H_{10}O_2)$) (11.0).

As could be expected in the formation of strong NH···N hydrogen bonds (9), in the ^1H NMR spectra of **3a** and **3b** registered in Cl_3CD, the complexation strongly affects the amine RNH···N= signals, which are deshielded by 3.55 and 3.07 ppm in relation to the free phenethylamine and homoveratrylamine respectively.

Comparison of the ^{13}C NMR spectral data of these complexes with those corresponding to the free guests and host (Table 1) affords some relevant structural information. The two methylene carbons closer to the complexation centre, as well as the *ipso* aromatic carbons of the guest amines experience considerable upfield shifts, which are larger for the β than for the α and C_1-Ar carbons (Table 1*a*). This behaviour agree with a reduction of electronic density at the sp^3 nitrogen, which takes place when the complex is formed (10). Furthermore, it may be noted that shieldings measured are much higher for homoveratrylamine (Δδ **3b**-Ho) than for phenethylamine (Δδ **3a**-Ph).

On the other hand, the comparison of the ^{13}C NMR data of **3a** and **3b** and those of the free host **3** (Table 1*b*) shows that the signals belonging to the pyrazole ring undergo in both complexes chemical shifts to downfield carbons C(3,5) and highfield carbons C(4), which are much more smaller but of identical sign to those previously observed in the formation of dipyrazolate anions by deprotonation of 26-membered dinuclear 1*H*-pyrazole macrocycles (6*b*). Furthermore, the pyrazole carbons C(3,5), which in **3** appear as a broad signal due to the pyrazole prototropic equilibrium, collapse after complexation to a sharp singlet. As it was previously observed from dioxa tetraester crown-derived complexes(7), the above behaviour confirms that in complexes **3a** and **3b**, the NH pyrazole protons are not ambigously located but fastened to the guest amines. The above situation agrees with a molecular association mainly stabilized by symmetric RN·HN(Pz) and RNH···N=(Pz) hydrogen bonds. On the other hand, taking as reference the basic nitrogens located in middle of the host flexible side chains, it can be observed that after complexation, the β methylene carbons (CH_2O) as well as the a methyl ones (MeN) experience in both complexes upfield shifts, which suggest an additional interaction between the sp^3 nitrogens and the guest amines.

Theoretical approach of the stability of diaza tetraester crown-derived complexes 3a and 3b

The stability of the complexes has been evaluated using molecular modelling GenMol software (11). This program based on molecular mechanics calculations is designed to build molecules and to find their preferred conformations (12). It also allows to model molecular interactions and to find the minimum energy of complex molecular systems (13).

We have previously shown that, for dinuclear complexes obtained from the dioxa tetraester crown **2** [L_2H_2] with phenethylamine (**2a**) and homoveratrylamine (**2b**), *syn*- conformations (both amines on the same face of the crown) were more stable than the *anti*-conformations (amines on the opposite faces of the crown) (7).

Now, starting from the *syn*-conformation of the diaza tetraester crown **3** [L_3H_2], we have calculated the interaction energy between the host (crown) and the guest (both

Table 2. Relative stability of dinuclear cyclic complexes **3a** and **3b** modelled from diaza substituted coronand **3**. (E_I, E_H, E_{vdw}, E_C are, respectively, the interaction, hydrogen bond, van der Waals, and coulombic energies (kcal mol^{-1}).)

Compound	E_I	E_H	E_{vdw}	E_C
3a (Ph)	–18.4	–5.3	–13.2	–0.01
3b (Ho)	–22.1	–5.8	–16.2	–0.12

molecules of amine), which is directly connected to the association constants.

In Table 2 are reported the interaction energies (E_I, kcal mol^{-1}) and the hydrogen bond energies (E_H, kcal mol^{-1}) corresponding to the new dinuclear complexes obtained from the diaza substituted receptor **3** [L_3H_2] with phenethylamine (**3a**) and homoveratrylamine (**3b**).

The value E_I is the sum of classic nonbond interactions occurring between the crown and the amines:

$$E_I = E_{vdw} + E_C + E_H$$

in which E_{vdw}, E_c, and E_H are, respectively, van der Waals, coulombic, and hydrogen bond energies. The more E_I is negative, the more the complex is stable.

Regarding the geometries of the most stable complexes obtained for **3a** and **3b** it seems that hydrogen bonds exist really between the guest amine nitrogen atoms and the host pyrazole nitrogen ones (the distance is close to 2.9 Å), while the distances with nitrogen atoms of the NMe groups (3.2 Å) may correspond to weaker hydrogen bonds.

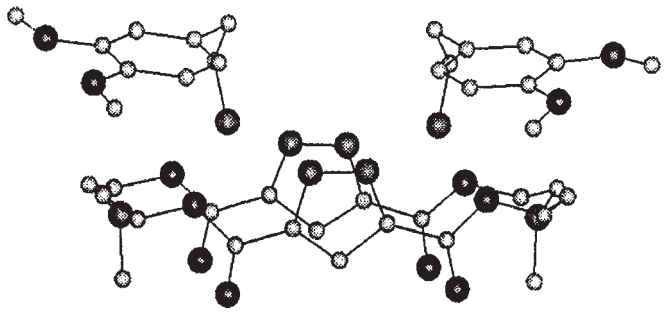
Comparison of the total interaction energies suggest that the theoretical stability of the homoveratrylamine complex **3b** is higher than that of the phenethylamine **3a**. Detail of the interaction energies (Table 2) shows that this increase is due at once to hydrogen bonding and van der Waals type interactions.

The more stable conformations of the diaza tetraester crown-derived homoveratrylamine complex **3b** is shown in Fig. 2.

Conclusions

(*i*) The synthesis of a new proton ionizable ester crown **3** (mp 190–92°C) has been performed in 10% yield by direct cyclization of 1*H*-pyrazole-3,5 dicarbonyl dichloride and 2,2-dibutyl-6-methyl-6-aza-1,3-dioxa-2-stannocyclooctane. (*ii*) Using chloroform as solvent, the reaction of crown **3** with phenethylamine and homoveratrylamine (molar ratio 1:2) affords solid dinuclear complexes, which after being crystallized from acetonitrile were obtained in high yield (**3a**, mp 140–142°C, 90%; **3b**, mp 170–72°C, 85%). (*iii*) The structure of the new compounds **3**, **3a**, and **3b** have been identified from their analytical and spectroscopic (FAB MS, IR, ^{1}H, and ^{13}C NMR) data. (*iv*) The ^{13}C NMR study is demonstrating that, in the new diaza substituted complexes **3a** and **3b**, simultaneously to a strong molecular association through NH···N=(Pz) and N·HN(Pz) hydrogen bonds, an additional weaker interaction between the host sp^3 nitrogens and the guest amines is contributing to the formation of these new solid complexes. (*v*) Comparison of the total interaction energies calculated for phenethylamine-derived

Fig. 2.



complexes (**3a**) and homoveratrylamine-derived ones (**3b**) is suggesting that the *o*-dimethoxy substitution of the guest aromatic ring could be improving the stability of **3b** in relation to **3a**. Now, work is in progress in order to evaluate the experimental stability constants of phenethylamine and homoveratrylamine dinuclear complexes **2a**, **2b** and **3a**, **3b**, as well as those formed from mescaline, amphetamine, and neurotransmitter catecholamines (dopamine and norepinephrine).

Experimental section

The IR spectra were recorded in KBr, and the NMR spectra in $CDCl_3$ solution, taking Me_4Si as internal reference. Analytical TLC and flash column chromatography were performed using silica gel 60 PF254 (Merck) and silica gel (Merck), 200–400 mesh, respectively. All reagents were of commercial quality from freshly opened containers. Thionyl chloride (Scharlau) was freshly purified prior to use as follows: distilled from quinoline (to remove acid impurities) followed by distillation from boiled linseed oil under argon. Pyrazole-3,5-dicarboxylic acid monohydrate (Aldrich), *N*-methyldiethanolamine (Aldrich), dibutyltin oxide (Merck), homoveratrylamine (Aldrich), phenethylamine (Aldrich), and reagent quality solvents were used without further purification.

1*H*-Pyrazole-3,5-dicarbonyl dichloride

Thionyl chloride freshly purified (350 mL) was slowly added to 1*H*-pyrazole-3,5-dicarboxylic acid monohydrate (2 g, 11.49 mmol) by stirring and heating until all the acid was completely dissolved. Then, the temperature was allowed to 140°C over 2 h. The hot reaction mixture was filtered, and the resulting solution evaporated to dryness to give the title compound (2 g, 10.3 mmol) as a white solid (mp 72–74°C) in 93% yield.

2,2-Dibutyl-6-methyl-6-aza-1,3-dioxa-2-stannocyclooctane (8)

To a solution of *N*-methyl diethanolamine (1.36 g, 11.46 mmol) in benzene (200 mL), solid dibutyltin oxide (2.85 g, 11.49 mmol) was slowly added. 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 into dry toluene (260 mL) and collected to be used in the following step.

6,18-Dimethyl-25(26),27(28)-*H*,*H*-3,9,15,21-tetraoxa-6,18,25,26,27,28-hexaazatricycle[21.2.1.2^{11,13}]-octacosa-1(26),13(28),11,23-tetraen-2,10,14,22-tetraone 3

The suspension obtained above was heated to 60°C under nitrogen, and a solution of pyrazole-3,5-dicarbonyl chloride (21 g, 11.46 mmol) in dry dimethoxyethane (80 mL) was added dropwise. The reaction mixture was kept at 60°C under nitrogen for 24 h. After that, the solvent was removed in vacuo to give a syrup that was purified by flash column chromatography, eluting with an ethyl acetate – ethanol – ammonium hydroxide (5:1:0.15 v/v) mixture. From the fraction of R_f = 0.36, compound **3** was isolated as a pure solid compound (mp 190–92°C) in 10% yield. IR (KBr, cm^{-1}): 3360, 2950, 1725, 1750, 1600, 1250, 1000, 760. ^{1}H NMR (300 MHz, Cl_3CD (after treated with D_2O)), δ (ppm): 7.36 (s, 2H, Pz-H), 4.48 (t, 8H, $COOCH_2$), 2.79 (t, 8H, C*H*$_2$-NMe), 2.42 (s, 6H, MeN). MS (FAB): 479 (MH^+) (100), 435 ($MH^+ - C_2H_4O$) (1.0), 422 ($MH^+ - C_3H_7N$) (3.0), 396 ($MH^+ - C_5H_9N$) (5.2), 359 ($MH^+ - C_5H_2N_2O_2$) (2.0), 341($MH^+ - C_5H_2N_2O_3$) (8.0), 240 ($M^+/2 + 1$) (7.0), 139 $(C_5H_3N_2O_3)^+$ (5.4), 122 $(C_5H_3N_2O_2)^+$ (5.4). Anal. calcd. for $C_{20}H_{26}N_6O_8\cdot 2H_2O$: C 46.69, H 5.83, N 16.34; found: C 46.36, H 5.42, N 16.69.

Cyclic dinuclear complex 3a

Crown **3** (18 mg, 0.037 mmol) was dissolved at rt in chloroform (5 mL), and a solution of phenethylamine (9.11 mg, 0.075 mmol) in chloroform (2 mL) was added dropwise under stirring. After that, the solvent was removed in vacuo to give a residue, which was crystallized from acetonitrile, affording the pure dinuclear complex **3a** as a white solid (mp 140–142°C) in 90% yield. IR (KBr, cm^{-1}): 3400–3100, 1720, 1630, 1265, 1220, 1035, 795, 760. ^{1}H NMR (300 MHz, Cl_3CD), δ (ppm): 7.31 (s, 2H, Pz-H), 4.40 (m, 8H, $COOCH_2$), 2.70 (m, 8H, C*H*$_2$-NMe), 2.31 (s, 6H, MeN), 4.70 (brs, 6H, NH), 3.00 (t, 4H, C*H*$_2$-NH_2), 2.80 (t, 4H, C*H*$_2$-C_6H_5), 7.18 (m, 10H, C_6H_5). MS (FAB): 664 ($MH^+ - C_3H_7N$) (0.1), 663 ($M^+ - C_3H_7N$) (0.2), 606 ($M^+ - 2(C_3H_7N)$) (0.1), 600 ($MH^+ - C_8H_{11}N$) (0.8), 578 ($M^+ - 2(C_4H_9N)$) (1.9), 567 ($MH^+ - 2(C_6H_5)$) (0.6), 551 ($MH^+ - 2(C_5H_{11}N)$) (11.0), 550 ($M^+ - 2(C_5H_{11}N)$) (26.3), 479 ($MH^+ - 2(C_8H_{11}N)$) (63.0), 122 $(C_5H_2N_2O_2)^+$ (100), 121 $(C_8H_{11}N)^+$ (14.0), 77 $(C_6H_5)^+$ (31.0), 85 $(C_5H_{11}N)^+$ (8.0), 71 $(C_4H_9N)^+$ (14.0), 57 $(C_3H_7N)^+$ (31.0). Anal. calcd. for $C_{36}H_{48}N_8O_8\cdot 3H_2O$: C 55.81, H 7.02, N 14.47; found: C 56.12, H 6.62, N 14.32.

Free phenethylamine; ^{1}H NMR (300 MHz, Cl_3CD), δ (ppm): 1.13 (brs, 2H, NH), 2.94 (t, 2H, C*H*$_2$$NH_2$), 2.72 (t, 2H, C*H*$_2$$C_6H_5$), 7.15 (m, 5H, C_6H_5).

Cyclic dinuclear complex 3b

Crown **3** (18 mg, 0.037 mmol) was dissolved at rt in chloroform (5 mL), and a solution of homoveratrylamine (13.63 mg, 0.075 mmol) in chloroform (2 mL) was added dropwise under stirring. After that, the solvent was removed in vacuo to give a residue, which was crystallized from acetonitrile, affording the pure complex **3b** in 85% yield as a white solid (mp 170–172°C). IR (KBr, cm^{-1}): 3480–3200, 2920, 1720, 1635, 1260, 1235, 1035, 785, 760. ^{1}H NMR (300 MHz, Cl_3CD), δ (ppm): 7.37 (s, 2H, Pz-H), 4.47 (m, 8H, $COOCH_2$), 2.78 (m, 8H, C*H*$_2$-NMe), 2.38 (s, 6H, MeN), 6.78 (brs, 6H, NH), 3.04 (t, 4H, C*H*$_2$-NH_2), 2.80 (t, 4H, C*H*$_2$-$C_6H_3(OMe)_2$), 6.76 (m, 6H, $C_6H_3(OMe)_2$), 3.87 (s, 6H, MeO), 3.85 (s, 6H, MeO). MS (FAB): 801 ($M^+(H_2O) - C_3H_7N$)) (0.2); 788 ($MH^+(H_2O) - (C_4H_9N)$) (0.2), 684 ($MH^+ - (C_3H_7N)$) (0.1), 744 ($M^+(H_2O) - 2(C_3H_7N)$) (0.2), 716 ($M^+(H_2O) - 2(C_4H_9N)$) (0.1), 703 ($M^+ - (C_8H_9O_2)$) (0.5), 702 ($M^+ - (C_8H_{10}O_2)$) (1.0), 660 ($MH^+ - (C_{10}H_{15}NO_2)$) (0.3), 606 ($M^+ - 2(C_5H_{11}NO_2)$) (0.1), 566 ($M^+ - 2(C_8H_9O_2)$) (0.5); 565 ($M^+ - (C_8H_9O_2) - (C_8H_{10}O_2)$) (0.5), 551 ($M^+ - (C_8H_{10}O_2) - (C_9H_{11}O_2)$) (8.0), 550 ($M^+ - (C_8H_{10}O_2) - (C_9H_{11}O_2)$) (18.0), 479 ($MH^+ - 2(C_{10}H_{15}NO_2)$) (39.0), 373 ($MH^+ - 2(C_9H_{10}O_2) - 2(C_5H_{10}N)$) (11.0), 181 $(C_{10}H_{15}NO_2)^+$ (9.0), 165 $(C_{10}H_{13}O_2)^+$ (66.0), 164 $(C_{10}H_{12}O_2)^+$ (31.0), 150 $(C_9H_{10}O_2)^+$ (11.0), 151 $(C_9H_{11}O_2)^+$ (21.0), 138 $(C_8H_{10}O_2)^+$ (17.0), 137 $(C_8H_9O_2)^+$ (31.0), 117 $(C_5H_{11}NO_2)^+$ (9.0), 73 $(C_4H_{11}N)^+$ (100%), 71 $(C_4H_9N)^+$ (36.0), 57 $(C_3H_7N)^+$ (70.0). Anal. calcd. for $C_{40}H_{56}N_8O_{12}\cdot H_2O$: C 55.94, H 6.75, N 13.05; found: C 56.33, H 6.49, N 12.94.

Free homoveratrylamine; ^{1}H NMR (300 MHz, Cl_3CD), δ (ppm): 1.38 (brs, 2H, NH), 2.92 (t, 2H, C*H*$_2$$NH_2$), 2.66 (t, 2H, C*H*$_2$$C_6H_3(OMe)_2$), 6.75 (m, 3H, $C_6H_3(OMe)_2$), 3.85 (s, 3H, OMe), 3.83, (s, 3H, OMe).

Molecular modelling

GenMol (11) is a molecular mechanics software including some specificities, able to treat atomic and molecular systems till 10^5 atoms of 96 types: (*i*) The program uses local stretching and bending parameters, which depend not only on the chemical neighbourhood (nature of the bonded atoms, which is the case in all molecular mechanic programs), but also of the geometrical neighbourhood. This concept allows to win an order of magnitude in the geometry accuracy if compared to X-ray data. (*ii*) An original algorithm deforming the molecule by rotation around the bonds, and based on empirical rules deduced from X-ray observations, allow to very quickly find the most probable conformation of a molecule. (*iii*) The π systems are taken into account. The program calculates the atomic charges.

For the design of the complex, different packing of molecules were tested, and the most stable corresponding to the minimum of the nonbonded energy (van der Waals, coulombic, and hydrogen bond) was considered. Then in a first step, a calculation imposing all the possible hydrogen bonds was performed, and in a second step these constraints were removed in order to find the true hydrogen bonds and the more stable assemblage of the molecules.

Acknowledgement

Financial support of this work by the Spanish *Comision Interministerial de Ciencia y Tecnología* (CICYT, Coordinated Project SAF-96–0242-CO2) is gratefully acknowledged.

References

1. C.D. Klaassen and C.P. O'Brien. *In* Goodman and Gilman's The pharmacological basis of therapeutics. *Edited by* J.G. Hardman, L.E. Limbird, P.B. Molinoff, and R.W. Ruddon. McGraw–Hill, New York. 1996. Chap. 4. p. 63; Chap. 24. p. 557.

2. (*a*) J. Pearson. *In* An introduction to neurotransmission in health and disease. *Edited by* P. Riederer, N. Kopp, and J. Pearson. University press, Oxford. 1990. Chap. 21 and 26; (*b*) The reaction of living cells. Biochemistry. *Edited by* D.E. Metzler. Academic Press, New York. 1977. Chap. 16, p. 1017.
3. (*a*) J.M. Lehn. Angew. Chem. Int. Ed. Engl. **27**, 89 (1988); (*b*) I.O. Sutherland. Chem. Soc. Rev. **15**, 63 (1986).
4. (*a*). J. Elguero, P. Navarro, and M.I. Rodriguez-Franco. Chem. Lett. 425 (1984); (*b*) J. Elguero, P. Navarro, M.I. Rodriguez-Franco, F.H. Cano, C. Foces-Foces, and A. Samat. J. Chem. Res. Synop. 312 (1985); J. Chem. Res. Miniprint, 3401 (1985); (*c*) P. Navarro, M.I. Rodriguez-Franco, and A. Samat. Synth. Commun. **17**, 105 (1987); (*d*) P. Navarro and M.I. Rodriguez-Franco. J. Chem. Soc. Chem. Commun. 1365 (1988); (*e*) P. Navarro, M.I. Rodriguez-Franco, C. Foces-Foces, F.H. Cano, and A. Samat. J. Org. Chem. **54**, 1391 (1989); (*f*) P. Navarro, E. Pueyo, M.I. Rodriguez-Franco, and A. Samat. Tetrahedron, **46**, 2917 (1990); (*g*) J.M. Bueno, P. Navarro, M.I. Rodriguez-Franco, and A. Samat. J. Chem. Res. Synop. 126 (1991); J. Chem. Res. Miniprint, 1101 (1991); (*h*) M. Fierros, S. Conde, A. Martinez, P. Navarro, M.I. Rodriguez-Franco. Tetrahedron, **51**, 2417 (1995); (*i*) M.I. Rodriguez-Franco, M. Fierros, A. Martinez, P. Navarro, and S. Conde. Bioorg. Med. Chem. **5**, 363 (1997).
5. P. Navarro and M.I. Rodriguez-Franco. Trends Org. Chem. **4**, 69 (1993).
6. (*a*) L. Campayo, J.M. Bueno, C. Ochoa, P. Navarro, and A. Samat. Tetrahedron Lett. **34**, 7299 (1993). (*b*) C. Acerete, J.M. Bueno, L. Campayo, P. Navarro, M.I. Rodriguez-Franco, and A. Samat. Tetrahedron, **50**, 4765 (1994).
7. J.M. Bueno, L. Campayo, P. Navarro, C. Ochoa, J. Jimenez-Barbero, A. Samat, and G. Pèpe. J. Org. Chem. **62**, 2684 (1997).
8. H. Shanser, J. Libman, H.E. Gottlieb. J. Org. Chem. **48**, 4612 (1983).
9. F. Hibbert. *In* Advances in physical organic chemistry. Vol. 22. *Edited by* V. Gold and D. Bethell. Academic Press, London. 1986. p. 138.
10. A.D. Hamilton. Tetrahedron Lett. **31**, 2401 (1990).
11. G. Pèpe and D. Siri. Stud. Phys. Theor. Chem. **71**, 93 (1990).
12. F. Cavelier-Frontin, G. Pèpe, J. Verducci, D. Siri, and R. Jacquier. J. Am. Chem. Soc. **114**, 8885 (1992).
13. (*a*) G. Pèpe, D. Siri, A. Samat, E. Pottier, and R. Guglielmetti. Mol. Cryst. Liq. Cryst. **246**, 247 (1994); (*b*) F. Vila, P. Tordo, D. Siri, and G. Pèpe. Free Radical Res. Commun. **19**, 517 (1993); (*c*) F. Cavelier-Frontin, A. Sadijah, G. Pèpe, J. Verducci, and R. Jacquier. THEOCHEM, **286**, 125 (1993).