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Cyclen substitution with urea-containing dendrimeric branches. Theoretical study considering the concept of collectivity

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Abstract Equilibrium structures of novel dendrimeric compounds consisting of 1,4,7,10-tetraazacyclododecane (cyclen) mono- to tetra-substituted with four different dendrimeric branches have been studied. It has been shown using molecular dynamics (MD) that, even in the presence of the macrocycle cyclen, the most stable conformations are those with a globular shape due to close contact interactions between poly-functional branches. No collapse of cyclen occurred, making this cavity available for metal complexation. Terminal branches A=NHCOOtBu, B=OSi(Me)₂tBu, C=Imidazole and D=CN have different molecular volumes in the decreasing order: B>A>C>D. This conclusion is in accord with the long range interaction energies, showing that the larger the volume the less the steric hindrance. Considering these energy values, the stability of the systems follows exactly the same tendency as observed for the molecular volume. More polar groups like A=NHCOOtBu and D=CN impart extra stability due to long range interactions between atoms separated by exactly three chemical bonds. The negative charge inside the cyclen cavity increases with the volume of the branches. Besides cyclen, urea groups located at the middle of the branches represent another independent point of negative charge for eventual interaction with small molecules. These compounds show a sum of small contributions of the functionalities in a collective fashion.

Keywords Cooperative effects · Dendrimers · Macrocycles · Molecular dynamics · Molecular mechanics

Introduction

Several years ago F. Menger [1] defined the concept of molecular collectivity in which it was assumed that the molecular behavior was a result of putting together different functional groups, quite different from that of the individual molecules. This concept can be adopted for the design of systems where molecules "work" together doing interesting and useful things, which is the main interest of the present work. As a part of the assemblage we decided to consider the macrocycle 1,4,7,10-tetraazacyclododecane (cyclen). It is known that macrocyclic ligands containing heteroatoms are important complexing agents for cations, anions and neutral molecules. Particularly nitrogen atom associates much more strongly with transition-metal ions than oxygens. Since nitrogen is less electronegative, the lone electron pair is more available for complexing purposes. Thus, peraza-crown macrocycles are most interesting ligands because they provide binding sites for transition metals and in certain cases for other heavy-metal ions as well as for alkali metal ions, although alkali metal ion complexation is usually weak. [2] Four different dendrimeric branches, previously reported by G. Newkome et al. [3] were considered to be attached to the nitrogen atoms of the cyclen, putting an aliphatic chain of three carbon atoms in order to avoid the steric hindrance by increasing the fractal pattern. Figure 1 shows the different dendrimeric branches A, B, C and D as well as an example of the cyclen substitution.

Changing the electronic nature of the functional groups attached at the periphery of dendritic branches, as well as those attached in the middle of branches, we try to ensure different long-range effects (repulsive and attractive interactions) in the presence of guest molecules.

Therefore, the aim of this paper are molecular mechanics and dynamics, as well as ab initio studies of above systems, in order to ascertain the effect of functionalities on the conformation and charge distribution of these systems.

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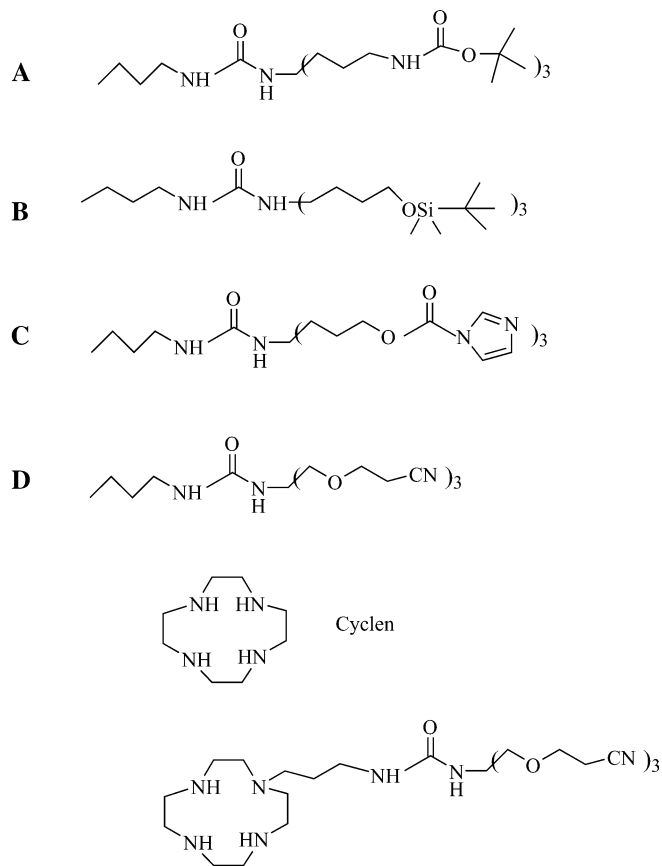


Fig. 1 Dendrimeric branches from A to D attached to cyclen

Computational details

All structures of the cyclen substituted by one to four branches A, B, C or D were generated with the Chem3D-ultra (version 7.0) package [4] and equilibrated using molecular dynamics at a heating rate of 1 kcal per atom per picosecond (ps) and a target temperature of 300 K during 20 ps. The MM2 force field was used for molecular mechanics [5] as implemented in the Chem 3D package. Geometries generated after equilibration were used for further analysis.

In order to study the effect of the branches on the charge distribution inside the cyclen, electrostatic potential-derived charges using the Breneman [6] scheme were used, running single point energy calculations at the B3LYP/6-31+G level of theory included in the Gaussian 98 package. [7] The molecules taken as models were those with one substituted nitrogen cyclen atom (A1, B1', with terminal groups $-\text{OSiMe}_3$ instead of $-\text{OSiMe}_2\text{tBu}$; C1 and D1).

Solvent-excluded molecular volumes of the equilibrated conformations were calculated using the Connolly scheme after molecular dynamics runs. Connolly's solvent-excluded volume [8] represents the volume contained within the contact molecular surface created when a probe sphere (representing solvent molecule) is rolled over the molecular shape. A probe radius of 1.4 Å was chosen to fit the van der Waals radius of elements

composing the molecules to ensure the correct estimation of the molecular volumes.

Results and discussion

The first case is the cyclen substituted with A branches (carbamate terminal groups). The geometries are shown in Figs. 2 and 3. Figure 4 shows a plot of the thermal equilibration of the cyclen substituted with branches A.

The steric energy was evaluated as a sum of energy terms including stretch, bend, torsion, van der Waals and electrostatic energies. It is noticeable that even for tri- or tetra-substitution, some attractive long-range interactions are present, overcoming steric hindrance, as can be seen in the corresponding plot showing a drop in the steric energy as structural equilibrium is reached. The geometries showed in Figs. 2 and 3 correspond to minima. In all cases the globular shape is preferred over the extended one.

When the cyclen is substituted with branches B (*t*-butyl(di-methyl)-silane terminal groups), the geometries adopted are those indicated in Figs. 5, 6 and 7. As expected, substitution with bulky aliphatic groups like *t*-butyl on Si atoms has repercussions in long-range interactions avoiding the stabilization (see plot in Fig. 8). Eventually, the steric energy reaches almost the same value in all cases. This result can be interpreted as a limit in attractive interactions independent of the number of branches. It can be observed that the rest of the branches that do not interact go to the periphery, as shown in Fig. 7. It is important to mention that compounds Cy-B1 to B4 have larger molecular volumes (Connolly molecular volumes), which is consistent with a drop in steric energy.

As seen from the plot in Fig. 9, cyclen substituted with C branches (imidazole terminal groups) shows the highest values of steric energy among the branches. Imidazole was chosen as a terminal group due to its importance in biological systems, for instance benzimidazoles are used as influenza-virus inhibitors. [9] Moreover, it is known that imidazole forms π -complexes as well as hydrogen bonds in solution [10] (see Fig. 10).

Looking at the conformations after equilibration (Figs. 11, 12 and 13 below), the distances between the imidazole rings are long enough to avoid interaction between electron clouds or even hydrogen-bond formation. The distances range from 3.9 Å to 5.4 Å. This is mainly due to the presence of aliphatic chains that separate the terminal groups, directing them to the periphery. This result indicates that imidazole terminal groups in the periphery are available for complexation. We carried out geometry optimization of a model compound at a higher level of theory (B3LYP/6-31+G) including the imidazole as a terminal group and performed an NBO (natural bond orbital) analysis of the molecule (Fig. 14).

According to this calculation, there is an important charge density localized on the nitrogen atoms, suggesting that some acid-base reaction on the dendrimeric

Fig. 2 Equilibrium conformations of cyclen substituted with one and two branches A (NHCOOtBu terminal groups). Hydrogen atoms have been avoided

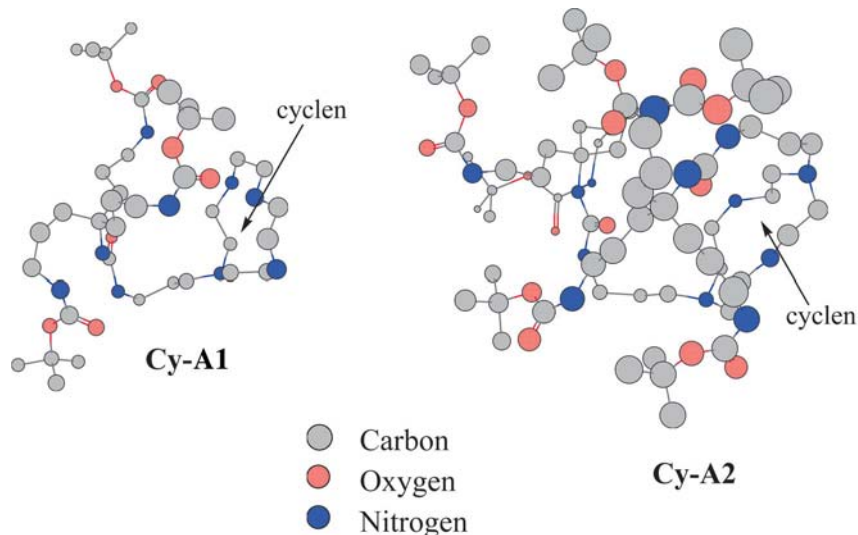


Fig. 3 Equilibrium conformations of cyclen substituted with three and four branches A (NHCOOtBu terminal groups). Hydrogen atoms have been avoided

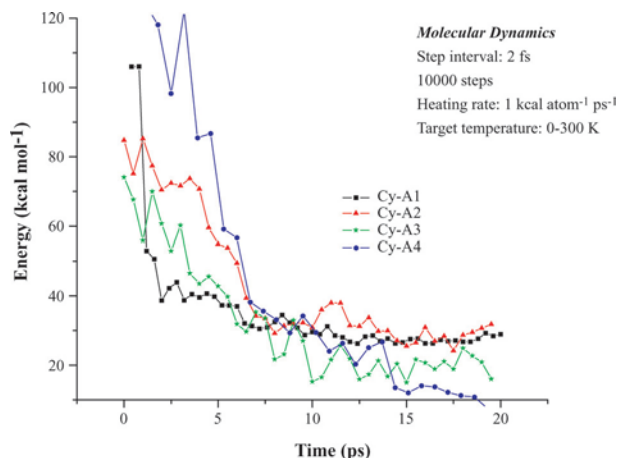
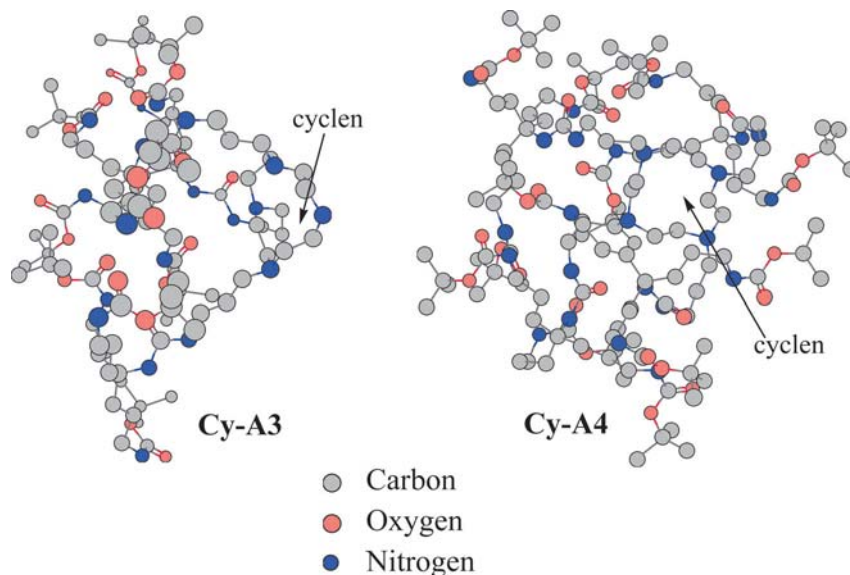


Fig. 4 Steric energy evaluation by molecular dynamics. Cy-A1 to Cy-A4 (Cy=cyclen; A=NHCOOtBu)

surface can take place, in other words, this environment confers nucleophilic character to the nitrogen atoms.

From the point of view of molecular recognition, here we have a reactive surface with the capability to attract acid species. Molecules Cy-C3 and Cy-C4 having imidazole groups in their structures distributed almost homogeneously on the periphery, thus ensuring reactivity at the surface.

Finally, the case of substitution with branches D (cyano terminal groups) is presented.

There is a direct relationship between the number of branches and the increment in steric energy (see plot in Fig. 15). Again, similar to imidazole terminal groups, all -CN groups remain outside, which is important in terms of chemical reactivity at the surface. It is well known that cyano groups are very useful acylating agents. Their hydrolysis in either acidic or basic media produce amide or carboxylic functional groups. Therefore one of these processes can occur in the periphery of these molecules.

Fig. 5 Equilibrium conformations of cyclen substituted with one and two branches B (Si(tBu)Me₂ terminal groups). Hydrogen atoms have been avoided

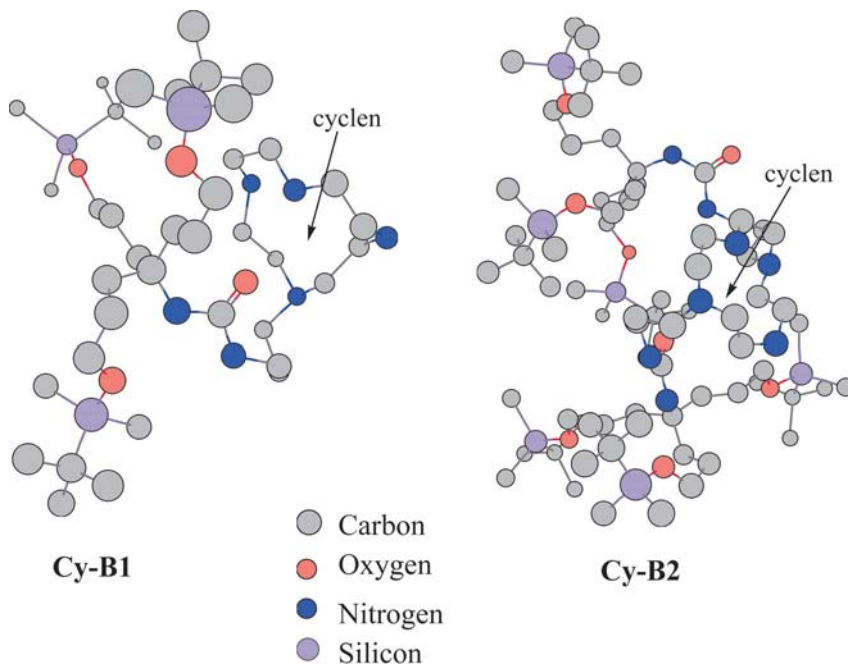
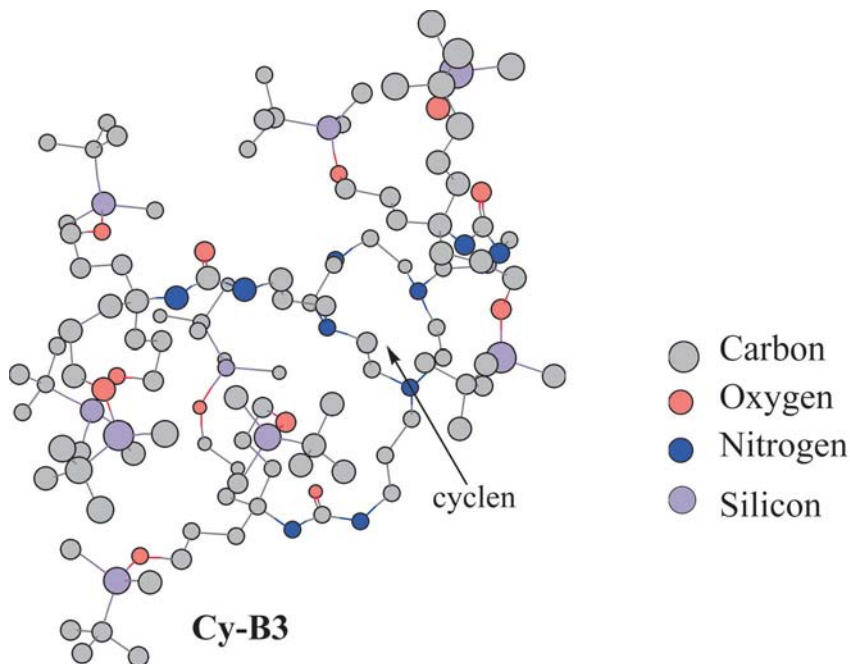


Fig. 6 Equilibrium conformations of cyclen substituted with three branches B (Si(tBu)Me₂ terminal groups). Hydrogen atoms have been avoided



The conformations located for the cyclen substituted with D branches have cyano groups positioned in the periphery, showing, on the other hand, a high availability to the interior of the macrocycle cyclen in comparison with the other cases (Figs. 16, 17 and 18). Molecular ovalities¹ calculated for cyano compounds using the

¹ Ovality: ratio of the molecular surface area to the minimum surface area. The minimum surface area is the surface area of a sphere having a volume equal to the solvent-excluded volume of the molecule. Ovality was computed from the Connolly molecular surface area and solvent excluded volume properties.

Connolly scheme were high, specially for the tetra-substituted compound (Cy-D4).

In order to gain a better understanding of the charge distribution, charges derived from the electrostatic potential were calculated at the B3LYP/6-31+G level using the Breneman scheme, which offers a reasonable level of rotational invariance in potential-derived point charges. For highly flexible molecules like dendrimers with many possible orientations, this invariance is essential to achieve more realistic charge values.

Fig. 7 Equilibrium conformations of cyclen substituted with four branches B (Si(tBu)Me₂ terminal groups). Hydrogen atoms have been avoided

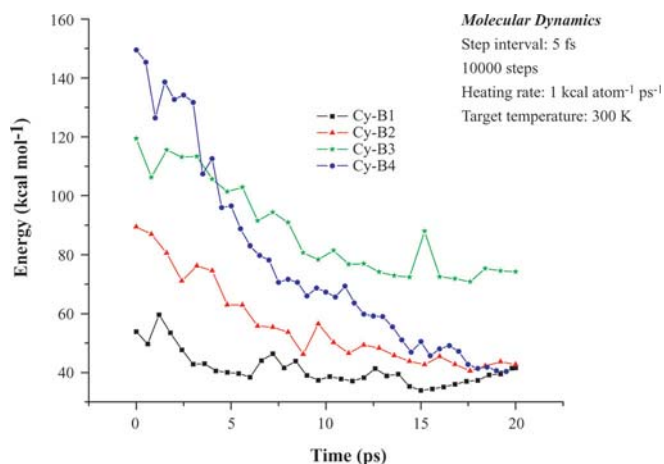
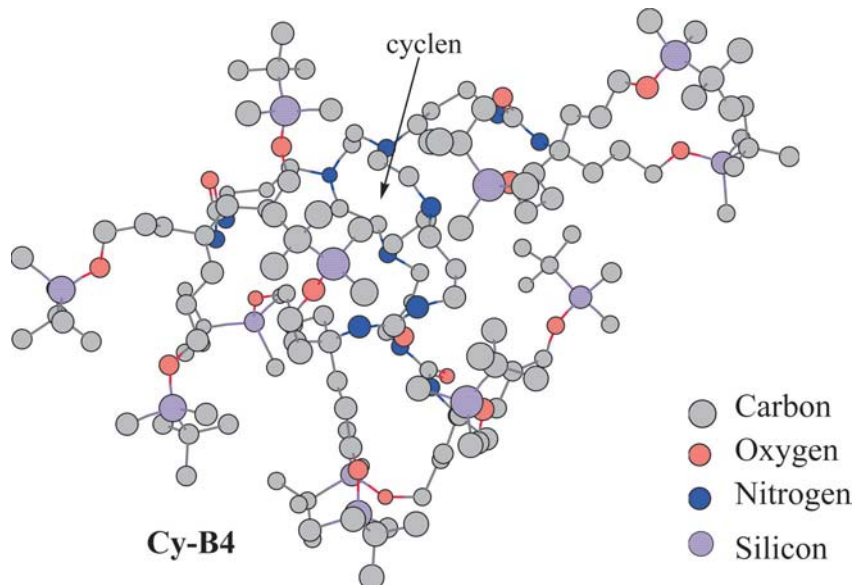


Fig. 8 Steric energy evaluation by molecular dynamics. Cy-B1 to Cy-B4 (Cy=cyclen; B=OSi(Me)₂tBu)

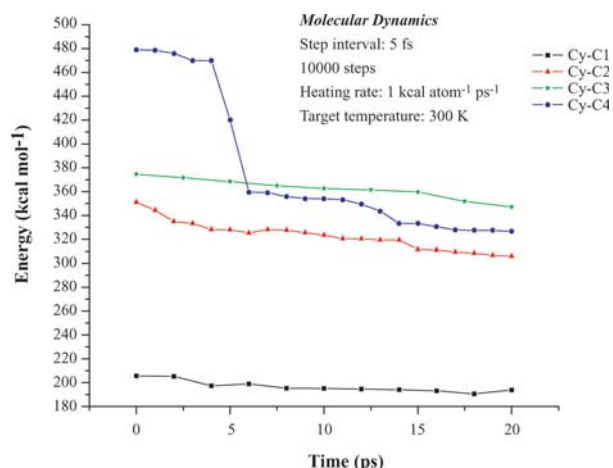


Fig. 9 Steric energy evaluation by molecular dynamics. Cy-C1 to Cy-C4 (Cy=cyclen; C=Imidazole)

Figure 19 shows the molecules studied and the calculated charge values.

Compounds Cy-A1 and Cy-B1' show the largest negative charge inside the cavity of the cyclen. The inductive effects of the branches do not affect the macrocycle in a clear manner. However, considering the conformational arrangements one can observe that branches A and B' adopt an umbrella shape over the cyclen (see Fig. 20) with the electronegative heteroatoms being closer to the hydrogen atoms of the cyclen, in comparison with the branches C and D, which remain in the periphery.

These long-range interactions seem to be responsible for the slight increase of negative charge inside the cyclen. On the other hand, urea groups in the middle of the branches are also capable of complexation judging from their charges, converting these groups into potentially reactive sites. Ether functionalities in the branches

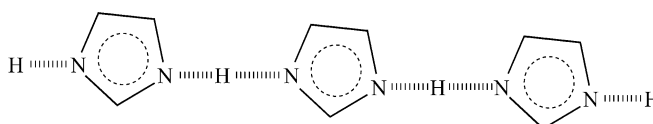


Fig. 10 Hydrogen bonding between imidazole units

B1' and D1 induce an increase in negative charges for the urea groups. The negative charge values follow the decreasing order: Cy-B1' > Cy-D1 > Cy-A1 > Cy-C1.

Therefore, the cavity of cyclen, urea groups and the terminal groups at the periphery can attract cationic species in catalytic or recognition processes simultaneously.

The aza-crown macrocycles generally form 1:1 complexes with metal ions (mainly Ni²⁺, Zn²⁺, Cd²⁺ and Cu²⁺) with the ion located at the central cavity of the

Fig. 11 Equilibrium conformations of cyclen substituted with one and two branches C (imidazole terminal groups). Hydrogen atoms have been avoided

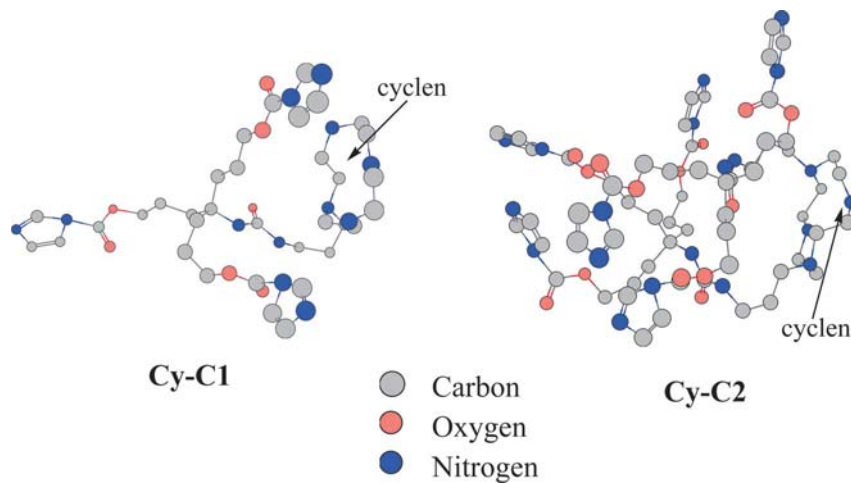


Fig. 12 Equilibrium conformations of cyclen substituted with three branches C (imidazole terminal groups). Hydrogen atoms have been avoided

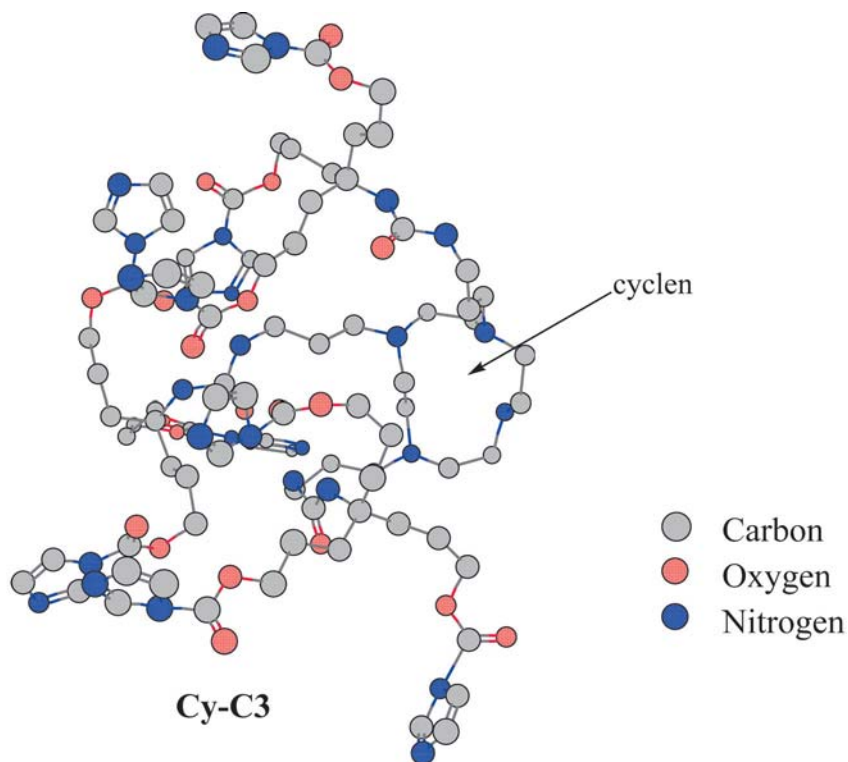
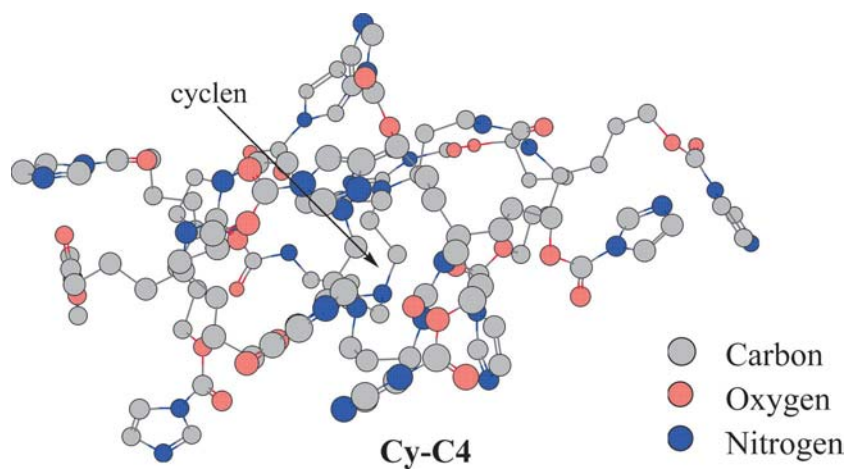


Fig. 13 Equilibrium conformations of cyclen substituted with four branches C (imidazole terminal groups). Hydrogen atoms have been avoided



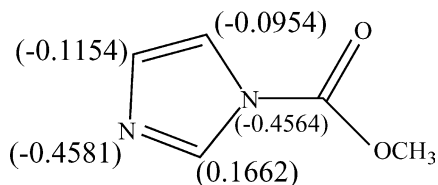


Fig. 14 NBO charges in imidazole model compound

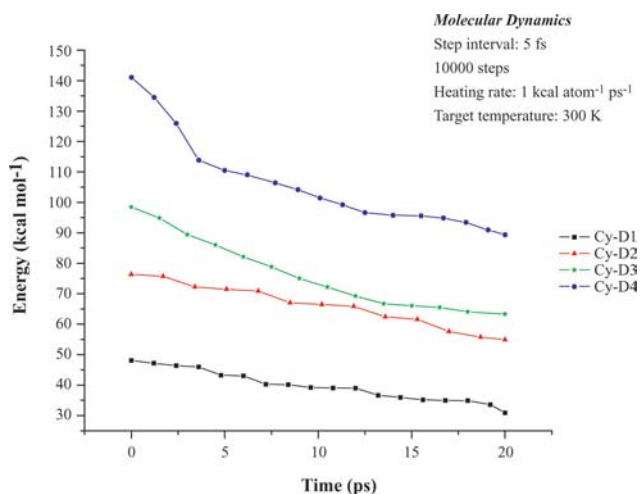


Fig. 15 Steric energy evaluation by molecular dynamics. Cy-D1 to Cy-D4 (Cy=cyclen; D=CN)

macrocycle. However, there are bi- and tri-nuclear complexes where two or three metal ions complex with one macrocycle, depending on the number of nitrogen atoms and also on the cavity conformation. In general, the cation selectivity of macrocycles depends on such factors as macrocyclic cavity dimensions, shape and topology, substituent effects, conformational flexibility/rigidity, donor atom type and number, and arrangement, among others. As for cavity dimensions, cross-distances inside

the cyclen as a function of the different substitution with branches A to D are shown in Table 1.

It is known that aza-cycloalkanes with three to six nitrogen atoms produce stable mononuclear complexes with transition metals. [11] This is the most probable event. Taking into account the cavity dimensions, considering early transition metal ions (Ti, V for instance), these molecules could form complexes due to combination of proximity of two nitrogen atoms and the electron deficiency of these metal ions (Table 1). Such a case corresponds to the cyclen substituted with one and two branches with terminal carbamate groups (branches A); with two branches including imidazole as a terminal group (branches C) and finally with two and three branches including nitrile as a terminal group (branches D). However, in the case of late transition metal ions (Ni, Cu, Zn), the most recommended situation will be that where the cavity has enough room to shelter such metal ions. Branches C with silicon terminal groups ($\text{OSi}(\text{tBu})\text{Me}_2$) have longer distances between the nitrogen atoms inside the cyclen, are the most appropriate molecules from the point of view of cavity dimensions to capture these metals.

Cyclen side groups drastically affect the cavity volume. Solvent-excluded molecular volumes were calculated according to the Connolly scheme and are listed in Table 2.

$E_{1,4 \text{ vdw}}$ refers to van der Waals interaction energy between atoms separated by exactly three chemical bonds while $E_{\text{non } 1,4 \text{ vdw}}$ shows interaction energies for atoms separated by more than three chemical bonds. In dendrimers, the non-bonded interactions become very important due to their spatial arrangement and they are in many cases responsible for intramolecular events within the molecule.

There is a direct relationship between molecular volume and the stabilization by long-range interactions

Fig. 16 Equilibrium conformations of cyclen substituted with one and two branches D (CN terminal groups). Hydrogen atoms have been avoided

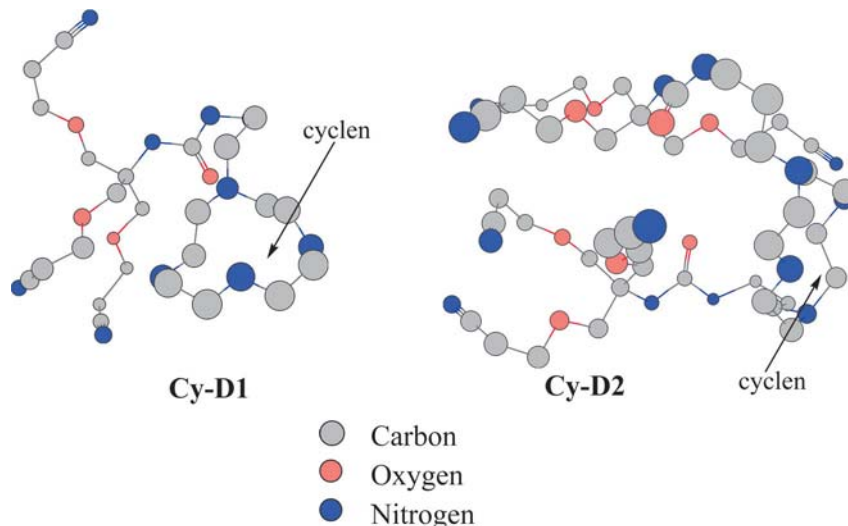


Fig. 17 Equilibrium conformations of cyclen substituted with three branches D (CN terminal groups). Hydrogen atoms have been avoided

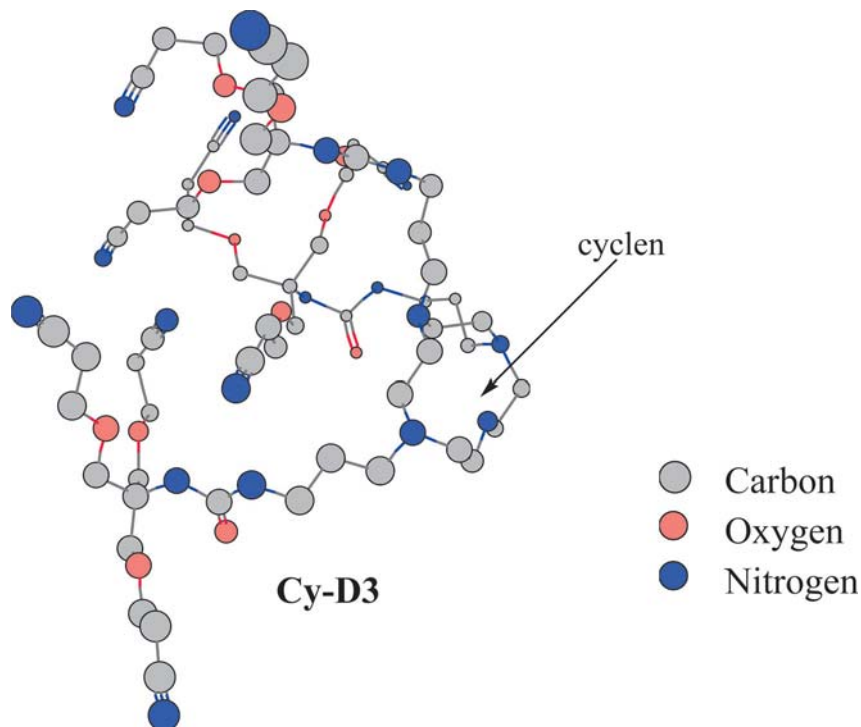
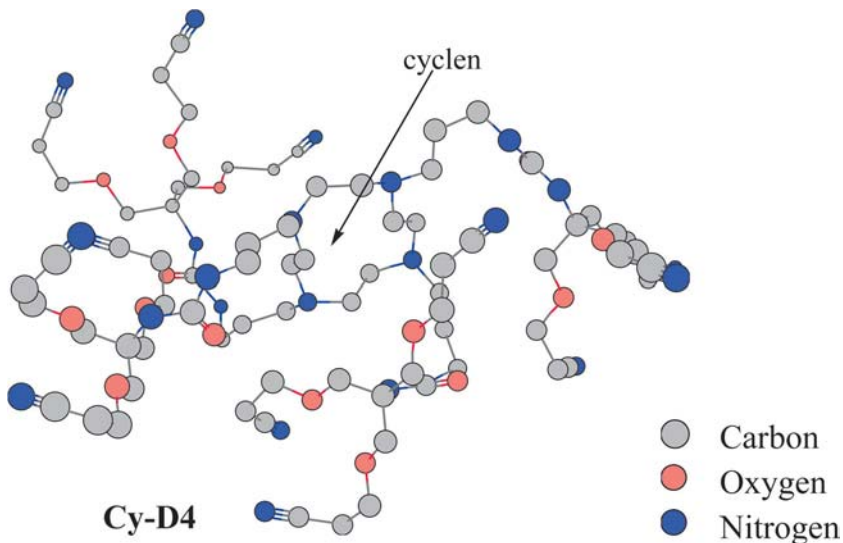
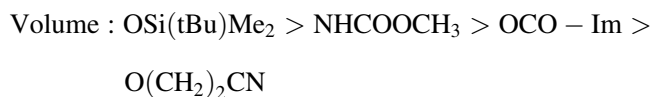


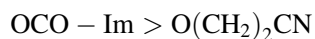
Fig. 18 Equilibrium conformations of cyclen substituted with four branches D (CN terminal groups). Hydrogen atoms have been avoided



over more than three chemical bonds. Considering the terminal groups, we have:



Stability ($E_{\text{non1,4vdw}}$): $\text{OSi(tBu)Me}_2 > \text{NHCOOCH}_3 >$



Thus, the higher the volume that is occupied by the molecules, the more efficient long-range interactions and

therefore the more stabilized the systems are. Besides, as has been stated before, the conditions of complexation inside the cyclen become more favorable with increasing molecular volume.

According to all these results, it is possible to have various effects in one molecular system that work together to offer various reactive sites.

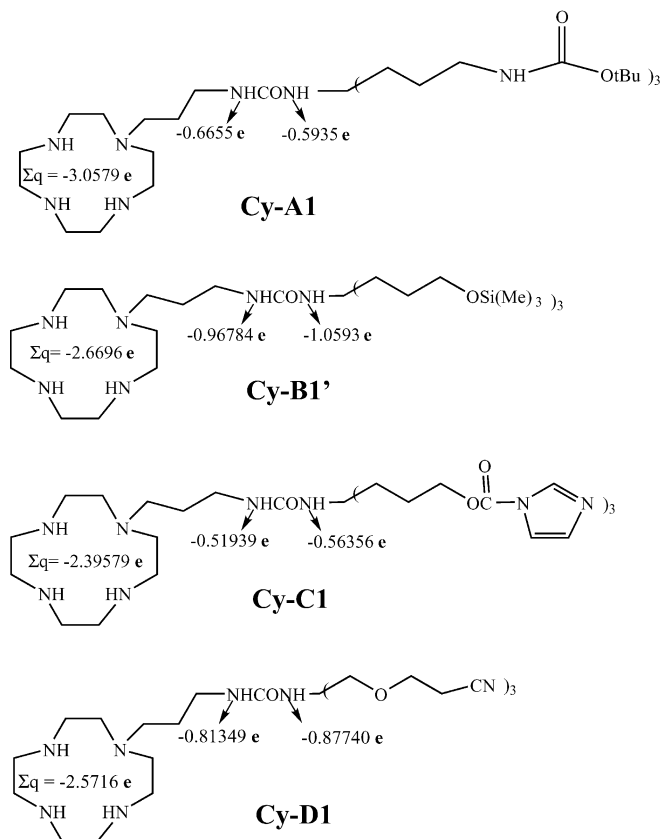
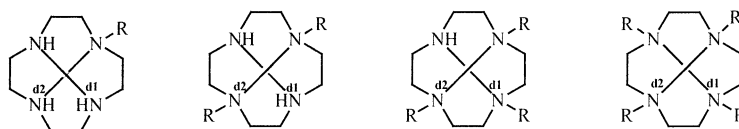


Fig. 19 Electrostatic potential-derived charges using Breneman's scheme

Conclusions

Dendrimeric molecules consisting of 1,4,7,10-tetraazacyclododecane (cyclen) mono- to tetra-substituted with four different dendrimeric branches were modeled. According to these calculations, the molecular volume follows a decreasing order: B>A>C>D (where A=NHCOOtBu, B=OSi(Me)tBu, C=Imidazole and D=CN) in accordance

Table 1 Cross-distances between nitrogen atoms going from mono- to tetra-substituted cyclen



R ^a	d1	d2 (Å)	d1	d2 (Å)	d1	d2 (Å)	d1	d2 (Å)
NHCOOtBu	5.551	3.953	3.679	5.999	5.139	4.883	5.053	5.688
OSi(tBu)Me ₂	4.845	4.060	4.082	5.046	5.134	4.215	4.095	5.815
OCO-Im	5.081	4.098	2.954	5.166	4.223	4.902	4.923	5.699
O(CH ₂) ₂ CN	5.121	4.121	3.701	5.956	3.737	5.927	5.103	5.655

^a Cross-distances for cyclen with no substituents are: $d1=4.07 \text{ \AA}$ and $d2=5.093 \text{ \AA}$

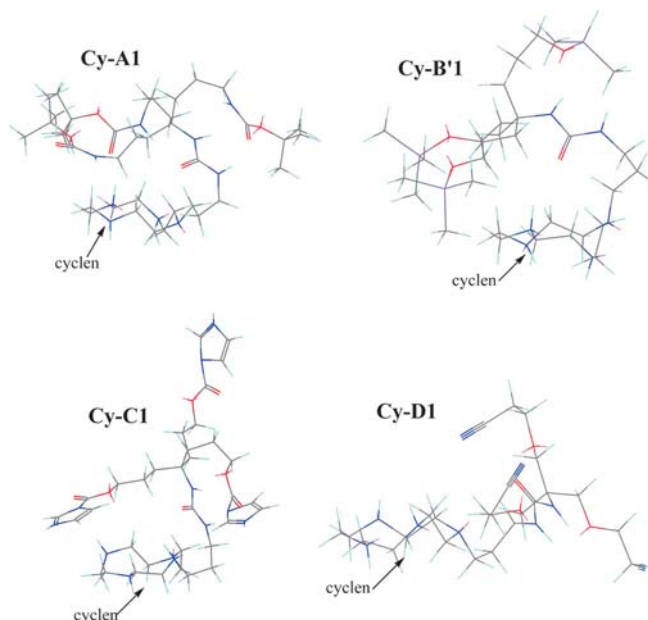


Fig. 20 Equilibrium geometries at B3LYP/6-31+G level of theory

with the long range interaction energies, revealing that the larger the volume, the less the steric hindrance. Considering these energy values, the stability of the systems follows exactly the same tendency observed for the molecular volume. More polar groups like A=NHCOOtBu and D=CN impart extra stability due to interaction between atoms separated by exactly three chemical bonds.

Electrostatic potential-derived charges calculated according to Breneman's scheme showed that the negative charge becomes larger inside the cavity with the volume of branches. Besides cyclen, the urea groups located at the middle of the branches represent another independent location of negative charge for interactions with small molecules. Thereby, these compounds as a whole show the sum of small contributions of the

Table 2 Molecular volumes and long-range energy terms

Terminal group	Solvent-excluded volume (Å ³) ^a	$E_{\text{non } 1,4 \text{ vdw}}$ (kcal mol ⁻¹)	$E_{1,4\text{vdw}}$ (kcal mol ⁻¹)
NHCOOtBu			
1	811.406	-23.303	25.8804
2	1507.14	-75.7228	44.7410
3	2203.73	-116.592	64.4450
4	2886.41	-178.051	85.13660
OSi(tBu)Me ₂			
1	928.865	-37.1655	30.8208
2	1787.42	-81.1578	51.9008
3	2602.21	-119.247	76.0066
4	3446.19	-186.5192	99.7427
OCO-Im			
1	699.427	-24.0291	36.4960
2	1311.56	-63.2849	66.8316
3	1829.46	-85.6883	84.1991
4	2462.11	-127.893	102.293
O(CH ₂) ₂ CN			
1	530.425	-13.3203	27.8298
2	947.969	-32.5223	48.0403
3	1308.35	-50.6610	67.8126
4	1647.76	-59.0659	86.3587

^a Probe radius=1.4 Å

functionalities, being an example of molecular collectivity.

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