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Synthesis, characterization and computational modeling of cyclen substituted with dendrimeric branches. Dendrimeric and macrocyclic moieties working together in a collective fashion

Jorge A. Cruz-Morales, Patricia Guadarrama*

Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Apartado Postal 70-360, CU, Coyoacán, México DF 04510, México

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Abstract

A molecular system, formed by the aza-macrocycle known as cyclen and functionalized dendrons, was synthesized in a convergent fashion. An aliphatic spacer between the two molecular units was incorporated to avoid the sterical hindrances. The *N*-acylation reactions to carry out the cyclen substitution, particularly those in solid state, resulted in very good yields since no further purifications were necessary. The obtained molecular system was characterized by common spectroscopic techniques. According to X-ray analysis (powder analysis), there is a random arrangement of the molecules, with an average interplanar distance (the most recurrent) of 4.8 Å between first neighbors. A theoretical study at DFT level of theory was carried out, simulating the inclusion process of Ni^{2+} into two different model molecules (**A** and **C**), with and without dendrons present. According to the calculated interaction energies in the inclusion process, there is a significant contribution in terms of energy (−60.89 Kcal/mol) due to the presence of functionalized dendrons, which enfold the metal ion, forming a molecular cage and increasing in this way the degree of pre-organization due to cooperative effects created by the dendrimeric environment. These molecular arrangements would be relevant in areas like catalysis, having influence on the selectivity of catalytic processes, by controlling the accessibility of the active site (the metal atom) via sterical hindrances.

Further experimental work of the incorporation of metal ions of the first transition series will be done in a rational way, taking into account the theoretical results obtained so far.

Keywords: Aza-macrocycles; Dendrimers; Collective effects; Convergent synthesis; DFT Methods

1. Introduction

Since their discover [1], the macrocyclic ligands have been successfully used in complexation processes by means of the possibility to have suitable cavity sizes and different donor atoms (N, O, S, etc) as well as for the observed extra thermodynamic stabilization due to the macrocyclic effect [2].

Among others, some applications founded for macrocycles are: (i) as ion-carriers between different phases; (ii) as ion separation agents; (iii) as ion-based sensors and (iv) as isotopes-separating agents.

Aza-macrocycles (with nitrogen as heteroatom) have found also many applications in medical diagnosis and therapy when they form complexes with metal ions; particularly the complexes with paramagnetic lanthanides like Gd (III) which are in current clinical use as contrast agents for magnetic resonance imaging [3]. In molecular recognition, aza-macrocycle-metal complexes have shown abilities as binding sites [4].

Macrocyclic compounds by themselves confer high pre-organization conditions, which are very convenient in terms of complexation stability and molecular recognition selectivity. This term of pre-organization, coined by Cram [5], refers to the degree of similitude in the arrangement of the donor atoms before and after the complexation, that is to say, the similitude between the free ligand as a host and the formed host-guest complex (e.g. a metal ion as guest).

* Corresponding author. Tel.: +52 55 56224594; fax: +52 55 56161201.
E-mail address: patriciagua@correo.unam.mx (P. Guadarrama).

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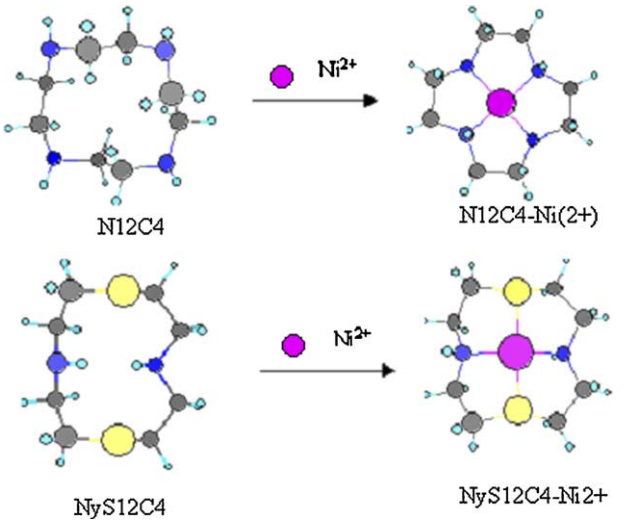


Fig. 1. Pre-organization of two different macrocycles.

The degree of pre-organization usually depends on the flexibility of the aliphatic framework forming the macrocycle and also depends on the hardness-softness features of the heteroatoms involved in the structures.

It was observed before [6] that there is a compromise in energy between the pre-organization of the macrocycles and their self-stabilization by means of internal hydrogen bonds (or another non-covalent interaction). In some cases (e.g. macrocycle N12C4 in Fig. 1), the macrocycles are conformationally able to interact with metal ions, whereas in other cases (e.g. macrocycle NyS12C4), the macrocycles become unable to interact 'easily' with metal ions because they are collapsed before the complexation occurs. To interact with metal ions, those 'collapsed' macrocycles must pay the energetic price by some conformational rearrangements, resulting in a lower interaction energy with metal guests.

Considering some of the factors involved in complexation processes, it has been generally established that the level of pre-organization expected in a variety of ligands follows the next order:

LIGAND

Unidentate Chelate Macrocyclic Macrocyclic + chelating donor groups Cryptand

→ Increasing level of pre-organization

According to the above information, the combination of macrocycles with an additional set of donor groups appears as an attractive alternative, in terms of pre-organization conditions. In the present study, the incorporation of such additional donor groups in a multifunctional fashion was carried out by the substitution of macrocycles like cyclen (1,4,7,10-tetraaza-cyclododecane) with functionalized dendrimeric branches (dendrons) bearing additional polar groups. Theoretical work previously done [6] showed that, among a series of macrocycles (like those illustrated in Fig. 2),

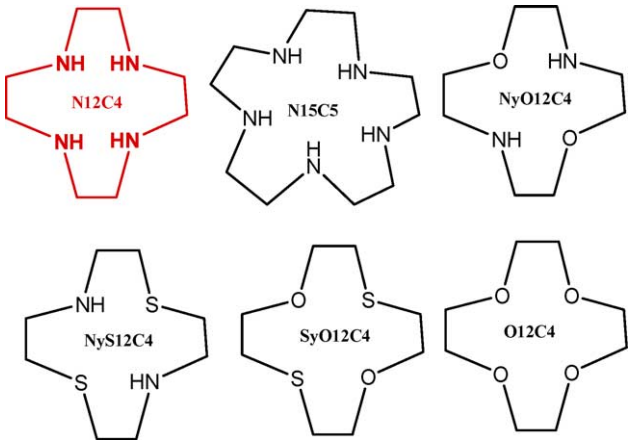


Fig. 2. Hetero-Macrocycles. Cyclen, labeled as N12C4, is shown in red (For interpretation of the reference to colour in this legend, the reader is referred to the web version of this article).

the macrocycle cyclen (labeled as N12C4 in red) was the best candidate in terms of interaction energy, when complexes with transition metals (Fe, Ni, Cu, Zn) are formed.

Furthermore, the previous calculations showed that the attachment of some model dendrons to cyclen results in an energetically favorable cooperative behavior ('umbrella-like' arrangements).

Therefore, in order to design and synthesize novel, chemically collective systems and, taking into account the preliminary theoretical results, the aza-macrocycle known as cyclen was substituted with dendrons separately prepared according to the procedures described by Newkome et al. [7]. Two different aliphatic spacers were incorporated between cyclen and dendrons to avoid sterical hindrances throughout the synthesis. In order to study the inclusion process of metal ions into the molecular systems synthesized, theoretical calculations were carried out at DFT (density functional theory) level. In terms of interaction energy, a collective effect due to the dendrimeric branches was observed when the incorporation of metal transition ions (e.g. Ni^{2+}) was simulated.

2. Experimental section

2.1. Materials and methods

2.1.1. Materials

Tosylate chloride was crystallized from petroleum ether. All other reagents were used as received from Aldrich and Baker.

2.1.2. Measurements

FT-IR spectra: Spectrometer Nicolet (FT-IR) 510p.

NMR ^{1}H, ^{13}C: Spectrometer Bruker 400 MHz.

X-Ray analysis: Diffractometer Brucker-AXS, model D8-Advance (radiation Cu Kα with graphite monochromator).

2.1.3. Dendron synthesis

Di-tertbutyl-4-nitro-4-[2-(tertbutoxycarbonyl)ethyl]-1,7-heptanodiate (**3**).

A mixture of nitromethane (6.1 g, 100 mmol) and benzylammonium hydroxide (3 ml of 40% solution in MeOH) was stirred at 65–70 °C in 20 ml of dioxane. Further addition of tertbutylacrylate (39.7 g; 310 mmol) was carried out, maintaining the temperature at 70–80 °C for 1 h. The mixture was concentrated and re-dissolved in $CHCl_3$ (200 ml) and washed with 50 ml of HCl (10%) and with brine (saturated solution NaCl/H_20) (3×50 ml) and then dried with $MgSO_4$. The solvent was removed, resulting in a yellow solid. By crystallization from EtOH, the compound (**3**) was obtained in 72% yield as a crystalline white solid (m.p. 98–100 °C). *FT-IR* (cm^{-1}): 2975 (C–H aliph.), 1724 (C=O), 1536 (–NO_2). NMR ($CDCl_3$) ^1H (∂(ppm)): 1.42 (s, 27H, OtBu), 2.25 (s, 12H, aliph.). ^{13}C: 26.89 and 28.53 (C_6 and C_9), 29.66 and 79.65 (C_5 and C_8), 92.46 and 170.42 (C_4 and C_7 (CO)).

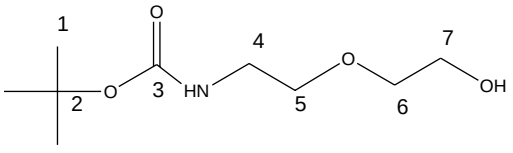
Di-tertbutyl-4-amino-4-[2-(tertbutoxycarbonyl)ethyl]-1,7-heptanodiate. (**4**)

A solution of compound (**3**) (4.46 g; 10 mmol) in absolute EtOH (100 ml) was prepared and Raney nickel catalyst (4 g) was added. The mixture was shaken under hydrogen atmosphere (40 psi) at room temperature during 28 h, time when no further hydrogen was consumed. The catalyst was filtered through celite and washed with absolute EtOH. The solvent was removed to give a yellow viscous liquid which was purified by chromatography on SiO_2 column, eluting with AcOEt to obtain a white solid in 88% yield (m.p. 51–52 °C). *FT-IR* (cm^{-1}): 3376 (–NH_2), 2979 (C–H aliph.), 1724 (C=O).

NMR ($CDCl_3$) ^1H (∂(ppm)): 1.43 (s, 27H, OtBu), 1.6 (t, 6H, aliph.), 1.9(s,2H, NH), 2.23 (t, 6H, aliph. CO). ^{13}C 28.3 (C_9), 30.20 and 34.61(C_6 and C_5), 52.56 and 80.53(C_4 and C_8), 173.27 (C_7(CO)).

Aliphatic spacer (**6**)

[*N*-tertbutoxycarbonyl-2-(aminoethoxy)] ethanol (precursor)



A solution of di-tertbutyl bicarbonate (t-BOC) (14.6 g, 66.9 mmol) in THF (50 ml) was stirred at room temperature and 2-(2-aminoethoxy) ethanol (7 g, 66.6 mmol) was added slowly with liberation of CO_2. The mixture was refluxed for 4 h. Afterwards the mixture was concentrated at vacuum to obtain an oil which was chromatographed on SiO_2 eluting with AcOEt to achieve the final product in 75% yield (yellow oil).

FT-IR (cm^{-1}): 3409 (OH), 2931 (C–H aliph.), 1700 (C=O), 3409 (–NH), 1100 (–O–).

NMR ($CDCl_3$) ^1H (∂(ppm)): 1.4 (s, 9H, methyl groups), 2.90 (s, 1H, NH), 3.28 (d, 2H, CH_2–OH), 3.52 (m, 4H, CH_2–O–CH_2) 3.69 (s, 2H, N–CH_2) 5.21 (s, 1H, OH). ^{13}C: 26.62 and 38.58 (C_1 and C_4), 59.83 and 68.52 (C_7 and C_2), 70.50 and 74.99 (C_5 and C_6) 154.50 (C_3).

[*N*-tertbutoxycarbonyl-2-(aminoethoxy)] ethyltosylate (**6**)

12 g (58.5 mmol) of precursor ([*N*-tertbutoxycarbonyl-2-(aminoethoxy)] ethanol) and 22 ml of pyridine was mixed in dichloromethane (100 ml) at room temperature and anhydride conditions. 13 g (58.6 mmol) of tosylate chloride newly crystallized was added and, after 1 day, the reaction mixture was treated with diluted HCl (10 ml). The product was extracted with $CHCl_3$ (2×100 ml), washed with H_20 (2×100 ml) and dried with $MgSO_4$. The solvent was removed to obtain the product as a yellow oil. Yield: 80%. *FT-IR* (cm^{-1}): 3403 (–NH), 2979 (C–H aliph.), 1727 (C=O), 1390 (–SO_2), 1159 (–O–), 1549 (C=C arom.).

NMR ($CDCl_3$) ^1H (∂(ppm)): 1.19 (s, 9H, methyl groups), 2.13 (s, 3H, arom-CH_3), 2.94 (d, 2H, NH_2), 3.21 (t, 2H,O–CH_2) 3.34 (s, 1H, NH) 3.41 (t, 2H, CH_2–O), 3.61 (t, 2H, CH_2-Tos), 7.76 (t, 4H, *ortho*-arom.), 7.57 (t, 4H, *para*-arom.). ^{13}C: 22.45 and 29.70 (C_{12} and C_1), 44.36 and 62.28 (C_4 and C_7), 70.05 and 71.30 (C_6 and C_2), 72.02 and 125.54 (C_5 and C_9), 131.24 and 138.54 (C_{10} and C_8), 149.99 and 157.49 (C_{11} and C_3).

1,4,7,10-Tetra-[*N*-(tertbutoxycarbonyl-2-(aminoethoxy (ethyl)))]-1,4,7,10-tetraazacyclo dodecane (**7**)

To a solution of cyclen (0.1 g, 0.58 mmol) in DMF (20 ml) was added K_2CO_3 (42 mg) under nitrogen atmosphere at $T=60$ °C. Slow addition of aliphatic spacer (**6**) (849 mg, 2.36 mmol) was carried out for 2 h. The reaction mixture was stirred for 1 day at 60 °C, then it was cooled at room temperature, the suspended solids were filtered and the solvent was removed in vacuum to obtain a brown oil which was crhomatographed on SiO_2, eluting with AcOEt. According to NMR spectra, mono-, di- and tri-substitution could happen.

Yield: 10%. FT-IR (cm^{-1}): 2975 (C–H aliph.), 1590 (–NH–), 1779 (C=O), 1153 (–O–).

NMR ($CDCl_3$) ^1H (∂(ppm)): 1.54 (s, 36H, -t-Boc), 2.33 (s, 16H, cyclen), 3.18 (m, 8H methylene groups, neighbors to cyclen), 3.37 (m, 8H, methylene groups, neighbors to amine), 3.90 (m, 16H, CH_2–O).

2.1.4. Solid-state reaction

1,4,7,10-Tetra-[3-carboxy-propanoyl]- 1,4,7,10-tetraazacyclododecane (**9**).

350 mg (3.50 mmol) of succinic anhydride and 150 mg (0.87 mmol) of cyclen were placed in a mortar and the reaction mixture was grinded by repeated contacts over and over again for 2 h, until the appearance was changed to a viscous solid. The product was obtained as a gray viscous solid in 90% yield. FT-IR (cm^{-1}): 3200–2900 (–COOH), 1750 (C=O), 1610 (N–C=O). NMR: (D_2O) ^1H (∂(ppm)): 1.80 (d, 8H, CO–CH_2–), 2.24 (d, 8H, –CH_2–COO–), 3.46 (s, 16H, macrocycle CH_2's), 10.40–13.60 (H-acids). ^{13}C: 27.96

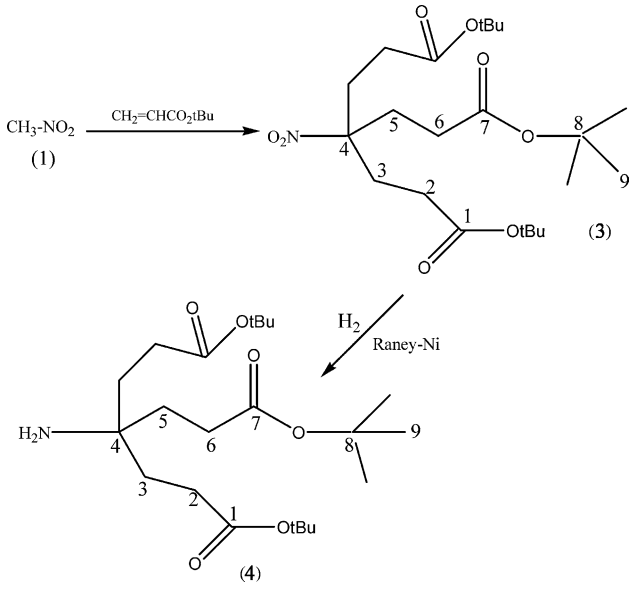


Fig. 3. Synthesis of Dendron (**4**).

and 29.01 (C_3 and C_4), 44.45 (C_1), 186.00 and 189.01 (C_2 and C_5).

1,4,7,10-Tetra-[1-propanoyl (*N*-[3′-(tertbutoxycarbonyl)-1′,1′-bis[2″-(tertbutoxycarbonyl) ethyl] propyl]-1′-amino]carbonyl])]-1,4,7,10-tetraazaciclododecane (**10**).

140 mg (0.24 mmol) of compound (**9**) was dissolved in $CHCl_3$ (15 ml) at pH = 5 and DCC (dicyclohexylcarbodiimide) (410 mg) was added. The reaction mixture was refluxed and, after 2 h, dendron (**4**) (409 mg, 0.98 mmol) was put in there. The reaction was followed by tlc (eluting with AcOET:hexane (2:1)). After 20 h, the mixture was cooled at room temperature, filtering the precipitate (dicyclohexylurea) formed in the course of the reaction. Unreacted DCC was eliminated by acetic acid (15 ml). The crude product was washed with $NaHCO_3$ − 10% (3 × 10 ml) and H_20 (1 × 10 ml) and dried with $MgSO_4$. The solvent was removed and the product was re-dissolved with petroleum ether. After evacuation of the solvent, a viscous solid yellow-colored was obtained. Yield: 45%. FT-IR (cm^{-1}): 2975 (C–H aliph.), 1727 (C=O), 1530 (–CO–NH–). NMR ($CDCl_3$) ^1H (∂(ppm)): 1.44 (s, 108H, OtBu), 1.76 (m, 24H, –N–C–CH_2–), 1.94 (m, 24H, –CH_2–COOtBu), 2.70 (m, 16H, –COO–CH_2–CH_2–COO–), 3.21 (m, 16H, cyclen CH_2's). ^{13}C: 25.62 and 26.10 (C_8 and C_3), 28.03 and 29.95 (C_{11} and C_4), 33.92 and 34.35 (C_6 and C_7), 52.29 and 80.28 (C_1 and C_{10}), 172.38 (C_2 and C_5), 173.03 (C_9).

2.1.5. Computational details

All the initial structures were equilibrated by conformational searching (Force Field OPLS-AA [8]) using the Monte Carlo statistical method [9] included in Macromodel software; choosing the algorithm of multiple minimum (MCMM) [10] without limits on the number of variable torsions allowed in the search. The Geometry optimizations were carried out at DFT level of theory, using the hybrid functional BHandHLYP [11], which considers the exchange term as 50% of exact Hartree-Fock (HF) exchange functional and 50% of Slater local exchange functional, and the correlation term as the Lee-Yang-Parr local and nonlocal functional [12]. The used basis set LACVP (included in Jaguar 5.0 program [13]); considers effective core potentials (ECP's) generated to replace the innermost core electron for third-row

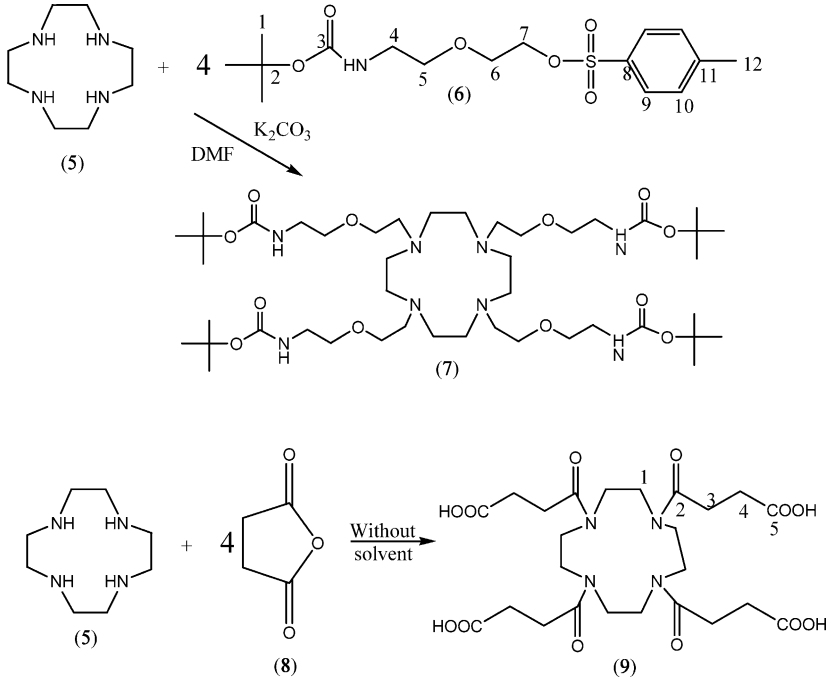


Fig. 4. Cyclen functionalization by *N*-alkylation (compound (**7**)) and *N*-acylation (compound (**9**)).

(K–Cu), fourth-row (Rb–Ag) and fifth-row (Cs–Au), in order to incorporate the relativistic effects in case of Nickel atom (many electrons). LACVP, as well as LAV3P and LACV3P basis sets use the pseudospectral method while all other ECP basis sets use the analytic method.

Molecular dynamics (MD) calculations were carried out at heating rate of 1 kcal per atom per femtosecond (fs) and a target temperature of 300 K [14]. Successive conformations of each system were generated by the integration of Newton's laws of motions, resulting in trajectories that specify how the positions and the velocities of the particles in the systems vary with time, under the Beeman's algorithm [15].

3. Results and discussion

3.1. Synthesis

According to Fig. 3, after successive Michael-type additions between the carbanion of nitromethane and tertbutylacrylate, aliphatic dendron (**3**) was obtained in good yield (72%) as a crystalline white solid. The NH_2 focal point, required to attach the dendrimeric moieties to cyclen, was incorporated by catalytic hydrogenation of dendron (**3**) at room temperature to achieve the dendron (**4**) in 88% yield (white solid).

An important feature of the dendron (**4**) is an appropriate equilibrium between the reactivity of the focal point ($-NH_2$) on the one hand, and the sterical effects on the other hand. Since a quaternary carbon is adjacent to the $-NH_2$ group, this reactive group posses a fairly low reactivity, enough to permit that structural rearrangements can take place when the dendron reacts with something else, avoiding in some extent the sterical hindrances.

In terms of design, the aliphatic framework of dendron (**4**) was incorporated to improve the solubility properties, but also to allow the free-movements for encapsulation purposes. The terminal carboxy groups are expected to interact in a collective fashion as a part of the molecular system.

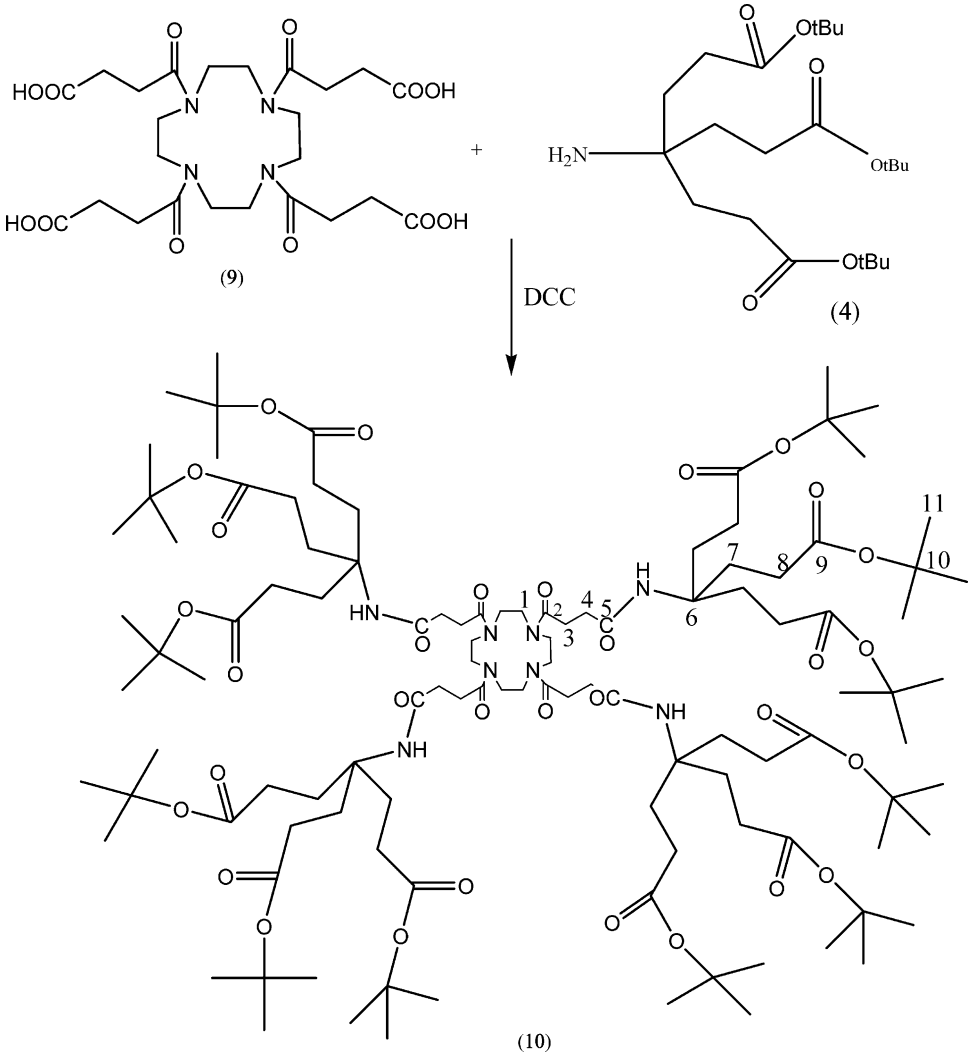


Fig. 5. Synthesis of molecule (**10**) by DCC coupling.

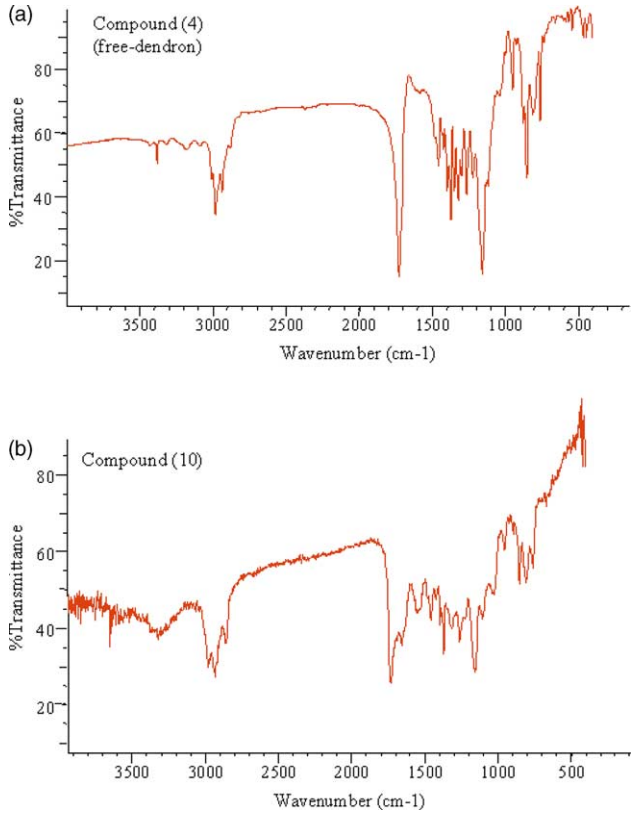


Fig. 6. Comparison of FT-IR spectra. Compound (**9**) is the precursor and Compound (**10**) is the product.

The functionalization of the aza-macrocycle, cyclen, started with the incorporation of aliphatic spacers to connect it afterwards with dendron (**4**). In Fig. 4 are shown the two alternatives tested to attach aliphatic spacers to cyclen, obtaining compounds (**7**) and (**9**).

As it has been reported, the main synthetic routes for the substitution of aza-macrocycles are: *N*-alkylation or *N*-acylation reactions. Comparing these two synthetic pathways, the *N*-acylation gave the best results in the present study. Whereas compound (**7**) was obtained in a very low yield (10%) by *N*-alkylation reactions of cyclen in presence of the alkyl-tosylate (**6**) previously prepared (see experimental section), the *N*-acylation reaction by the ring opening of succinic anhydride resulted in a very good yield (90%) to obtain compound (**9**). Further purification in case of compound (**9**) was not necessary since the reaction was carried out in solid state (in absence of any solvent). Compound (**9**) was soluble in common organic solvents, even in water. The solid–solid reaction required repeated contacts over and over again but it was very efficient and waste-free, which is environmentally important. The solid state reactions has been described as thermal intracrystalline conversions where loss of volatile fragments might be involved [16]. Thus, reactions like complexation, hydrogenation, aliphatic substitutions among others, can be carried out in solid state.

By *N*-acylation reactions, not only higher yields were obtained but also further reactions considered here as part of the synthetic route, were avoided. If we compare compounds (**7**) and (**9**), while compound (**9**) is ready to react with the dendron (**4**) by means of the COOH groups, in a convergent fashion, compound (**7**) needs to be transform, removing the t-BOC protecting groups for the subsequent formation of the isocyanate groups, in presence of triphosgene, in order to react afterwards with the $-NH_2$ focal point of the dendron (**4**).

The coupling of compounds (**9**) and (**4**) in presence of DCC resulted in compound (**10**) in 45% yield (Fig. 5)

Infrared spectra gave a good insight of the coupling reaction shown in Fig. 5. The disappearance of the broad band due to –COOH group at 3200 cm^{-1} (O–H vibration) coming from the cyclen-spacer moiety, as well as the enlargement of the N–H bond in compound (**10**) in comparison with that bond present in the free dendron (**4**), are both evidences of the transformation. The vibration

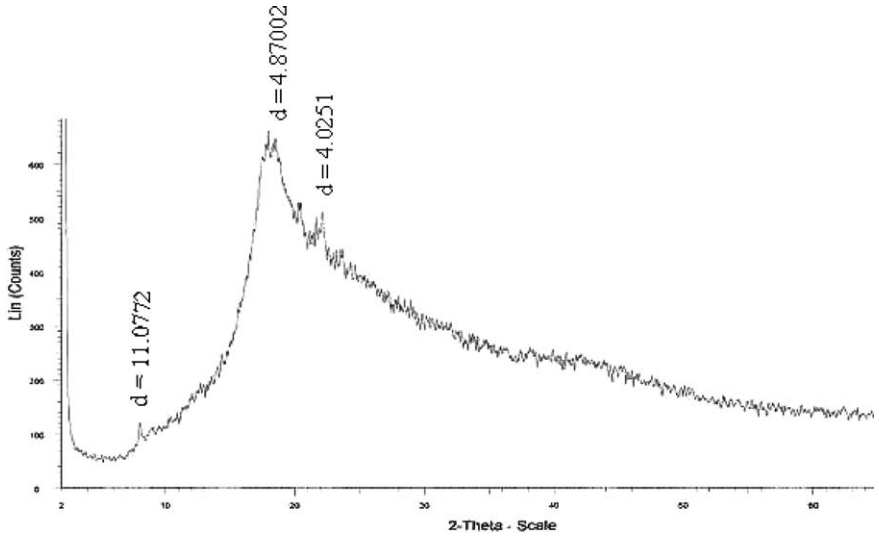


Fig. 7. Diffraction pattern of compound (**10**).

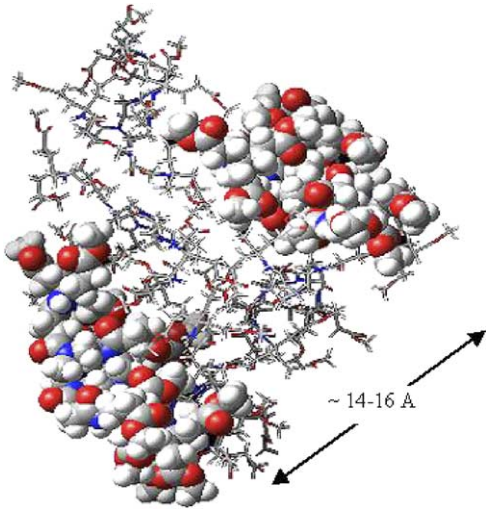


Fig. 8. Cumulus modeled by molecular dynamics, with six molecules in an approximate interplanar distance of 16/4 angstroms.

frequency (μm) of the N–H bonds in compound (**10**) and free dendron (**4**) are 6.06 (1650 cm^{-1}) and 6.66 (1500 cm^{-1}), respectively. Considering that the frequencies are inversely proportional to the bond distance, the slight elongation of the N–H bond adjacent to the carbonyl group in compound (**10**) is an indication of the aliphatic substitution (Fig. 6).

The NMR ^{1}H data described above in experimental section are in agreement with the proposed structures. Compound (**10**) is a viscous solid (amorphous) randomly oriented, according with the powder X-ray diffraction analysis (Fig. 7). From the gaussian-like curve, generated over 2 h approximately (step: 0.020°, step time:2.4 s) at room temperature, it is only possible to distinguish an average distance of 4.87002 Å between molecular planes, at first neighbors, as predominant distance. This molecular arrangement can be visualized in Fig. 8 where, arbitrarily, six of the molecules under study were put together and a molecular dynamics calculation was carried out (see computational details).

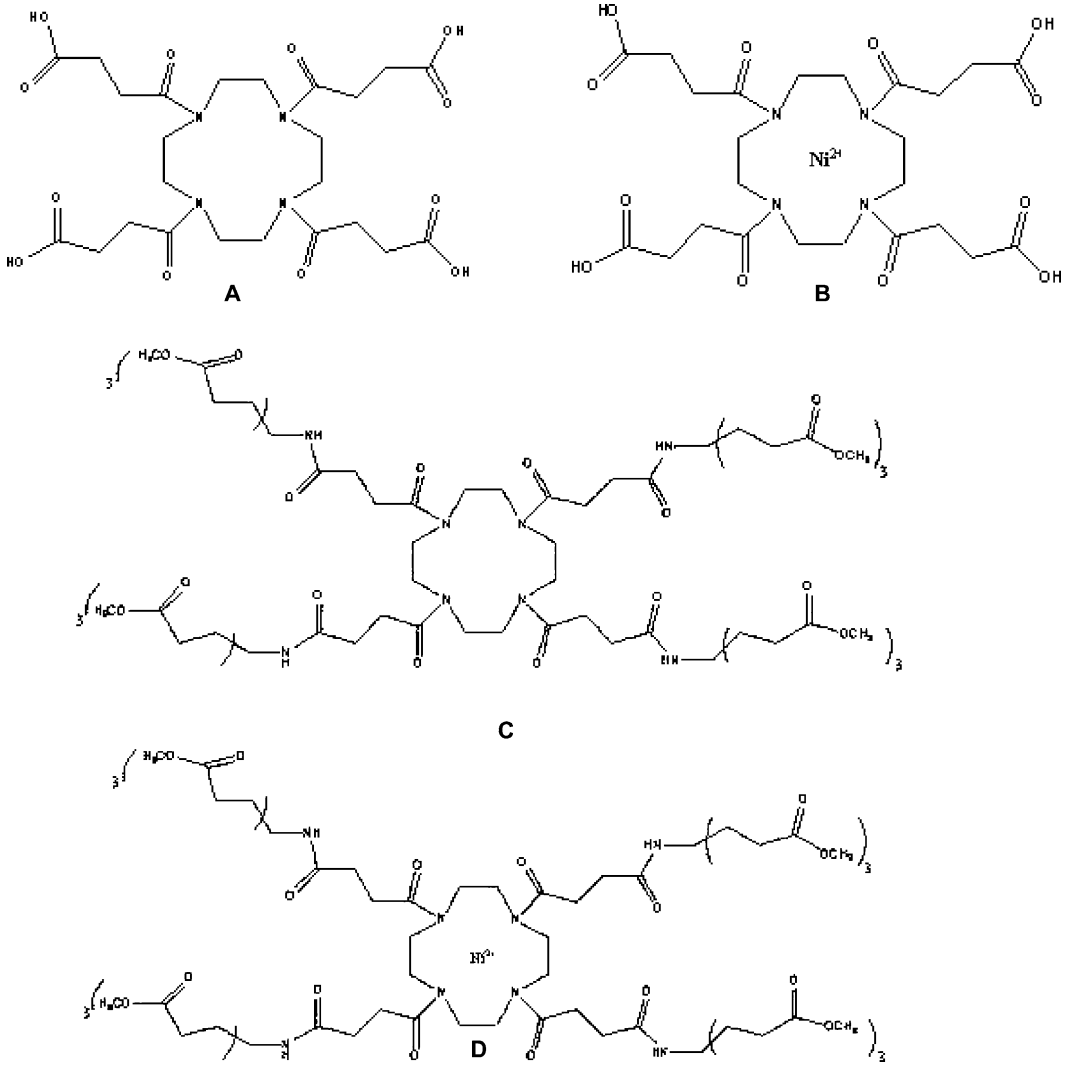


Fig. 9. Model compounds taken for the theoretical study. Molecules **B** and **D** correspond to the hypothetical inclusion of Ni^{2+}. Molecules **A** and **C** correspond to the synthesized compounds (**9**) and (**10**), respectively.

Table 1
Total energies (Ha) calculated at BHandHLYP/LACVP level of theory

Molecule	Total energy
A	−2038.095299
B	−2205.964385
C	−5755.766243
D	−5923.732370
Ni^{2+}	−167.320198

1Ha = 627.51 kcal/mol.

To distinguish the limits of each molecule, the two terminal entities are illustrated as full-filled models whereas the other four are showed in a wire type. It can be observed that roughly 4 of the 6 molecules are aligned along the double arrow showed in the Fig. 8, in a nearly distance of 16 Å which is in agreement with the more recurrent distance of 16/4 Å observed in X-ray spectrum.

3.2. Theoretical study

3.2.1. Interaction energy calculations

In order to evaluate the collective effects, presumably due to the dendrimeric environment, theoretical calculations were carried out considering, on the one hand, the molecule (**10**) with and without metal ion incorporated and, on the other hand, the precursor (**9**) (without dendrones) in the same two situations described above for molecule (**10**). In both cases the Ni^{2+} was considered as guest, in a configuration of low spin (square planar geometry). Interaction energies were obtained according to the variation method [17] which indirectly estimates such energies as the difference between the energy of the 'complex' and the energies of their isolated parts ($\Delta E = E_{complex} - (E_{host} + E_{metal\ ion}$).

As it was mentioned in computational details, the basis set labeled as LACVP was used in order to incorporate the relativistic effects caused by the many electrons of atoms like transition metal ions [18]. Into the DFT method, the hybrid functional chosen was BHandHLYP, in spite of its good results in the evaluation of non-covalent interactions [e.g. Ref. 19]. The model compounds calculated are shown in Fig. 9. Molecules **B** and **D** correspond to the initial structures for the hypothetical inclusion of Ni^{2+}. Molecules **A** and **C** correspond to the synthesized compounds (**9**) and (**10**), respectively.

It is important to mention that the metal ion in structures **B** and **D** was deliberately put inside the aza-macrocycle, as initial input, only to start the geometry optimization calculations with an initial square geometry for the Ni^{2+}. Hence, the electronic distribution around the metal, apparently unlikely due to the presence of amide groups (formed after the cyclen substitution), may possibly change during the full-geometry optimization, as a result of the assistance of the neighbor groups, with the possible shift of the metal ion through the molecule and the consequent lost of a square planar geometry. The total energies obtained after the geometry optimization of the four model molecules are shown in Table 1.

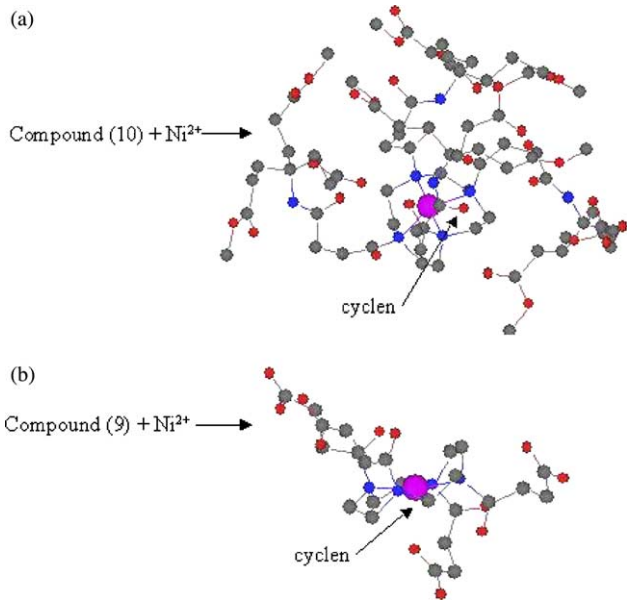


Fig. 10. (a) Model compound **D** involving dendrimeric branches; (b) Model compound **B** without dendrimeric branches.

Thus, the calculated interaction energies for the two different modeled inclusion complexes (Fig. 9) are:

(a) $\mathbf{A} + Ni^{2+} \rightarrow \mathbf{B}$ $\quad E_{interaction} = -344.4316$ Kcal/mol
(b) $\mathbf{C} + Ni^{2+} \rightarrow \mathbf{D}$ $\quad E_{interaction} = -405.3269$ Kcal/mol

(Comparative information: Binding energy calculated for Porphyrin-Ni^{2+} complex: −412.1604 kcal/mol [6]).

As it can be observed, there is a significant contribution in energy due to the dendrimeric environment ($\Delta E_{D-B} = -60.89$ Kcal/mol) in the process of inclusion of Ni^{+2}. The resulting structures (Fig. 10) showed that the metal ion remains in both cases in the middle of the aza-macrocycle, after the full-optimization of the geometries, maintaining a little distorted square geometry by the assistance of both, the cyclen and the neighbor groups. The introduction of carbonyl groups, directly attached to the nitrogen atoms of cyclen, undoubtedly reduces their basicity; however, there are still some interactions with the metal. The distances between Ni^{2+} and N (cyclen) atoms are enlisted in Table 2.

As a reference, the reported average distance between Zn^{2+} and deprotonated N atoms of cyclen is 2.136 Å [20]. Comparing with the distances shown in Table 2, there are similar ranges of interaction.

Table 2
Theoretical interaction distances (Å) between Ni^{2+} and N atoms of cyclen

Molecule	Distance 1	Distance 2	Distance 3	Distance 4
B	2.62	2.45	1.807	1.802
D	1.94	1.87	1.85	1.87

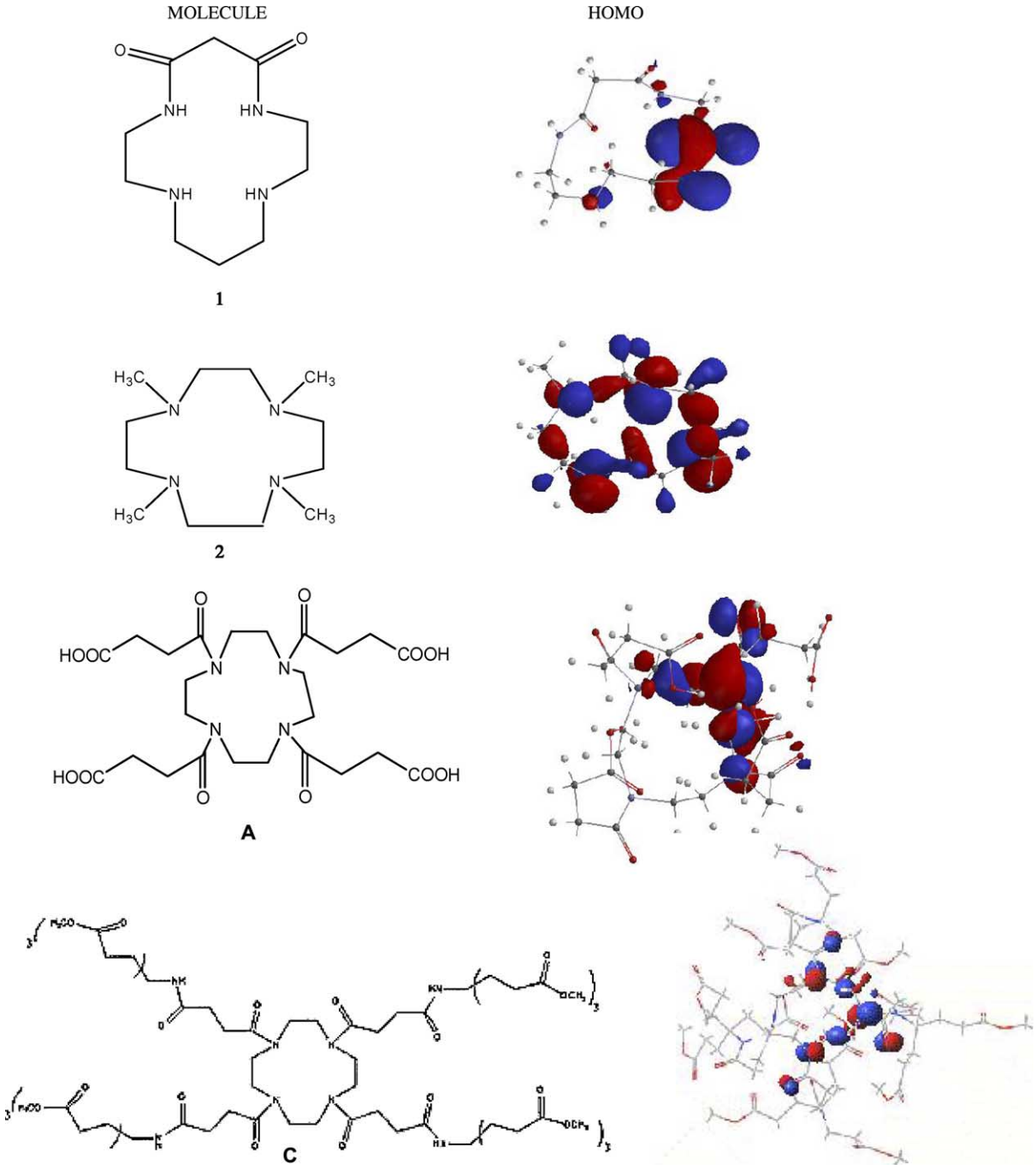


Fig. 11. Several aza-macrocycles (including those under study; **A** and **C**) and the visualization of their HOMOs.

It is possible to find many examples in the literature where aza-macrocycles form complexes with metal ions, by the deprotonation of the nitrogen atoms at basic pH (pH > 13) [21–23]; generating a strong interaction M–N. Since the potential application of the molecules reported here is as molecular cages for metal ions, where such ions would be eventually involved in a catalytic cycle, the strong interactions M–N might not be necessarily convenient. According with the obtained results, there is a compromise between geometrical and energetic environment, and the best situation seems to be that one where the square geometry is kept and the neighbor groups are assisting the inclusion of the metal ion. An examination of the frontier orbitals (HOMO–LUMO) of the model molecules **A** and **C** (before de inclusion of Ni^{2+}) give an idea of the participation of nitrogen atoms to these molecular orbitals. The HOMO–LUMO orbitals of other aza-macrocycles were also calculated with comparative purposes. Fig. 11 shows the atomic contribution to the HOMOs only.

Molecules **1** and **2** actually form complexes with transition metal ions [24]. The carbonyl groups in Molecule **1** are not directly attached to nitrogen atoms; however,

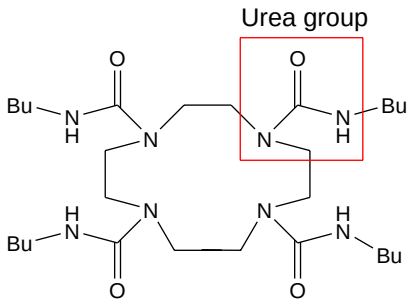


Fig. 12. Koning's aza-macrocycle.

the effect on the HOMO orbital is rather similar to that observed in case of model molecules **A** and **C**. To overcome this effect, in case of Molecule **1** exists the possibility to deprotonate the nitrogen atoms, to induce strong interactions with metal ions. In the case of the model molecules under study, the assistance of neighbor groups (like oxygen atoms) helps to hold the metal ion, but evidently in a weakest way. The Molecule **2**, without N–H's, forms complexes with Ni^{2+} and, judging for the atomic contributions to the HOMO, this complexation is highly assisted by inductive effects. Thus, there are different effects operating when a process of inclusion occurs.

An interesting paper published by Koning's group [25], dealing with the synthesis of a series of substituted aza-macrocycles, showed experimentally that the presence of urea groups, formed when the nitrogen atoms of the aza-macrocycle are substituted, (Fig. 12) results in no complexation of metal ions (e.g. Zn (II) and Cu(II)). Thus, there is a thin line dividing the appropriate and non-appropriate conditions to carry out inclusion processes by the aza-macrocycle nitrogen atoms.

Returning to Fig. 10(a), it is clear that the binding process is assisted by dendrimeric branches, when they are present, by means of encapsulation effects, evolving the metal ion.

Once that the theoretical evaluation has demonstrated the complexation properties of the synthesized molecular system, the obvious further work will be the experimental encapsulation of metal ions of the first transition series, like Ni, keeping in mind that the incorporation of collective effects contributes in a favorable way in these processes.

4. Conclusions

Compound (**10**), formed by the aza-macrocycle known as cyclen and a functionalized dendron, was synthesized in a convergent fashion, incorporating an aliphatic spacer to avoid, in some extent, the sterical hindrances. *N*-acylation reactions to carry out the cyclen substitution, particularly those in solid state, resulted in very good yields since no further purifications were necessary. The molecule (**10**) was characterized by common spectroscopic techniques. According to X-ray powder analysis, there is an average interplanar distance of 4.8 Å between first neighbor molecules, randomly accommodated. As a result of a theoretical study at DFT level of theory, the comparative interaction energies of the inclusion complexes formed by compound (**9**) (without dendrones) and (**10**) (with dendrones) with Ni^{2+} were obtained, showing that there is a significant contribution in terms of energy (−60.89 Kcal/mol) due to the functionalized dendrons which enfold the metal ion in a molecular cage. In terms of pre-organization, the presence of flexible dendrones results in more organized molecular arrangements, being more efficient the encapsulation of guests like metal ions. In areas like catalysis, the relevance of this kind of molecular arrangements might be the possibility to influence on the selectivity of catalytic processes by controlling the accessibility of active sites.

The experimental further work of the formation of complexes with metal ions of the first transition series will be aimed in a rational way, taking into account the theoretical results obtained so far.

References

[1] C.J. Pedersen, J. Am. Chem. Soc. 89 (1967) 2495; C.J. Pedersen, J. Am. Chem. Soc. 89 (1967) 7017.
[2] R.M. Izatt, J.S. Bradshaw, S.A. Nielsen, J.D. Lamb, J.J. Christensen, D. Sen, Chem. Rev., 85271; Y. Inoue, G.W. Gokel, Cation Binding by Macrocycles, Marcel Dekker, New York, 1990.
[3] S. Aime, M. Botta, M. Fasano, E. Terreno, Chem. Soc. Rev. 27 (1998) 19.
[4] B. Konig, M. Pelka, M. Klein, I. Dix, P.G. Jones, J. Lex, J. Incl. Phenom. Macrocycl. Chem. 37 (2000) 39.
[5] D.J. Cram, T. Kaneda, R.C. Helgeson, S.B. Brown, C.B. Knobler, E. Maverick, K.N. Trueblood, J. Am. Chem. Soc. 107 (1985) 3645.
[6] D. Soto-Castro, P. Guadarrama, J. Comput. Chem. 25 (2004) 1215.
[7] G.R. Newkome, C.D. Weis, B.J. Childs, Designed Monomers Polym. 1 (1998) 3.
[8] W.L. Jorgensen, D.S. Maxwell, J. Tirado-Rives, J. Am. Chem. Soc. 118 (1996) 11225.
[9] I. Kolossváry, W.C. Guida, J. Am. Chem. Soc. 118 (1996) 5011.
[10] G. Chang, W.C. Guida, W.C. Still, J. Am. Chem. Soc. 111 (1989) 4379; M. Saunders, K.N. Houk, Y.D. Wu, W.C. Still, M. Lipton, G. Chang, W.C. Guida, J. Am. Chem. Soc. 112 (1990) 1419.
[11] A.D. Becke, J. Chem. Phys. 98 (1993) 1372.
[12] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1998) 785; B. Miehlich, A. Savin, H. Stoll, H. Preuss, Chem. Phys. Lett. 157 (1989) 200.
[13] Jaguar 5.0, Schrodinger, LLC Portland, OR, 2000.
[14] M.J. Dudek, J.W. Ponder, J. Comput. Chem. 16 (1995) 791.
[15] D. Beeman, J. Comput. Phys. 20 (1976) 130.
[16] G. Kaupp, Top. Curr. Chem. 254 (2005) 1.
[17] K. Müller-Dethlefs, P. Hobza, Chem. Rev. 100 (2000) 143.
[18] P.J. Hay, W.R. Wadt, J. Chem. Phys. 82 (1985) 299.
[19] E. Ruiz, D.R. Salahub, A. Vela, J. Am. Chem. Soc. 117 (1995) 1141.
[20] E. Kimura, T. Koike, T. Shiota, Y. Iitaka, Inorg. Chem. 29 (1990) 4621.
[21] E. Kimura, T. Koike, R. Machida, R. Nagai, M. Kodama, Inorg. Chem. 23 (1984) 4181.
[22] S. Aoki, H. Kawatani, T. Goto, E. Kimura, M. Shiro, J. Am. Chem. Soc. 123 (2001) 1123.
[23] E. Kimura, T. Goto, S. Aoki, M. Shiro, Inorg. Chem. 41 (2002) 3239.
[24] M.J. D'Aniello Jr., E.K. Barefield, J. Am. Chem. Soc. 98 (1976) 1610.
[25] B. Koning, M. Pelka, M. Subat, I. Dix, P.G. Jones, Eur. J. Org. Chem. (2001) 1943.