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Synthesis, Complexing Properties and Molecular Modelling of Open Chain Receptors of Barbiturates Derived from 2,6-Diamino Pyridine

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Abstract. Three new derivatives of 2,6-diacyldiaminopyridine are reported. NMR shift titrations were performed in $CDCl_3$ with barbiturates. The diamide **1** affords a greater complexation energy (–13.00 kJ mol^{-1}) with bemegride than the dithioamide **2** (–9.15 kJ mol^{-1}). This result, unexpected on the basis of the proton acidities, is explained by the great torsion energy induced in **2** by the bulky sulfur atom. Compounds **3** and **4** present unusual four and five H-bond features with barbital and relatively weak complexation energies (–9.53 and –16.34 kJ mol^{-1}, respectively). Molecular mechanics indicates that ligand **4** displays a helical secondary structure which is disrupted by complexation. Calculations of the H-bond energies ($\Delta E_{calc.}$) of the intermolecular assemblies with barbital or phenobarbital and other host–guest complexes given in the literature give a good correlation ($r = 0.98$) with experimental values: $\Delta E_{calc.} = 1.07\ \Delta G_a - 42.0$. Limitations of this relation are discussed.

Key words: Barbiturate receptors, stability constants, molecular modelling.

1. Introduction

Many supramolecular structures described in the literature are based upon the formation of hydrogen bonds between the host and the guest molecules. In order to enhance the complexing properties of crown ethers, Reinhoudt *et al.* introduced a carboxylic group inside the cavity of the ring [1], or prepared macrocycles allowing the formation of ternary complexes where an immobilized cation such as UO^{2+} plays the role of an efficient electrophilic site leading to strong complexes with urea [2a] or barbiturates [2b]. Other approaches consisted in designing receptors possessing high hydrogen bonding-based complementarity with the neutral host [3]. In particular Hamilton *et al.* [3a–e] used the complementarity of the 2,6-diamidopyridine moiety and the imide function (Scheme 1) to prepare complexes of barbiturate compounds such as barbital (see complex **5**/bar in Scheme 1). Macrocyclic receptors containing one or two of these moieties were synthesized by this group leading to complexes possessing stability constants ranging from 10^2 to 10^6 M^{-1} (see complexes **6–8**/bar in Scheme 1). Rebek *et al.* [3i, j] also described barbiturate receptors based on two Kemp's acid derivatives spaced by a naphthalene group.

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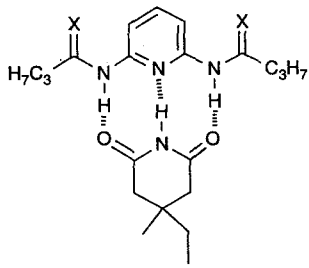
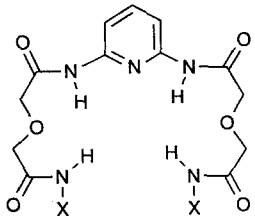
Scheme 1



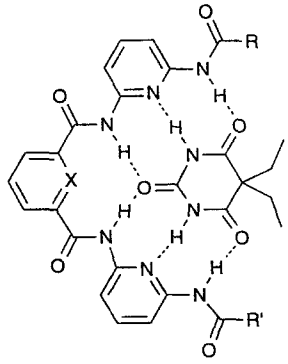
1/bem X = O

2/bem X = S

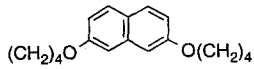


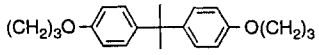
3 X = $C_{12}H_{25}$

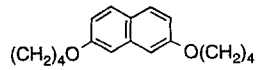
4 X = 2-Py



5/bar X = CH
R = R' = $(CH_2)_2CH_3$

6/bar X = CH
R, R' = 

7/bar X = CH
R, R' = 

8/bar X = N
R, R' = 

While the complexing ability of the 2,6-diamidopyridine moiety was known through compound **1**, that of the corresponding dithioamide **2** (see complex **2**/bem in Scheme 1), which is potentially a better hydrogen bond donor at the level of the N–H group [4], has not been reported.

On the other hand we report in this paper the synthesis and the complexation study of compounds **3** and **4** where additional hydrogen bonds may reinforce the formation of a complex with barbital.

Moreover, these compounds can give complexes with the rarely observed four and five H-bonds feature compared with the more usual six H-bonded complexes. Thus, the extension of the energy range is favourable to the determination by molecular mechanics of the energies of association between host ligands and their barbiturate guests. A correlation with the experimental values is presented.

2. Experimental

General. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC 250 instrument in deuterochloroform. IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer in 0.025 M chloroform solutions using NaCl 0.5 mm cells or KBr disks. Elemental analyses were carried out by the 'Service Commun de Microanalyse Elementaire UPS-INP' in Toulouse. Starting materials were used as purchased from Aldrich or Fluka, except for 2,6-diaminopyridine which was recrystallized twice from benzene. Diglycolic anhydride [5] and *N*, *N'*-2,6-pyridine diylbisbutanamide [6] **1** were prepared as previously reported. THF was freshly distilled from sodium before use.

Molecular mechanics calculations were performed on an IRIS 4D30 silicon graphics workstation using the MACROMODEL V 3.5 X program.

*N, N'-2,6-Pyridinediylbisbutanethioamide (**2**).* The diamide **1** (0.5 g, 2 mmol) and 0.89 g (2.2 mmol) of Lawesson's reagent were stirred in 10 mL of dry toluene at reflux temperature under argon for 4 h. After cooling, the solvent was evaporated and the residue was purified by chromatography on silica gel using dichloromethane/ethyl acetate (95/5) as eluent to give 0.486 g (86%) of **2** as yellow crystals; m.p. = 86–87°C; r_f = 0.41; IR (KBr), ν 3198 (NH), 1379 cm^{-1} (C=S); ^{1}H NMR ($CDCl_3$), δ 0.99 (t, 6H, J = 7 Hz, CH_3), 1.87 (sext, 4H, J = 7 Hz, CH_3CH_2), 2.79 (t, 4H, J = 7 Hz, CH_2), 7.81 (t, 1H, J = 8.3 Hz, H_4 arom.), 8.90 (d, 2H, J = 8.3 Hz, H_3–H_5 arom.), 9.10 (s, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 13.4 (CH_3), 23.0 (CH_3–CH_2), 52.1 (CH_2), 112.7 (C_3, C_5 arom.), 140.3 (C_4 arom.), 150.0 (C_2, C_6 arom.), 204.7 (C=S); *Analysis : calculated* for $C_{13}H_{19}N_3S_2$, C 55.48, H 6.80, N 14.93; *found* C 55.30, H 6.72, N 15.05%.

N, N'-2,6-Pyridinediylbis (3-oxa glutaramic acid). A solution of 2,6-diaminopyridine (1.31 g, 12 mmol) in dry THF (15 mL) was added dropwise to a stirred solution of diglycolic anhydride (2.79 g, 24 mmol) in dry THF (20 mL), heated at 50°C. The mixture was stirred at the same temperature for 12 h. After cooling, the solvent was evaporated under reduced pressure and the white solid was washed with THF, methanol, ether and dried *in vacuo* to give 4 g (98%) of the expected diamide diacid; m.p. = 270°C, r_f = 0.15 (butanol/water/acetic acid 5/4/1); IR (KBr), ν 3076 (NH), 1723 (CO acid), 1643 cm^{-1} (CO amide); ^{1}H NMR (80 MHz, DMSO), δ 4.23 (s, 8H, CH_2O), 7.81 (s, 3H, H arom.), 9.75 (s, 2H, NH), ^{13}C NMR (DMSO), δ 67.9 (OCH_2COOH), 70.0 (OCH_2), 108.9 ($C_{3,5}$ arom.), 140.6 (C_4 arom.), 149.4 ($C_{2,6}$ arom.), 168.3 (C=O amide), 171.5 (C=O acid).

*N, N'didodecyl N'', N'''-2,6-Pyridinediylbis (3-oxa glutaramide) (**3**).* Triethylamine (0.4 g, 4 mmol) was added dropwise to a stirred suspension of *N*, *N'*-2,6-pyridinediylbis(3-oxa glutaramic acid) (0.68 g, 2 mmol), dodecylamine (0.74 g, 4 mmol) and BOP reagent (1.77 g, 4 mmol) in DMF (60 mL). The reaction mix-

ture was stirred at room temperature for 15 h, saturated sodium chloride solution (30 mL) was added and the mixture was extracted three times with ethyl acetate. The combined organic phases were washed successively with a 5% tartaric acid solution, 5% $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica with dichloromethane/ethanol (94/6) as eluent to give 0.99 g (73%) of compound **3** as a white solid; m.p. = 140°C; $r_f = 0.38$; IR (KBr), ν 3385, 3324 (NH), 1657 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 0.87 (t, 6H, $J = 6.3$ Hz, CH_3), 1.23–1.29 (m, 40H, CH_2), 3.30 (q, 4H, $J = 6.3$ Hz, CH_2N), 4.13 (s, 4H, CH_2O), 4.19 (s, 4H, CH_2O), 7.06 (t, 2H, $J = 5.7$ Hz, HN–CH_2), 7.75 (t, 1H, $J = 8.1$ Hz, H_4 arom.), 7.96 (d, 2H, $J = 8.1$ Hz, H_3, H_5 arom.), 9.03 (s, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7, 27.1, 29.4, 29.7, 31.9 (CH_3–$(CH_2)_{10}$–CH_2), 39.4 (CH_2N), 71.2 (CH_2O), 110.5 (C_3, C_5 arom.), 140.8 (C_4 arom.), 149.0 (C_2, C_6 arom.), 167.5, 168.7 (C=O); *Analysis : calculated* for $C_{37}H_{65}N_5O_6$, C 65.75, H 9.69, N 10.36; *found* C 65.58, H 9.76, N 10.45%.

*N, N'di-2-Pyridyl N'', N'''-2,6-Pyridinediylbis (3-oxa glutaramide) (**4**).* Triethylamine 1.11 g (11 mmol) was added to a solution of *N, N'*-2,6-pyridinediylbis (3-oxa glutaramic acid) (1.7 g, 5 mmol) prepared *in situ* in dry THF (30 mL). Isobutyl chloroformate (1.5 g, 11 mmol) was added dropwise to the stirred mixture at 0°C under argon. The reaction mixture was then stirred at 0°C for 1 h and filtered. The filtrate was cooled to −30°C and 2-lithioamino pyridine [7] (1.2 g, 12 mmol) diluted in 15 mL of THF was added dropwise over a period of 15 min under argon. The reaction mixture was then stirred for 1 h at −30°C, 3 h at room temperature, hydrolysed with 1N HCl (pH 5–6) and extracted three times with ethyl acetate. The combined organic phases were washed successively with saturated $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica with dichloromethane–ethanol (94/6) as eluent to give 0.49 g (20%) of compound **4** as a white solid; m.p. = 118 − 120°C; $r_f = 0.33$; IR (KBr), ν 3387, 3275 (NH), 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 4.26 (s, 4H, CH_2O), 4.29 (s, 4H, CH_2O), 7.00–7.06 (m, 2H, H arom.), 7.66–7.75 (m, 3H, H arom.), 7.92–7.95 (m, 2H, H arom.), 8.19–8.23 (m, 4H, H arom.), 9.02 (s, 2H, NH), 9.40 (s, 2H, NH); ^{13}C NMR ($CDCl_3$–CD_3OD), δ 72.4 (CH_2O), 111.8, 116.1, 121.8 ($C_{3,5}$ arom.), 140.2, 142.0 (C_4 arom.), 149.1, 150.6, 151.9 ($C_{2,6}$ arom.), 169.4 (C=O); *Analysis : calculated* for $C_{23}H_{23}N_7O_6$, C 55.98, H 4.70, N 19.87; *found* C 55.84, H 4.66, N 19.79%.

^1H NMR Titrations. All measurements of chemical shifts were obtained in deuterochloroform at 298°K with TMS as an internal standard. In all cases exchange was observed to be rapid on the NMR time scale, i.e., only average spectra were observed. Incremental amounts of guest were added to a solution of host ([H] = 40 mM, [G] = 4 mM – 160 mM). For each titration experiment 12 spectra were recorded by varying host/guest ratios. Measurements are made using the amide NH protons signals of the host and of the substrate. In all cases titration curves can be

TABLE I. Association constants (K_a) in chloroform, experimental ΔG_a and calculated (ΔE_{calc}) association energies for complexes between amido host and bemegride or barbital guest.

	K_a (M^{-1})	Ref.	ΔG_a (kJ mol^{-1})	ΔE_{calc} (kJ mol^{-1})	number of H-bonds
1/bem	1.9×10^2	this work	–13.00	–39.29	3
2/bem	40	"	–9.15	–29.68	3
3/bar	47	"	–9.53	–51.0	4
4/bar	7.37×10^2	"	–16.34	–60.61	5
4/phbar	2.1×10^3	"	–18.94	–58.94	5
5/bar	2.08×10^4	3b	–24.62	–71.06	6
6/bar	1.35×10^5	3c	–29.26	–72.73	6
	2.5×10^5	3d	–30.76		
6/phbar	2.8×10^5	3c	–31.06	–73.57	6
7/bar	1.37×10^6	3b. 3c	–34.99	–77.33	6
	6×10^5	3d	–32.94		
8/bar	4.1×10^4	3d	–26.29	–71.90	6

simulated with a 1 : 1 stoichiometry.

Complexation Constants. Complexation constants were calculated using the RMN-STAB program adapted from that of Shapiro and Johnson [8]. The dimerization of the barbituric hosts was considered in the calculation of the complexation constants. For bemegride a value of $K_{dim} = 4\ M^{-1}$ was taken by comparison with urea [9], while for barbital and phenobarbital the values [10] of $K_{dim} = 7\ M^{-1}$ and $8.1\ M^{-1}$ were used. The results are summarized in Table I.

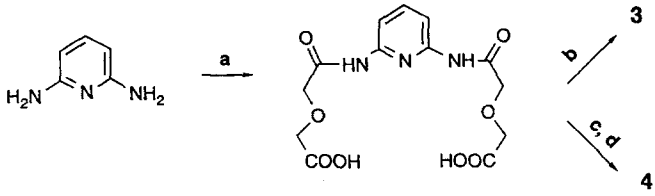
3. Results and Discussion

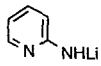
3.1. SYNTHESIS

The dithionoamido compound **2** was easily obtained in 86% yield by refluxing **1** with the Lawesson's reagent in toluene for 4 h.

The synthesis of compounds **3** and **4** is outlined in Scheme 2 and involves an intermediate diamide diacid compound prepared in THF from diglycolic anhydride and 2,6-diaminopyridine (98% yield). Condensation of this diamide diacid with dodecylamine in the presence of BOP reagent as an *in situ* activating coupling agent affords **3** in 73% yield. In contrast with the easy reaction of dodecylamine, 2-aminopyridine, used to prepare **4**, does not react whatever the coupling agents selected (BOP, BOP-Cl, isobutyl chloroformate). However, we found that when the 2-lithioamino pyridine is condensed with the mixed anhydride of the diamide diacid, **4** is formed in 20% yield. An alternate route involving reaction of the

Scheme 2



a) diglycolic anhydride, THF, 50°C ; b) BOP, $C_{12}H_{15}NH_2$; Et_3N ;
c) $ClCO_2iBu$, Et_3N ; d) 

dichloride of the diamide diacid and 2-lithioamino pyridine affords **4** in a lower yield.

3.2. MOLECULAR MECHANICS CALCULATIONS

Hydrogen-bonded associations involve the participation of at least three interaction mechanisms [11]: electrostatic, dispersive and charge-transfer. The predominant role of electrostatic forces is supported by *ab initio* calculations and by experimental correlation between the stability of X–H- -Y complexes and the acidity of the donor or the basicity of the acceptor. Thus, the calculations of structures for such types of complexes are generally carried out on the basis of electrostatic potentials. See for instance hydrogen bonding in MM2 [12].

In this work the MM2* force field was used with MACROMODEL V. 3.5x and the association energies were calculated as follows: in a first step the complex is minimized until RMS < 0.001 giving a value of the electrostatic energy. In a second step the two members of the complex are disconnected without any modification of their conformation and the electrostatic energies of the host and of the guest in such conformations are noted. The difference between the electrostatic energy of the complex and the sum of those of the isolated components gives an estimation of the expected H-bond energies. These values (ΔE_{calc}) are reported in Table I for the complexes **1**–**2**/bem and **3**–**8**/bar or phbar vs. the experimental values calculated from $\Delta G_a = -RT \log K_a$.

3.3. COMPLEXATION OF DIAMIDE **1** AND DITHIOAMIDE **2** WITH BEMEGRIDE

The bemegride molecule was selected as a guest because the structure of its complex **1**/bem has been determined by X-ray diffraction by Feibush *et al.* [6]. This result allows a rational basis for the comparison with the structures of the two complexes found by molecular modelling.

The determination of the complexation constants of both complexes was carried out by 250 MHz ^{1}H NMR with 0.2 M solutions in $CDCl_3$ (Figure 1). The N–H

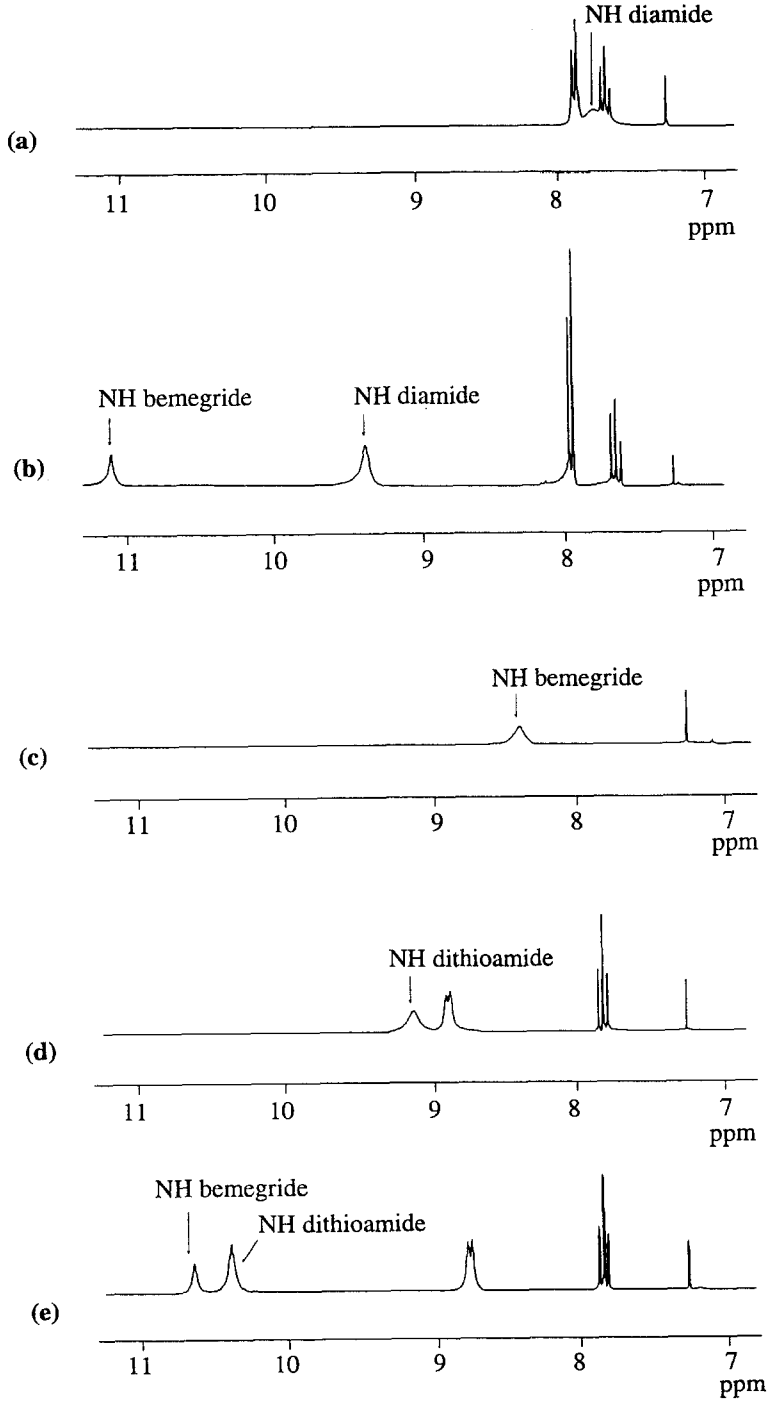


Fig. 1. ^{1}H-NMR spectra recorded in 0.2 M $CDCl_3$ solutions for diamide **1** (a), complex **1**/bem 1 : 1 (b), bemegride (c), dithioamide **2** (d), complex **2**/bem 1 : 1 (e).

protons of the ligand and of the host are deshielded indicating the formation of hydrogen bonds between the two species in solution. The complexation constants were obtained by monitoring the chemical shift of the N–H proton of the ligand as a function of the ratio ρ = [ligand]/[substrate] and subsequent calculations by the RMNSTAB program. The titration of the ligand by bemegride indicated in both cases that the equilibrium is $L + S \rightleftharpoons LS$ where L is the ligand and S the bemegride. The determination of the stability constants gave $K_a = 190 \pm 10\ M^{-1}$ for **1** and $K_a = 40 \pm 5\ M^{-1}$ for **2**. These results are contrary to the expectations based on the relative acidities of the N–H protons of the amide group compared to the thioamide group. However, they can be rationalized with the results of molecular modelling.

The validity of this modelling approach can be justified by comparing the very close distances between the ligand **1** and bemegride found by X-ray diffraction and by modelling: 2.89, 2.90 and 3.08 Å respectively for the two N. . .O and the N. . .N distances (2.93, 2.94 and 3.09 Å by X-ray diffraction) [6].

The energy of the complex with the diamide **1** is lower (–179.3 kJ mol^{-1}) than that found with the dithioamide **2** (–108.7 kJ mol^{-1}) and experimental and calculated association energies are proportional (ratio 3.1). Moreover, these calculations indicated that the carbonyl groups of the ligand **1** form angles of 12° and 26° with respect to the pyridine ring (outside and inside the guest barbital, respectively), while for the thioamide groups it is near 50° on the same side with respect to this pyridine ring. This great torsion angle reveals an important proper torsion energy (58.5 kJ mol^{-1}) which is twice that of the amide derivative. Thus, the bulky sulfur atoms induce a conformational trend which leads to weaker interactions between the ligand **2** and bemegride although NH thioamide hydrogens may be stronger acids than amides [4].

3.4. COMPLEXATION OF LIGANDS **3** AND **4** WITH BARBITAL

The addition of one equivalent of barbital in 0.04 M $CDCl_3$ solutions of compounds **3** and **4** give very little variations in ^1H NMR spectra of pure compounds, except for the NH signals (Figure 2). For compound **3**, the NH signals belonging to the 2,6-diamidopyridine moiety and those of barbital are deshielded by 0.16 and 0.9 ppm, respectively. For compound **4**, the two types of NH signals undergo a weak downfield shift (0.86 and 0.52 ppm) while those of barbital are greatly deshielded by 3.99 ppm.

In the two cases, these downfield variations suggest the formation in chloroform solution of H-bonds between the host **3** and **4** and the guest barbital. IR spectroscopy confirms this behaviour (Figure 3) i.e. the addition of barbital to compound **4** in 0.025 M chloroform solution increases the intensity of the broad stretching band (bound NH) at 3275 cm^{-1} and decreases the bands at ca. 3400 cm^{-1} (free NH for ligand and barbital).

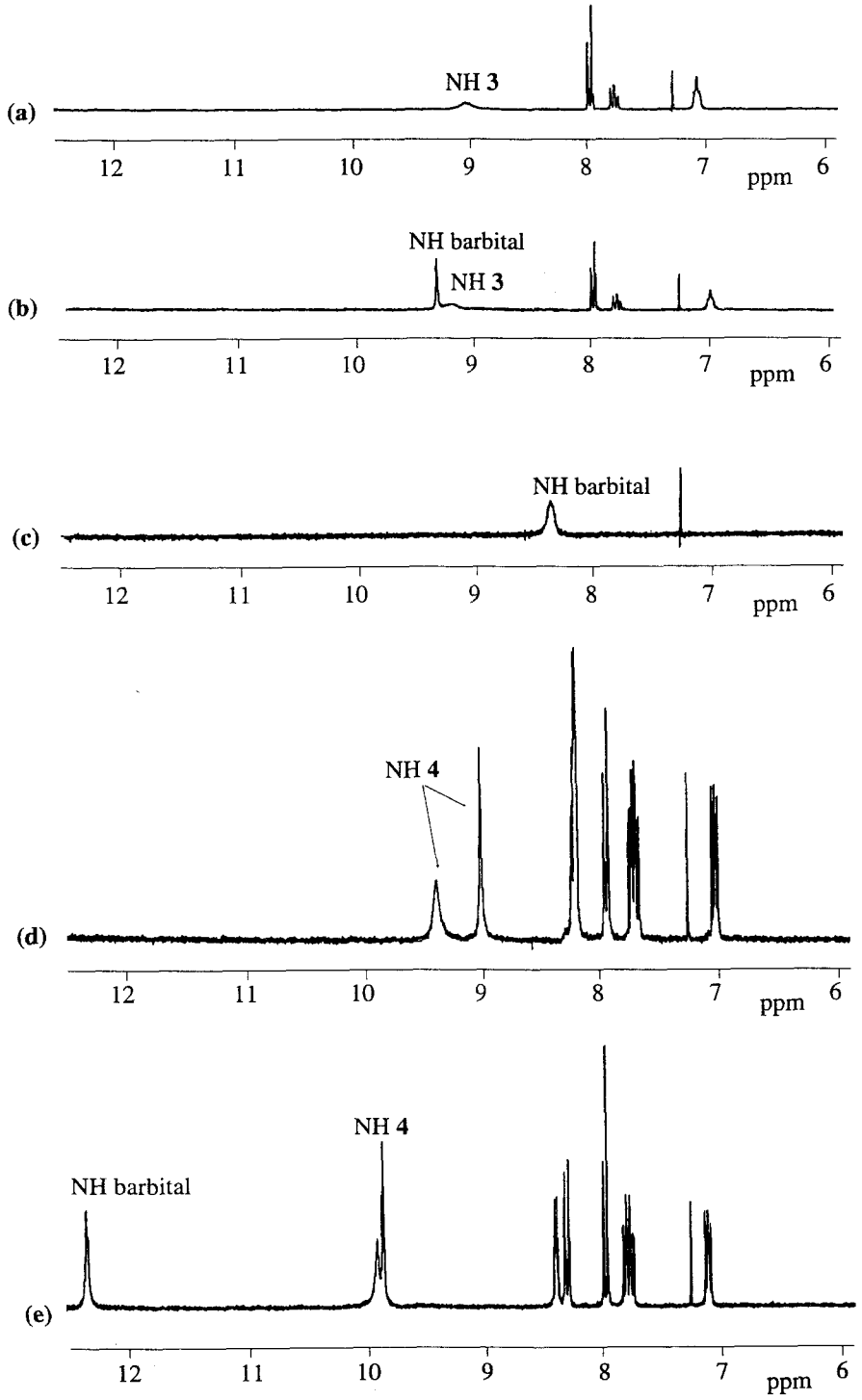


Fig. 2. ^{1}H-NMR spectra recorded in 0.04 M $CDCl_3$ solutions for compound **3** (a), complex **3**/bar 1 : 1 (b), barbital (c), compound **4** (d) and complex **4**/bar 1 : 1 (e).

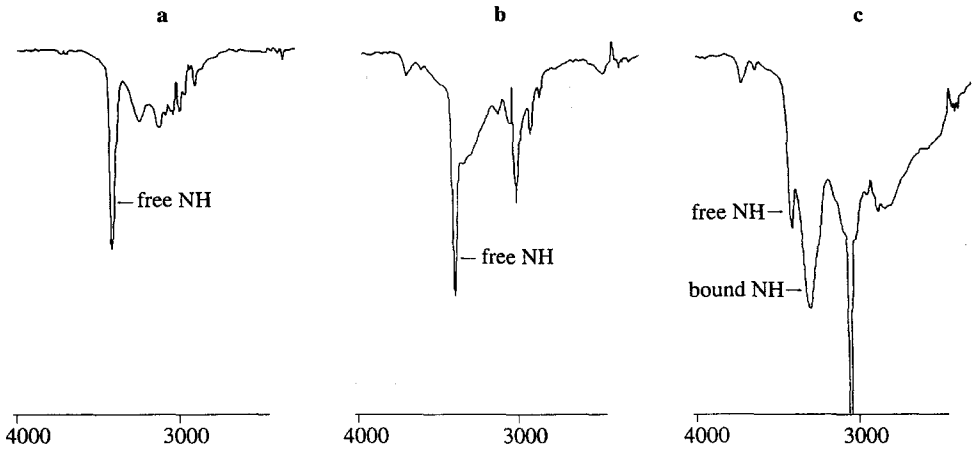
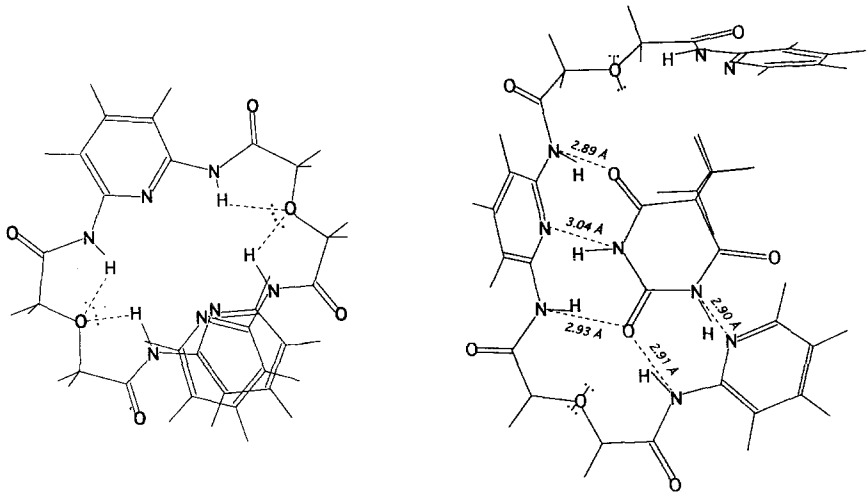


Fig. 3. Representation of νNH bands in $CHCl_3$ (M/40) of barbital (a), compound **4** (b) and a 1 : 1 mixture of **4** and barbital (c).



4 **4**/bar

Fig. 4. Minimum energy conformation of the compound **4** and the complex **4**/bar.

The stability constants were measured with 0.04 M solutions of ligand in $CDCl_3$ in a similar manner as for **1** and **2** giving the values $K_a = 47 \pm 9\ M^{-1}$ for **3**/bar and $K_a = 737 \pm 70\ M^{-1}$ for **4**/bar.

Molecular modelling experiments were performed for compounds **3**, **4** and also for compounds **5**–**8** described by Hamilton [3b–d] (Scheme 1) and their complexes with barbital.

TABLE II. ΔG_a experimental and calculated as a function of the number of effective H-bonds.

number of H-bonds	$-\Delta G_a^{exp}$ (kJ mol^{-1})	$-\Delta G_a^{calc}$ (kJ mol^{-1})
3	9.15–13.00	15.3 ± 3
4	9.53	20.4 ± 4
5	16.34–18.94	25.5 ± 5
6	24.62–34.99	30.6 ± 6

For the free ligand **4** it is noteworthy that this compound displays a helical secondary structure [13] as seen in Figure 4. The two terminal pyridinyl rings overlap each other in a face-to-face arrangement. This behaviour compares well with that recently observed [14] by X-ray diffraction and NMR methods on similar compounds derived from 2,6-pyridine carboxamide and anthranilamide. The pitch of the helix is also narrow, with close contact between the terminal pyridinyl rings, i.e. a distance of only 3.71 Å between the two pyridine N atoms (3.69 Å in the quoted example).

For the complex the recognition of barbital involves hydrogen bonding in a dissymetric manner with respect to the plane of symmetry of barbital with four hydrogen bonds for **3** and five for **4** (Figure 4). For the complex with compound **5** six hydrogen bonds are involved and the symmetry of the complex is the same as that of the host barbital molecule. While the complex **3**/bar presents one supplementary hydrogen bonding stabilization, it is less stable than the **1**/bem complex by a factor of 4. This can be related to the lack of symmetry of the complex and to the influence of the resulting interactions involving the ethyl groups of the barbital. When the guest barbital is replaced by the phenobarbital, the stability constant for the complex with **4** ($K_a = 2100 \pm 100$ M^{-1}) is multiplied by a factor of 3. This increased stability can be mainly related to stacking interactions between the phenyl group and one of the terminal pyridinyl groups (3.4 Å between the two planes).

If we assume that the main stabilizing factor is roughly related to the number of hydrogen bonds formed in the complex [15], it is noteworthy that the stability constant for **4** (five hydrogen bonds) is 16 times higher than that of **3** (four hydrogen bonds).

The correlation between ΔG_a and the H-bond energies calculated on the basis of 5.10 ± 1 kJ mol^{-1} for one H-bond [11, 15] is very approximate (see Table II).

On the contrary, a good correlation ($r = 0.98$) is obtained by molecular mechanics calculations as previously described and shown in Figure 5 for complexes with barbital and phenobarbital. The results obtained for bemegride clearly deviate from this correlation.

This study illustrates the limitations of the method. Particularly, taking into account that electrostatic interactions as, for instance, simulated by MM2* constitutes only a rough determination of the H-bond interaction for purine or pyrimidine

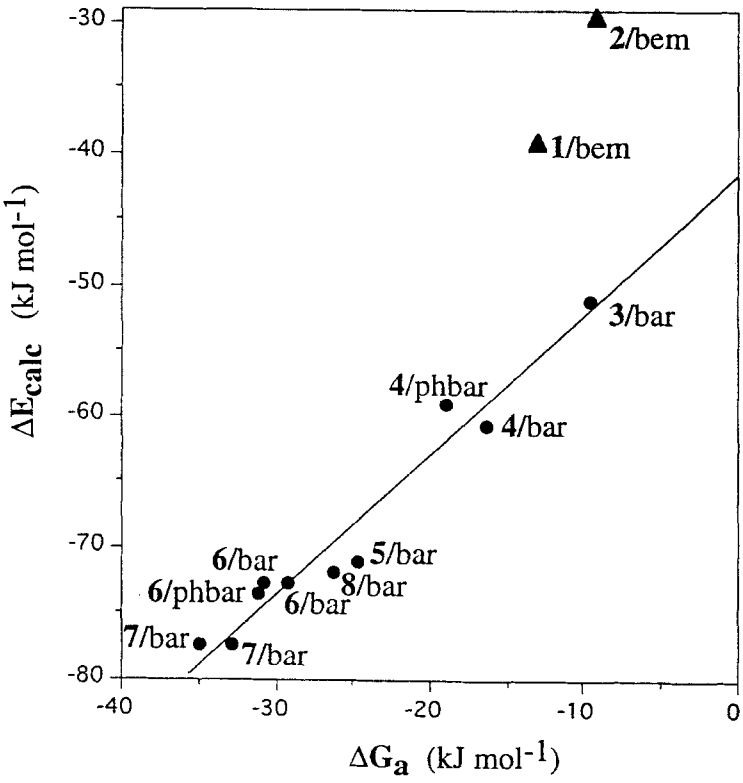


Fig. 5. Correlation ΔG_a vs. ΔE_{calc} for a series of complexes between ligands **1–8** and barbital, phenobarbital or bemegride.

base pairs, Jorgensen [16], using the OPLS potential functions and the BOSS program, recently showed that secondary electrostatic interactions might play an important role in the stability of complexes involving three hydrogen bonds. Such a result shows that a good correlation might be obtained only in a homogeneous series of neutral host–guest complexes. On the other hand, the energy of reorganization of the ligand seems to play a minor role in the association phenomenon of these molecules.

4. Conclusions

Three new derivatives of 2,6-diaminopyridine were synthesized. The dithioamide derivative **2** vs. the diamide **1** does not display the greatest association constant as expected based on the relative acidities of the N–H protons of the thioamide and amide groups. This behaviour is explained by the bulky sulfur atom and its influence on the association phenomenon.

The two tetramide derivatives **3** and **4** with two dimethyleneoxy moieties give examples of unusual diamidopyridine compounds displaying four or five H-bonds with barbital. For these latter compounds and other ligands reported in the literature displaying six H-bonds, the complexation free energies ΔG_a in deuterochloroform are reasonably correlated with the calculated H-bond energies. However, due to the complexity of the H-bond phenomenon and its poor translation in the MM2 force field the correlation cannot be extended to other barbiturates like bemegride.

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