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Influence of the rigid spacer to macrocyclization of poly(thialactones): synthesis and computational analysis

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Formation of macrocyclic lactones 8-19 by ring-opening condensation of corresponding stannathianes 1-4 with diacyl dichlorides 5-7 was studied experimentally and theoretically. The cyclization reactions afforded mixtures of corresponding monomers (M), dimers (D), and trimers (T). In order to rationalize the influence of type and size of the spacer on the products ratio in the M-D-T mixtures we performed a force field based molecular modeling study. Monte Carlo conformational search was conducted and lowest energy conformations in chloroform were determined. Results of the molecular modeling in combination with the assumed kinetic parameters enabled better understanding of the experimentally obtained composition of the M-D-T-mixtures. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: polycyclic compounds; adamantane; poly(thialactones); macrocyclization

INTRODUCTION

The chemistry of thiamacrocyclic and related ligands is an area of chemistry that has received much attention over recent years because of the ability of these macrocycles to strongly coordinate transition metal ions and stabilize unusual oxidation states and geometries.[1] Since a major aspect of research in macrocycles is controlling their binding selectivity, it is important to emphasize two main factors that make a ligand selective for the target ion. The first is pre-organization,[2,3] defined as conformational change required for the ligand to adopt optimal architecture that satisfies the geometrical requirements of the metal ion. The second factor is metal-ligand complementarity,[4,5] or, to be more precise, a degree of structural and electronic correspondence between the ligand structure and a metal ion binding site. So far various modifications have been made to the basic crown thiaether structures in an attempt to enhance the selectivity of these ligands and stability of complexes formed.[6,7] Among these modifications are the incorporations of different moieties in the thiamacrocyclic ring.[8–11]

Although it is known that rigid moieties help in ligand pre-organization by 'freezing' optimal conformation, there is a relatively small number of polythia-ligands which incorporate such moieties,[12–16] mostly due to difficult synthesis and low yields. The main problem during the synthesis of macrocycles, and especially macrocycles with embedded rigid molecule, is to establish balance between intra- and intermolecular reactions, the latter leading to oligomers formation. In order to increase the rate of intramolecular reactions leading to cyclic products formation, and at the same time to decrease the intermolecular reactions responsible for polymerisation, special cyclization techniques are used.[7] Most common are high dilution techniques[17] or template synthesis[18,19] which accelerate intramolecular reactions and facilitate closing of the macrocylic ring. The experimental yield of cyclic products depends on their thermodynamic properties and on kinetics of their formation.[20] Kinetic parameters depend on the activation energy, related to the strain energy in the ring being formed, and on statistical probability of chain's ends meeting each other, which is reciprocally proportional to the number of degrees of freedom in the acyclic system.[20] Thermodynamic properties are determined by compound free energy of formation which can be estimated from the force field energy terms (enthalpy contributions), the number of conformations found in a predefined energy window (entropy contributions), and the solvation term (enthalpy and entropy contributions).[20]

In this paper, we report the influence of the rigid spacer, such as bulky adamantane moiety, on the formation of thiamacrocyclic molecules. In order to rationalize the experimental results, the

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role of the spacer in the cyclization and the conformational freedom of the product molecules, we performed Monte Carlo conformational search. Energies of the most favorable conformers were analyzed in order to evaluate thermodynamic properties of products and the approximate free energy differences were used to support the experimental findings. By combining the thermodynamic and the kinetic data we established relationship between the structural parameters of the thiamacrocyclic compounds and their experimentally obtained yields.

RESULTS AND DISCUSSION

Cyclization reactions of stannapolythianes 1-4 and diacyl dichlorides 5-7

Thiamacrocyclic ligands **8-19** were prepared via ring-opening condensation of the corresponding stannapolythianes **1-4**[21] and diacyl dichlorides **5-7**. Stannapolythianes function as active dithiols and also as covalent templates serving both, as a template for chain assembly, and as a reaction site for subsequent ring closure of the chains locking them in right position.[7] Since it is known that macrocyclization can be directed by adjustment of experimental conditions, we used the method that favors formation of macrocyclic dimers.[22] All the experiments were carried out under the same conditions by slow addition of equimolar quantities of **5**-**7** to the corresponding stannapolythiane **1**-**4** (refer Experimental Section). The coupling reaction of stannapolythianes **1-4** with the corresponding acyl dichloride afforded monomer, dimer, or trimer form of polythialactones **8**-**19**, and in some cases the disulfides **11S** and **15S**, as shown in Scheme 1 and Table 1. Separation of obtained cyclic products proved to be very difficult owing to quite similar structural properties of the products. Therefore, repeated column chromatography is necessary to isolate pure products.

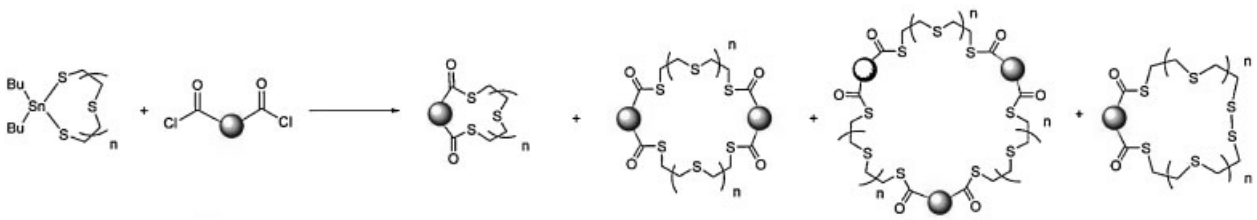
We have noticed that the ratio of the obtained monomer, dimer, and trimer depends on the ring size and also on the number and type of incorporated spacers. The highest product yields (>50%) were obtained in the synthesis of 14–18-membered ligands. Rings containing more than 20 atoms were prepared in low yield (5–20%) due to reduced statistical probability of reaction between two reactive ends (which is also a consequence of high conformational entropy of the acyclic precursor).

Our assumption that the polycyclic units would decrease conformational entropy of the reactant while significantly increasing the ring strain proved to be correct. The 9- and 12-membered monomers **8M** and **11M**, with incorporated polycyclic unit, were not observed during the condensation. Instead, the 18- and 24-membered dimers **8D** and **11D**, with two adamantane units, were obtained as main products. However, larger analogs, the 15- and 18-membered monomers, **14M** and **17M**, were obtained as major products in addition to dimers **14D** and **17D**. Increase of the ring strain in the macrocyclic molecules could also be observed by analysis of their ^{1}H NMR spectra. Due to steric hindrance and reduced conformational mobility, compounds with 18 or less ring atoms containing a bulky adamantane molecule, like **8D**, **14M**, and **17M** showed considerable differences in chemical shifts of methylene-H atoms bonded to an adamantane cage (Table 2, Fig. 1).

On the other hand, in the spectra of the macrocycles **8T**, **11D**, **11T**, containing 24 or more atoms in a ring, methylene-H atoms appeared as broad singlet, indicating high degree of conformational mobility (Fig. 1). In the reactions carried out with acyclic diacyl dichlorides **6** and **7**, monomer products were obtained as major products with significantly smaller portion of dimers. Inspection of Table 1 also reveals that trimer products were not observed in reported reactions. Exception is reaction of stannathiane **1** with glutaryl dichloride **6** in which monomer **9M** was not observed. This result is in agreement with Mandolini theory, that the formation of 8–11-membered rings is most difficult due to unfavorable bond formation opposing forces, as the result of imperfect staggering and transannular interactions caused by repulsive interactions between atoms in the ring when they are forced to be close to each other.[20]

Computational analysis

In order to rationalize our experimental results we performed the molecular modeling study. Our concern was aimed to investigate degree of the steric strain caused by embedding of the polycyclic unit into macrocyclic rings of various sizes, and also to evaluate the free energy differences for the formation of products. For this purpose, we used the MM3 force field which is well



Scheme 1.

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Table 1. Reactions of stannathianes **1**-**4** with acyl dichlorides **5**-**7**

Stannathiane	Acyl dichloride	Products	Ring size	(k'_n)[a]	Product yield (%)[b]	Total yield (%)[c]
1	5	**8M**	9	—	—	51
		8D	18	3.3	30	
		8T	27	8.3	21	
1	6	**9M**	9		—	45
		9D	18		29	
		9T	27		16	
1	7	**10M**	11		35	61
		10D	22		21	
		10T	33		5	
		11M	12	—	—	
2	5	**11D**	24	4.0	39	55
		11T	36	14.9	15	
		11S	19		1	
2	6	**12M**	12	0.1	35	62[d]
		12D	24	0.3	17	
		12T	36	—	—	
2	7	**13M**	14	0.2	60	80
		13D	28	0.8	20	
		13T	44	—	—	
3	5	**14M**	15	0.9	61	72
		14D	30	6.6	11	
		14T	45	—	—	
		15M	15	0.4	52	
3	6	**15D**	30	—	—	60
		15T	45	—	—	
		15S	25		8	
3	7	**16M**	17	0.9	45	54
		16D	34	6.2	9	
		16T	51	—	—	
4	5	**17M**	18	1.1	69	74
		17D	36	6.9	5	
		17T	54	—	—	
4	6	**18M**	18	0.3	70	75
		18D	36	0.7	5	
		18T	54	—	—	
4	7	**19M**	20	1.0	28	35
		19D	40	6.9	7	
		19T	60	—	—	

[a] HPLC capacity factor of the eluted compound ($k'_n = t_n - t_0/t_0$).
[b] Product ratio is determined by HPLC analysis of fractions isolated by column chromatography.
[c] Isolated yield.
[d] HPLC analysis revealed presence of higher oligomers in 10% yield.

parameterized for the small molecules containing sulfur[23] and has successfully been used in the analysis of thia-crown ethers.[24] For the selected adamantane embedded macrocycles **8M-D-T**, **11M-D-T**, **14M-D-T**, and **17M-D-T** and the chain analogs **12M-D-T** and **13M-D-T**, we accomplished the conformational search by Monte Carlo Multiple Minimum (MCMM) method available in MacroModel software[25] (for details of the calculations refer Computational Methods in Experimental section) and obtained a set of different conformations within a predefined energy window. The most favorable conformers were subsequently geometry optimized and their conformational and solvation energy terms, as well as the number of conformations in the specified energy window, are given in Table 3.

The conformations of **11D**, **12M**, **12D**, and **13M** were earlier determined by X-ray diffraction analysis.[26,27] As expected, they differ from the lowest energy conformers determined by MCMM conformational search in chloroform. Apparently, environment influences distribution of conformers, and the most stable conformers in chloroform differ from those in crystals.

From Table 3 it is obvious that the molecules with the rigid adamantane spacer, **8**, **11**, **14**, and **17**, have much higher conformational energy than those with the flexible spacer, **12**

Table 2. Chemical shifts (δ/ppm) of H atoms bonded to adamantane methylene-C atoms in macrocycles **8D**, **8T**, **11D**, **11T**, **14M**, and **17M**

Macrocycle	Ring size	δ/ppm
14M	15	1.76 (d, H-a, 4H, $J = 12.4$ Hz), 2.18 (d, H-b, 4H, $J = 12.4$ Hz)
8D	18	1.83 (d, H-a, 8H, $J = 11.7$ Hz), 1.98 (d, H-b, 8H, $J = 11.7$ Hz)
17M	18	1.81 (d, H-a, 4H, $J = 12.3$ Hz), 2.06 (d, H-b, 4H, $J = 12.3$ Hz)
11D	24	1.86–1.93 (m, 8H)
8T	27	1.81–1.92 (m, 8H)
11T	30	1.80–1.91 (m, 8H)

and **13**. Since change in the conformational energy is the main constituent of the cyclization enthalpy it is not surprising that those with the highest conformational energy, **8M** and **11M** were not experimentally detected. Apparently, the large ring strain is the main reason why these compounds were not formed.

To learn more about adamantane influence on product formation, we compared the experimental yields of the molecules with the same number of atoms in the ring, but different spacers (Table 1), namely **11 M**-**D**-**T** with **12 M**-**D**-**T**. The most stable conformers of these molecules obtained by conformational search are presented in Fig. 2. Although the macrocyclic molecule **12M** contains only 12 atoms in the ring, it is obtained as the main product in cyclization reaction overtaking the formation of the 24-membered dimer **12D** (refer Scheme 1 and Table 1). Product ratio suggests that strain in the 12-membered flexible ligand **12M** is low, and this assumption is confirmed by calculations (i.e., the conformational energy of monomer **12M** is about five times lower than that of **11M**). Calculations clearly showed that presence of the adamantane unit significantly increases the reaction enthalpy (refer Table 3). As a consequence, the total products yield is reduced and its distribution is shifted toward dimers and trimers (refer Table 1).

The experimental results could not be explained solely by the conformational energy. Instead, the enthalpy, approximated by the potential energy (U), and the entropy terms should be considered, $\Delta F = \Delta U - T\Delta S$. Regarding entropy, both, the solvation and conformational contributions are relevant. Solvation term ($-T\Delta S^{sol}$) can be approximated with the calculated solvation energy. Conformational entropy is proportional with the number of flexible bonds in the single molecule (intrinsic entropy), as well as the total number of molecules. For example, it is much higher for six monomers than two trimers. Since the product molecules are obtained as a mixture of macrocycles it is impossible to quantify the conformational entropy of the system. However, by approximating the cyclization free energy (ΔF) of the products (obtained from the identical number of reactant precursors) either six M, or three D, or two T with the sum of the conformational and solvation energies only (Table 3), the correlation between the experimental yields and the calculated energies was found. The cyclization free energy differences ($\Delta\Delta F$) between M, D, and T obtained from the same precursor can be estimated from differences of their potential energies and the entropy contributions (the free energy of the initial set of molecules is the same).

For the purpose of quantitative explanations of the experimental yields with the thermodynamic data we considered systems consisting of sets of homogenous product molecules that emerged from the systems consisting of identical six reacting precursor molecules and defined *F*6 energies as an

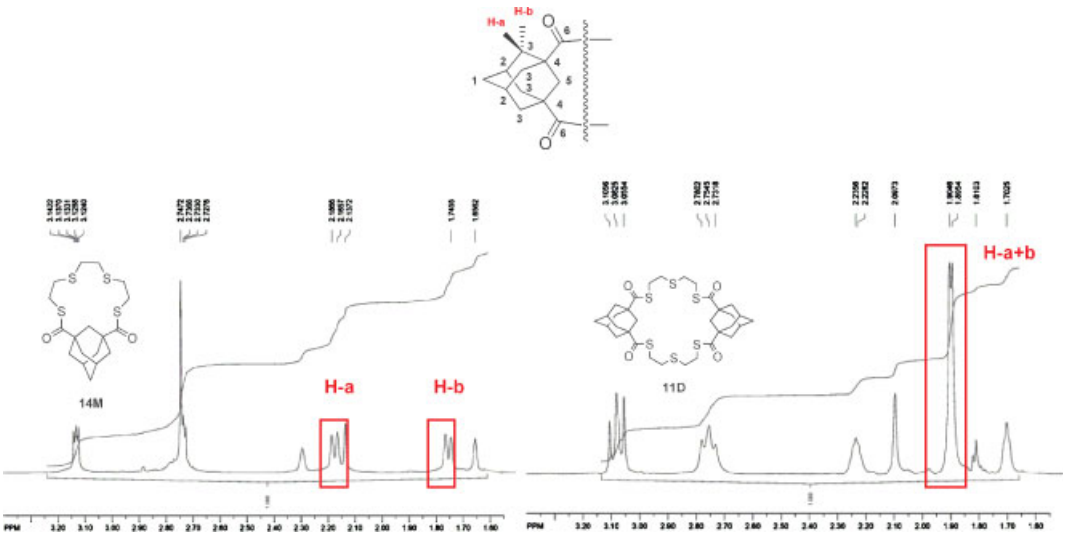

Figure 1. ^{1}H NMR spectra of adamantane embedded monomer **14** and dimer **11**.

Table 3. Calculated energy terms (kJ/mol) for the most favorable conformations of macrocycles **8**, **11**, **12**, **13**, **14**, and **17** obtained by Monte Carlo conformational searches

Macrocycle	N^a	E^b_{conf}	E^c_{sol}	$F6^d$	NS[e]	Yield[f]
8M	9	227.1	−35.4	1150	1	—
8D	18	91.2	−28.4	188	81	30
8T	27	91.2	−24.9	133	186	21
11M	12	120.1	−38.9	487	6	—
11D	24	97.0	−33.9	189	168	39
11T	36	94.9	−27.3	135	95	15
14M	15	105.0	−44.6	364	12	61
14D	30	105.3	−37.4	204	128	11
14T	45	99.3	−29.7	139	21	—
17M	18	114.9	−49.2	394	204	69
17D	36	109.0	−39.2	209	62	5
17T	45	110.0	−40.6	138	27	—
12M	12	24.1	−32.6	−51	7	35
12D	24	14.0	−32.6	−56	84	17
12T	36	12.3	−27.2	−30	9	—
13M	14	29.5	−37.7	−49	79	60
13D	28	22.3	−33.2	−33	91	20
13T	44	21.1	−29.1	−16	19	—

[a] The number of atoms in the ring.
[b] Energies for the lowest energy conformation found: conformational,
[c] Energies for the lowest energy conformation found: solvation.
[d] Sum of conformational and solvation energies calculated for the same number of corresponding building units (6), that is, energies calculated for monomer, dimmer, and trimer are multiplied with 6, 3, and 2, respectively and summed.
[e] Number of structures found within the energy window of 10 kJ/mol.
[f] Experimentally determined yield (%) of isolated compounds.

approximation of cyclization free energies. To obtain a mixture of M+D+T in one reaction, minimally six reacting precursor molecules are needed; however, these six precursors can also give either six M, or three D, or two T. Therefore, *F6* energy is the sum of conformational and solvation energies of the system comprising either six monomers or three dimers or two trimers (Table 3). If we compare these energies (*F6*) calculated for small molecules with the rigid spacer, we can see that they are very high for monomers (**8M** and **11M**). For dimers (**8D** and **11D**) and trimers (**8T** and **11T**) they are much lower and similar, *ca*. 188 and 134 kJ/mol for dimmers and trimers, respectively. The experimental yields for **8M**-**D**-**T** and **11M**-**D**-**T** are also similar and in agreement with the calculated energies that is, no monomers, and yield of **D**+**T** is 51 and 55% respectively. Difference in the D/T yields between **8** and **11** can be explained by the higher intrinsic entropy of **11** resulting in the yield shift toward dimers. The *F6* energies calculated for corresponding **14M**-**D**-**T** and **17M**-**D**-**T** products are also similar as are their experimental yields. When we compare energy ratios for molecules with the flexible spacer for example, **12M**/**12D** and **13M**/**13D**, ($F6^{12M}/F6^{12D}$):($F6^{13M}/F6^{13D}$), with ratios of their experimental yields (Y), ($Y6^{12M}/Y6^{12D}$):($Y6^{13M}/Y6^{13D}$) we see that they are similar, 1:1.6 and 1:1.5, respectively.

Beside energies, the population of different conformers determined by MCMM conformational search is given in Table 3 (NS column). Low populations of trimers can be associated by lower energy barriers between different conformers. During optimization (refer Computational Methods for calculation details) the transition to more stable conformer occurs easily.

When conformational energies (i.e., the major part of the enthalpy) of different macrocyclic products (M, D, and T) are similar, larger experimental yield of monomers and dimers *versus* trimers can be explained by entropy and by kinetic parameters. Namely, the statistical probability for separate closing of two or three chains (i.e., formation of two or three monomers) is higher than probability that they will meet each other in a solution to form a dimer or trimer, respectively. For the molecules with flexible spacer or with rigid spacer but large monomeric unit (number of atoms in the ring is 15 or larger) trimers were not even observed.

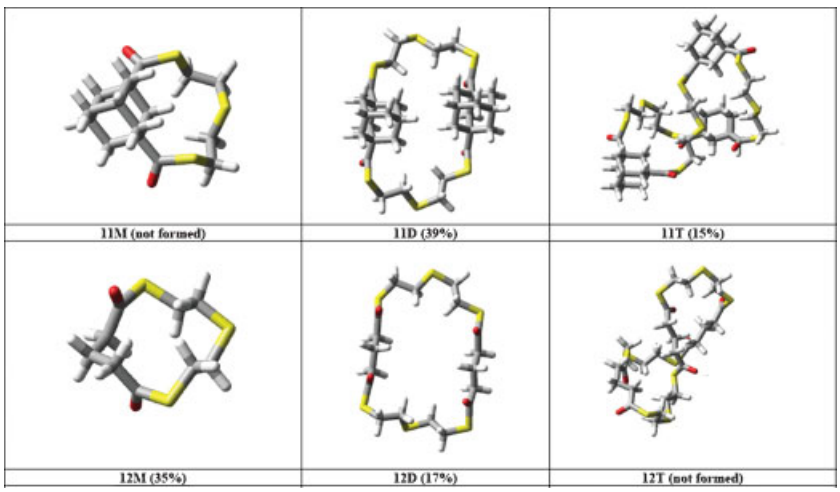

Figure 2. The most stable conformers of monomer, dimer, and trimer of **11** and **12** in chloroform as determined by MCMM conformational search. Corresponding macrocycles of **11** and **12** have the same number of atoms in the ring; however, the products yields differ significantly.

The calculated energies, the number of ring atoms and the molecular masses were correlated with the experimental yields. The correlations of $R^2 = 0.74$ and $R^2 = 0.98$ were obtained for the macrocyclic molecules with the rigid and flexible alkyl spacer, respectively.

CONCLUSION

The cyclization reactions of series of macrocyclic polythialactones such as **8**-**19** have been studied experimentally and theoretically. Cyclization reactions afforded mixtures of monomer, dimer, or trimer products depending on the ring-size formed and the type of spacer used. Computational analysis accomplished for cyclic polythialactones with and without rigid spacer clearly showed that the addition of adamantane significantly increases ring strain and, as a consequence, the potential energy of the molecule. Accordingly, products with the highest conformational energies, the monomers **8M** and **11M**, were not observed experimentally.

Generally, the conformational energy of monomer is higher than those of dimer and trimer. Yield of monomers with flexible spacer and those with rigid spacer but large ring is higher than those of dimers and trimers. Apparently their formation is entropically and kinetically driven. Kinetic parameters directly depend on the ring size (number of atoms in the ring), that is, for the smaller system the probability that two atoms will make a bond and close the ring is higher. The energy ratios calculated for the related compounds (M, D, T) nicely correlate with their experimental yield ratios.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 300 and Bruker AV 600 spectrometers in $CDCl_3$ using TMS as the reference. The assignment of the signals is based on 2D homonuclear (correlated spectroscopy, COSY) and heteronuclear multiple quantum coherence (HMQC). For thin-layer chromatography (TLC) analysis, precoated TLC plates (Kieselgel 60 F254) were used, and column chromatography was done by using Kieselgel 60 (70-230 mesh) as the stationary phase. HPLC-analyses were performed on Varian ProStar instrument equipped with a UV detector operated at $\lambda = 230$ nm. An OmniSpher C18 (250 × 4.6 mm) chromatography column was employed by eluting with CH_3CN at a flow rate of 1 ml/min. Adamantane-1,3-dicarbonyl dichloride (**5**)[28] and tin-templates **1**-**4**[21] were prepared according to the procedure described in literature. Glutaryl dichloride (**6**) and pimeloyl dichloride (**7**) are commercially available. Unless stated otherwise, reagent grade solvents were used.

General procedure for the cyclization reactions of stannathianes 1-4 with acyl dichlorides 5-7

To a solution of corresponding stannathiane **1**-**4** (1 mmol) in dry $CHCl_3$[29] (80 ml) heated on reflux temperature, was added dropwise during 2 h a solution of corresponding diacyl dichlorides **5**-**7** (1 mmol) dissolved in dry $CHCl_3$ (20 ml). After being stirred at reflux temperature for additional 1 h the solution was cooled to a r.t. and treated with 2,2′-bipyridyl (1 mmol). Next, the solution was filtered through small pad of silica to remove the complex, and the filtrate was concentrated *in vacuo*. A gross mixture of products was thereby obtained as thick, colorless oil. The crude reaction product was purified by repeated column chromatography on silica gel using a 0 → 20% of EtOAc-CH_2Cl_2 gradient elution scheme to afford corresponding products **8-19** (**M**, **D**, **T**, or **S**) in a yield as shown in Table 1. The NMR spectra of compounds **8D, 8T**, **9D**, **9T**, **10D**, **10T**, **11D, 11T**, **14M, 14D**, **17M**, **17D**, **12M**, **12D**, **13M**, **13D**, **16M**, **16D**, **19M**, and **19D** were identical to that described in literature.[21,26,27,30]

3,6,9,10,13,16-Hexathia-1(1,3)-adamantanacycloheptadecaphane-2,17-dione (11S)

^{1}H NMR ($CDCl_3$) δ/ppm: 1.69 (br.s, 2H), 1.80–1.89 (m, 4H), 1.97–2.10 (m, 6H), 2.23–2.31 (m, 2H), 2.73 (t, 4H, $J = 6.5$ Hz), 2.90 (br.s, 8H), 3.11 (t, 4H, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$) δ/ppm: 28.16 (d, 2C), 29.00 (t, 2C), 32.06 (t, 2C), 32.18 (t, 2C), 35.24 (t, 1C), 37.51 (t, 4C), 38.04 (t, 2C), 42.96 (t, 1C), 48.76 (s, 2C), 204.63 (s, 2C).

2,5,8,11-Tetrathiacyclopentadecane-1,12-dione (15M)

^{1}H NMR ($CDCl_3$) δ/ppm: 2.04–2.12 (m, 2H), 2.59–2.75 (m, 8H), 2.82 (br.s, 4H), 3.00–3.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ/ppm: 21.10 (t, 1C), 29.08 (t, 2C), 30.96 (t, 2C), 31.35 (t, 2C), 43.66 (t, 2C), 197.70 (s, 2C).

2,5,8,11,12,15,18,21-Octathiacyclopentacosane-1,22-dione (15S)

^{1}H NMR ($CDCl_3$) δ/ppm: 2.01–2.11 (m, 2H), 2.60–2.72 (m, 8H), 2.85 (br.s, 8H), 2.97 (br.s, 8H), 3.01–3.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ/ppm: 21.01 (t, 1C), 29.09 (t, 2C), 31.35 (t, 2C), 31.40 (t, 2C), 31.74 (t, 2C), 31.99 (t, 2C), 38.36 (t, 2C), 42.54 (t, 2C), 197.96 (s, 2C).

2,5,8,11,14-Pentathiacyclooctadecane-1,15-dione (18M)

^{1}H NMR ($CDCl_3$) δ/ppm: 2.03–2.16 (m, 2H), 2.63–2.80 (m, 8H), 2.86 (br.s, 8H), 3.04–3.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ/ppm: 20.82 (t, 1C), 29.35 (t, 2C), 31.72 (t, 2C), 32.00 (t, 2C), 32.46 (t, 2C), 42.44 (t, 2C), 197.95 (s, 2C).

2,5,8,11,14,20,23,26,29,32-Decathiacyclohexatriacontane-1,15,19,33-tetraone (18D)

^{1}H NMR ($CDCl_3$) δ/ppm: 1.96–2.09 (m, 4H), 2.58–2.76 (m, 18H), 2.85 (br.s, 14H), 3.02–3.13 (m, 8H); ^{13}C NMR ($CDCl_3$) δ/ppm: 20.99 (t, 2C), 29.02 (t, 4C), 31.63 (t, 4C), 31.98 (t, 4C), 32.08 (t, 4C), 42.54 (t, 4C), 197.94 (s, 4C).

Computational methods

Molecular modeling was performed for 18 thiamacrocyclic compounds (Table 3) using the software MACROMODEL,[25] which enables efficient conformational search of cyclic compounds. The initial 3D molecular structures were obtained by submitting the smile codes to CORINA, a 3D structure generator program, (http://www.molecular-networks.com/online_demos/corina_demo.html).

Allinger's MM3 force field[31–33] was used for parameterization of the molecules and solvent effect was modeled using the generalized Born-solvent accessible surface area continuum solvent model (GB/SA) for chloroform.[34] For the conformational search 7000 steps of MCMM procedure was used. In order to make the search as extensive as possible, the conformation that has being found the least times (within 80 kJ/mol) from the most favorable conformation, was used as the starting one in the subsequent run. Even so, some conformations were found several

tens of times leading to the conclusion that the conformational space was thoroughly sampled. The conformations that were within 10 kJ/mol from the energetically most favorable one were further geometry optimized by Polak-Ribiere and Truncated Newton algorithms until the gradient of 10^{-2} kJ/(mol Å) was achieved. The most favorable conformation of each compound was further energy optimized and different energy terms (conformational, van der Waals, electrostatic and solvation) were calculated.

The calculated solvation and conformational energies, the number of atoms in a ring, and molecular masses were correlated with the experimental yields using the Partial Least Square (PLS) analysis.[35]

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