Synthesis of Thiamacrocycles and Conformational Studies on Their Precursors

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Received July 16, 1999

1-(4-Nitrophenyl)-7-phenylthioheptane (**1**) and -9-phenylthiononane (**2**) have been synthesized and their conformations studied in solution and in the solid state. MMX calculations suggest that the global energy minimum structures are bent in the gas phase, probably owing to edge-to-face intramolecular attractive interaction between the electron rich and the electron poor terminal aryl groups. These conformations were confirmed in solution using 2D NOESY NMR. In the solid state, **1** and **2** exist in the staggered, linear conformation, stacked head-to-tail, with the plane of the nitro group being tilted above the plane of the benzene ring. It appears that the crystal lattice forces overcome the weak edge-to-face intramolecular aromatic interactions that dominate in the gas phase and in solution. The corresponding azides were treated with trifluoromethanesulfonic acid to generate the nitrenium ions, which underwent intramolecular ring-closure to give the corresponding 17- and 19-membered ring thiamacrocycles in modest yields. These results support the suggestion that MMX calculations on appropriate model compounds may be useful in predicting which precursors will lead to macrocycles and which will not.

Introduction

The synthesis of macrocyclic compounds has attracted extensive attention from synthetic chemists owing to the existence of a number of macrocyclic natural products that exhibit useful biological activities, e.g., vancomycin,[1a] RA-VII,[1b] arnabinol,[1c] combretastatin D-2,[1d] myricanone,[1e] sinuloriolide,[1f] to name but a few. Many effective methods have been developed during the past 20 years, especially for macrolide synthesis. Some involve high-dilution techniques to enhance intramolecular interaction. There was also some consideration of the effect of the conformation of the precursor in the process leading to macrocycle formation. For example, in the synthesis of macrolides,[2−4] intermediates were formed that brought the reacting sites close together, thus favoring lactonization. More recently, Marshall and co-workers[5] have synthesized a series of 12−16-membered propargylic alcohols in good yields through Lewis acid promoted electrophilic ring closure. Post facto molecular modeling calculations (MMX) on the corresponding formyl-O-protonated precursor[6a] showed that the global MMXE minimum is the bent structure in which the reacting alkene site is right under the C═OH$^+$ group. Roussi, Beugelmans, and co-workers[7] formed a 15-membered ring biaryl ether intramolecularly in very good yield and attributed this to a favorable conformation of the cyclization precursor, indicated by molecular modeling to have the two interacting sites within 4.86 A of each other, resulting in a low activation energy (−187.5 kJ/mol) and a favorable entropy for cyclization.

In 1989 we reported the formation (in 30% isolated yield) of a 16-membered ring involving intramolecular aromatic amination by an arylnitrenium ion under normal solution concentration (40 mM) conditions).[8] It was suggested that, in a long flexible chain bearing electron-acceptor and electron-donor end groups, these groups could "recognize" each other and get close enough such that, if this resulted in a lower activation energy for intramolecular cyclization compared with other possible intermolecular pathways (thus satisfying the Curtin-Hammett hypothesis), intramolecular cyclization would take place.

That this novel idea was plausible was first tested by computing the docking of benzene and nitrobenzene in several different approaches.[9] The two lowest energy orientations (nitrobenzene approaching benzene, and benzene approaching nitrobenzene) from MM were carried into MOPAC and minimized. The distance of nearest approach between a hydrogen of one molecule and a carbon of another was 2.8 Å. Nitrobenzene approaching benzene (the plane of the $C_6H_5NO_2$ is above, and orthogonal to that of benzene) had a computed MOPAC energy of 153.7 kJ/mol. The reverse approach (plane of C_6H_6 above, and orthogonal to the plane of $C_6H_5NO_2$) had an energy of 157.9 kJ/mol. This suggested that edge-to-face aromatic interaction may account for the proposed molecular recognition.

(1) (a) Evans, D. A.; Dinsmore, C. J. *Tetrahedron Lett.* **1993**, *43*, 6029. (b) Itokawa, H.; Suzuki, J.; Hitoyanagi, Y.; Kondo, K.; Takaya, K. *Chem. Lett.* **1993**, 695. (c) Yaa, X.-S.; Ehizukz, Y.; Noguchi, H.; Kiuchi, F.; Shibya, M.; Itaka, Y.; Seto, H.; Sankawa, U. *Chem. Pharm. Bull.* **1991**, *39*, 2956. (d) Boger, D. L.; Sakuya, S. M.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 4204. (e) Whiting, D. A.; Wood, A. F. *Tetrahedron Lett.* **1978**, *26*, 2335. (f) Tius, M. A. *Chem. Rev.* **1988**, *88*, 719.

(2) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

(3) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(4) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, *28*, 2455.

(5) (a) Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527. (b) Marshall, J. A.; Anderson, M. W. *J. Org. Chem.* **1993**, *58*, 3912.

(6) (a) Abramovitch, R. A. Unpublished results, 1993. (b) Abramovitch, R. A.; Shi, Q. *Heterocycles* **1994**, *38*, 2347.

(7) Roussi, G.; Zamora, E. G.; Carbonnelle, A.-C.; Beugelmans, R. *Tetrahedron Lett.* **1997**, *38*, 4405.

(8) Abramovitch, R. A.; Chinnasamy, P.; Evertz, K.; Huttner, G. *J. Chem. Soc., Chem. Commun.* **1989**, 3.

(9) Abramovitch, R. A.; Boche, R. Unpublished results, 1993.

10.1021/jo991139z CCC: $19.00
Published on Web 12/29/1999

There has been a great deal of interest lately in edge-to-face aromatic interactions, particularly as regards protein folding patterns[10] and host−guest complexes.[11] These weak, noncovalent interactions are thought to be of fundamental importance in determining the three-dimensional structures and functional properties of molecular systems in biology, chemistry, and material sciences.[10e] It has been stated[10e] that direct measurement of energies of weak noncovalent interactions at room temperature is not possible because these interactions are not strong enough to cause intermolecular complexation in a well-defined orientation. The present paper addresses this topic as well.

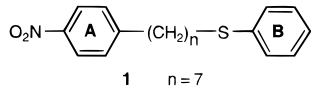
MMX calculations on 1-(4-nitrophenyl)-9-phenylnonane as a model for 1-(4-phenylnitrenium)-9-phenylnonane (the nitro group was used as an erzatz $-NH^+$ since no MM parameters are available for the latter) predicted that the ground state (global energy minimum) conformation was a bent structure in which the nitro group was close to the para position of the 9-phenyl group (ring **B**), and this was confirmed experimentally by 2D NOESY, UV−vis and fluorescence spectroscopy.[6b] On the other hand, and in agreement with the above hypothesis, both 1,9-diphenylnonane and 1-(4-aminophenyl)-9-phenylnonane were predicted to have linear global energy minimum conformations. Thus, replacing the electron-withdrawing nitrophenyl group by the electron-rich aminophenyl eliminates the intramolecular recognition. Subsequently, the corresponding nitrenium ion was found to cyclize to an 18-membered ring in 44% isolated yield.[6b] (The protonated azide and the nitrenium are both highly electron-withdrawing.) The end groups in the corresponding butane were predicted (MMX, 2D NOESY) to be further apart and, in agreement with this prediction, macrocyclization took place in much lower yield.[6b]

More recently, the cyclization of 1-(3-benzyloxy)-2-(4-azidophenyl)ethane (a simpler version of the precursor to our original macrocycle[8]) was studied.[12] MMX calculations predicted, and 2D NOESY confirmed, that, unlike the above-mentioned precursor,[8] this nitrophenyl one had a bent conformation that, if carried over to the nitrenium ion, would lead to six-membered ring formation rather than to a macrocycle. Experimentally, this was indeed found to be the case.[12] These results, together with the earlier ones, suggested that simple MMX calculations could provide a rapid empirical indicator of which precursors would have readily accessible conformations that could then be predictors of whether macrocycles could be formed from these or not.

We now report studies on the formation of the corresponding thiamacrocycles, and conformational studies on the nitrenium ion precursors, model compounds **1** and **2,** which have a phenylthio as the electron-rich end and a *p*-nitrophenyl as the electron-poor end group, separated by a polymethylene chain, to examine further the concept of intramolecular recognition in such systems.

Results and Discussion

We started by using MMX force field calculations[13] to try and predict the global minimum energy conformation of nitro compounds **1** and **2** in the gas phase. Changing

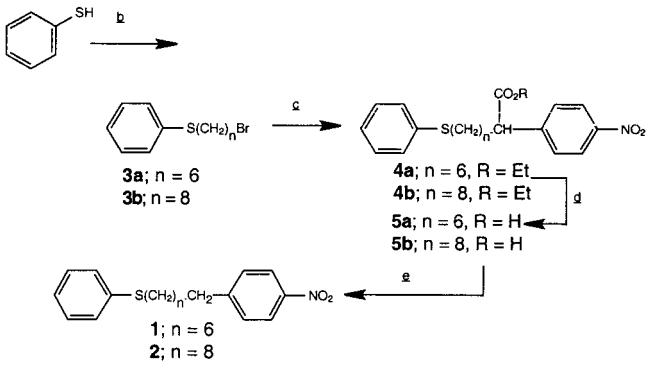


1 n = 7
2 n = 9

the dielectric constant in the computation from 1.5 to 30 had little effect if any on the calculated conformations: the bent conformations (**1B** and **2B**) were the global energy minima, preferred by ca. 29 kJ/mol over the "linear" ones (Figures 1 and 2). If the nitro group is replaced by NH_2 then the "linear" conformations are calculated to be global energy minima, as expected on the basis of the above hypothesis. In **1B** the N-atom is within 3.72−4.72 Å of the ortho- and para-positions of ring **B** at the other end. Similarly, in **2B** the N-atom is within 4.77−5.49 Å of the ortho- and para-positions of ring **B**, further away but still within possible bonding distance of each other.

The synthesis of compounds **1** and **2** is shown in Scheme 1. Phenylthioalkanyl bromides were synthesized

Scheme 1[a]



[a] Reagents and conditions: [b] $Br(CH_2)_nBr$, 10% NaOH, TBAB, 46 °C, overnight, 47−57%. [c] 1.5 equiv of ethyl *p*-nitrophenylacetate, NaH, DMF, 2 days, 76−88%. [d] 10% NaOH, EtOH, 2 h, then HCl, 100%. [e] $CuOCrO_3$, quinoline, 2 h, 72−73%.

in 47−57% yield by the slow addition of thiophenol in benzene solution to a solution of the dibromoalkanes in benzene in the presence of tetrabutylammonium bromide and aqueous sodium hydroxide solution. Temperature seemed to be the key factor for ensuring adequate reaction rates and minimal double substitutions. The bromides were then treated with the sodium enolate of ethyl 4-nitrophenylacetate in DMF, giving the corresponding alkylated products in very good yields. These were hydrolyzed to yield the corresponding acids in excellent yields. Decarboxylation of the acids in quinoline−copper chromite gave the model compounds in good yields.

(10) (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23−28. (b) Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101−109. (c) Kim, E.-I.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192−11193. (d) Burley, S. K.; Petsko, G. A. *Adv. Protein Chem.* **1988**, *39*, 125. (e) Adams, H.; Carver, F. J.; Hunter, C. A.; Morales, J. C.; Seward, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1542−1544. (f) Wedermayer, G. H.; Patten, P. A.; Wang, L. H.; Schultz, P. A.; Stevens, R. C. *Science* **1997**, *276*, 1665.

(11) (a) Rotello, V. M.; Viani, E. A.; Deslongchamps, G.; Murray, B. A.; Rebek, J. *J. Am. Chem. Soc.* **1993**, *115*, 797−798. (b) Schladetzky, K. D.; Haque, T. S.; Gellman, S. H. *Science* **1997**, *276*, 1665.

(12) Abramovitch, R. A.; Ye, Xiaocong. Paper presented at the 211th National Meeting of the American Chemical Society, ORGN 446, New Orleans, LA, March 1996; *J. Org. Chem.* **1999**, *64*, 5904.

(13) Using PC Model from Serena Software. To ensure that a global minimum energy had been reached, the various local minimal structures were altered repeatedly until the lowest energy conformation was reached consistently. Though these computations do not take into account the influence of solvent, they do allow changes in the dielectric constant. The latter has been changed from 1.5 to 30.0 D without much change resulting in the global energy minimum conformations.

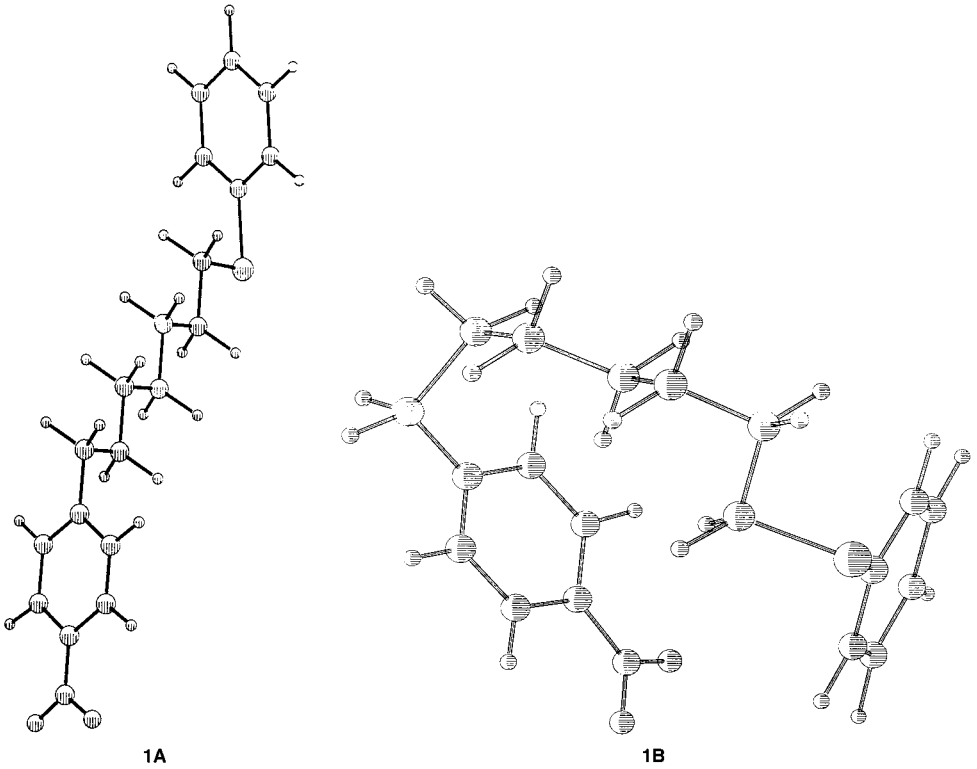


Figure 1. Global minimum energy conformation of compound **1** calculated by MMX force field, compared with a stretched out minimum energy conformation. Relative energies: **1A**, 27.80 kJ/mol; **1B**, 0.00 kJ/mol.

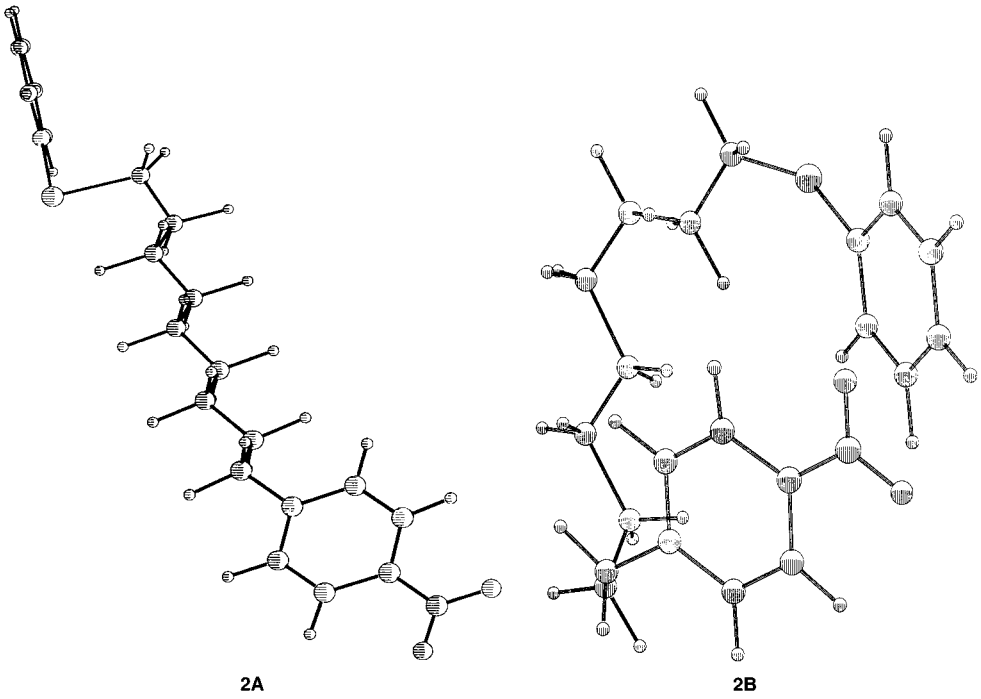


Figure 2. Global minimum energy conformation of compound **2** calculated by MMX force field, compared with a stretched out minimum energy conformation. Relative energies: **2A**, 30.73 kJ/mol; **2B**, 0.00 kJ/mol.

The ground state conformations predicted by the MMX calculations were confirmed using 2D NOESY NMR. In properly executed NOESY experiments, cross-peaks between two hydrogen atoms can only be observed if these are separated by a distance shorter than 5 Å.[14] If the model compounds are indeed in a bent conformation in their ground state in solution, NOE signals between the remote proton sets associated with the aromatic rings will be observed.[14] This was indeed found to be the case.

In the cases of **1** and **2**, cross-peaks for the two aromatic ring protons were not easily observed in $CDCl_3$ solution (cf. refs 6b and 12) because the signals for the protons meta to the nitro group in ring **A** overlap those

(14) Wuthrich, K. *J. Biol. Chem.* **1990**, *265*, 22059. Wagner, G.; Braun, W.; Havel, T. F.; Schaumann, T.; Go, N.; Wuthrich, K. *J. Mol. Biol.* **1987**, *196*, 611.

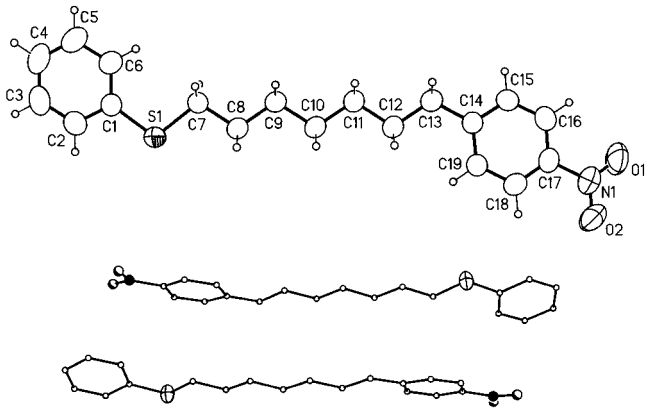


Figure 3. Thermal ellipsoid plot (50% probability) of **1** and pair of "head-to-tail" stacked molecules.

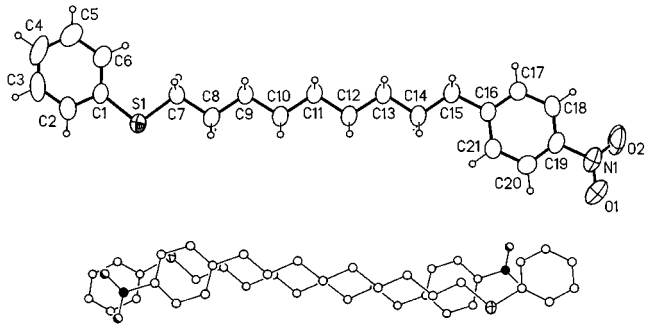


Figure 4. Thermal ellipsoid plot (50% probability) of **2** and pair of "head-to-tail" stacked molecules.

in ring **B**. On the other hand, cross-peaks for the α methylene protons (δ 2.88−2.93 ppm) on the carbon directly attached to the S atom and those directly attached to the nitrophenyl benzylic carbon (δ 2.67−2.72 ppm) are clearly seen in both cases, providing strong evidence for the bent conformations in solution, as predicted by MMX for the gas phase. The cross-peaks were unchanged when the solution was diluted, indicating that they are due to intra- rather than intermolecular interaction (see also ref 6b in which the NOESY data were also supported by UV−vis and fluorescence spectroscopy; see as well the edge to face interactions in the X-ray structures of the *linear* molecules in the *solid phase*: Figures 3 and 4). An acetonitrile solution of **2** showed the same NOE cross-peaks, but these were weaker than in $CDCl_3$. It seems that while hairpin looping of the hydrocarbon chain should be favored by the more polar solvent owing to hydrophilic−lipophilic interactions,[15] this was partly offset by the stronger solvation of one (probably PhS) or both of the terminal aryl groups. As expected, there should be no attraction (electrostatic or edge-to-face aromatic interaction) between an aminophenyl and a phenylthio group, and this was confirmed by both MMX calculations (stretched out global energy minimum conformation) and the absence of **any** NOE cross-peaks for the corresponding primary amines (**6**) run under the same conditions as for the nitro derivatives. This eliminates the possibility that the cross-peaks may be attributed to baseline incorrectness as suggested by a referee.

(15) Jiang, X. K.; Hui, Y. Z.; Fei, Z. X. *J. Chem. Soc., Chem. Commun.* **1987**, 689.

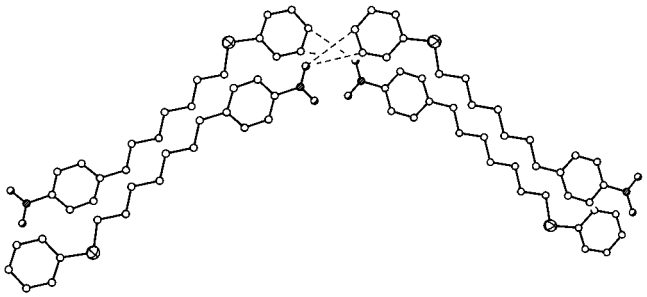


Figure 5. Crystal packing in **1**.

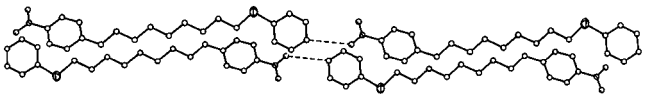


Figure 6. Crystal packing in **2**.

Unlike nitro compounds studied earlier,[6b,12] **1** and **2** were crystalline so that their crystal structures could be determined. These are shown in Figures 3 and 4.[16] Remarkably, it was found that both **1** and **2** exist in the staggered (linear) conformation in the solid state, in marked contrast to their conformations in solution in $CDCl_3$. The molecules are stacked head to tail, with the nitrophenyl above, and make a dihedral angle of 21.9° for **1** and 19.6° for **2** with the phenyl group of the adjacent molecule. The plane of the nitrophenyl group is tilted above the plane of the benzene ring (a compromise between the desired orthogonal approach and steric repulsion). Interestingly, despite very similar molecular conformations and common formations of "head-to-tail" stacked dimers, the crystal packing of the two compounds (shown in Figures 5 and 6) is quite different. In **1**, the molecules assume a "herringbone" pattern in which the dimers stack end-to-end in a zigzag fashion, while in **2** the end-to-end stacking of the dimers is linear. Both of these packing motifs involve weak C−H···O interactions between oxygen atoms of the nitro group and hydrogen

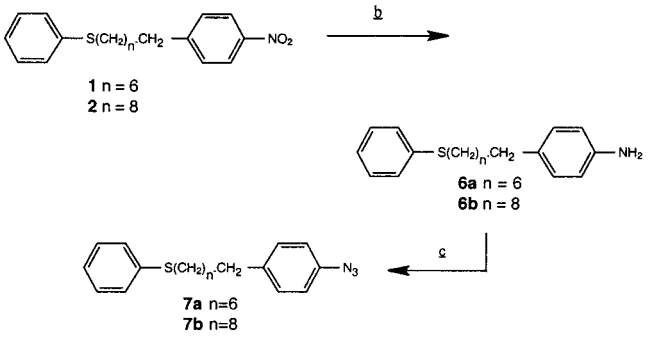
(16) **X-ray crystallographic analysis.** The crystal structures of **1** and **2** were determined from a crystal of dimension 0.10 × 0.30 × 0.35 mm for **1** and 0.12 × 0.29 × 0.46 mm for **2**. Intensity data for both compounds were measured at 22 ± 1 °C by using $\omega/2\theta$ scans ($2\theta_{max}$ = 50 °C) with graphite monochromated Mo Ka radiation (λ = 0.710 73 Å); measurements for **1** were made on a rotating anode-based (18 kW) Rigaku *AFC7R* diffractometer and those for **2** were made on a Nicolet *R3m*V diffractomer. Periodic measurement of three intensity standards indicated no need for a decay correction for either compound. Absorption corrections based on azimuthal scans (ψ-scans) of several moderately intense reflections resulted in normalized transmission factors of 0.94−1.00 for **1** and 0.93−1.00 for **2**; Lorentz and polarization corrections were also applied to the data for both compounds. The structures were solved by using direct methods and refined by using full-matrix least squares techniques. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in optimized positions (d_{C-H} = 0.96 Å) and were allowed to ride on the atom to which they were bonded; isotropic group thermal parameters were refined for all of the hydrogen atoms in each compound (U_{iso}(H): 0.076(2) Å^2 for **1**, 0.068 (2) Å^2 for **2**). Crystal data for **1**: $C_{19}H_{23}NO_2S$, fw 329.44 u, monoclinic space group, *C*2/*c* (No. 15), a = 26.721(5), b = 6.677(1), c = 20.352(4) Å, β = 105.38(3)°, V = 3501(2) Å^3, Z = 8, D_{calc} = 1.25 g cm^{-3}. Final residual values of R = 0.038 and R_w = 0.046 for 1725 observed ($I > 2\sigma(I)$) data. Crystal data for **2**: $C_{21}H_{27}NO_2S$, fw 357.50 u, triclinic space group, *P*1 (No. 2), a = 10.041(3), b = 15.092(4), c = 6.827(2) Å, α = 92.61(2)°, β = 99.09 (2)°, γ = 105.83 (2)°, V = 978.6(4) Å^3, Z = 2, D_{calc} = 1.21 g cm^{-3}. Final residual values of R = 0.041 and R_w = 0.045 for 1774 observed ($I > 2\sigma(I)$) data. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-113072 for compound **1** and CCDC-113073 for compound **2**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

atoms of the thiophenyl group (C···O distances of 3.499(4)−3.520(4) Å in **1** and 3.397(4)−3.509(4) Å in **2**). Apparently, minor differences in these subtle forces and, quite possibly, in crystallization conditions lead to the very different crystal packing patterns observed. It is expected that these two compounds could exhibit polymorphism and that each could form stable crystals of the alternate form.

Thus, while in solution in $CDCl_3$ (and undoubtedly in the gas phase as well) weak attractive intramolecular recognition of the electron-withdrawing and electron-donating end groups leads to the bent structure for these compounds (and hence the expectation that the corresponding nitrenium ions will cyclize to give macrocycles), crystal lattice forces overcome the *intra*molecular attractions and lead to *inter*molecular attraction favoring the linear antiparallel stacking.

Compounds **1** and **2** were then reduced to the corresponding amine using Fe/AcOH, conditions that did not affect the C−S bond. The azides were then obtained as usual (Scheme 2).

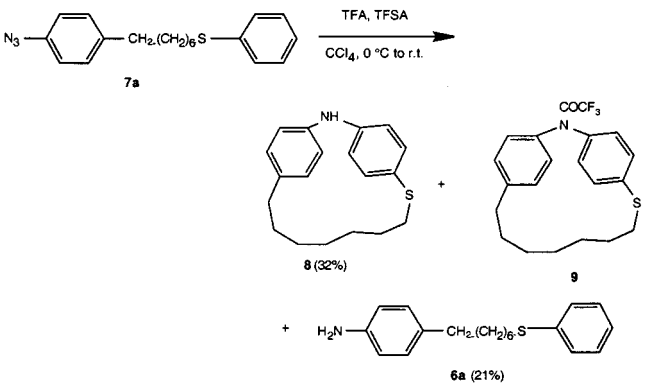
Scheme 2[a]



[a] Reagents and conditions: [b]Fe, AcOH, EtOH, N_2, reflux, 6 h, 98%. [c]HCl, $NaNO_2$, then NaN_3, 65−71%.

Acid-catalyzed decomposition of 1-(4-azidophenyl)-7-phenylthioheptane (**7a**) (Scheme 3) was carried out in carbon tetrachloride solution in the presence of trifluoroacetic acid (TFA) and trifluoromethanesulfonic acid (TFSA) at 0 °C, and the solution was then allowed to come to room temperature and stirred for 24 h. Neutralization and workup gave a mixture whose GC−MS indicated that it consisted of mainly three components: the major one had a parent ion peak at *m*/*z* 297. Of the other two, one had a parent ion peak at *m*/*z* 393 (minor component), and the other at *m*/*z* 299. The one with a molecular weight of 299 is obviously the hydrogen-abstraction product because it gives exactly the same fragmentation

Scheme 3



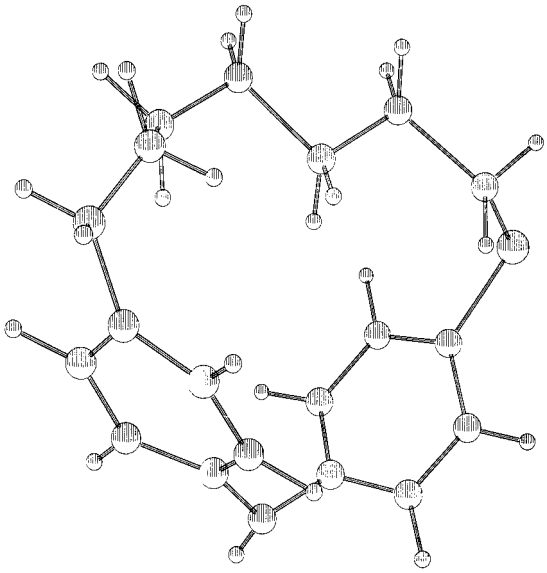


Figure 7. MMX force field calculated global minimum energy conformation of **8**.

patterns as does amine **6a**. The two components with molecular weights of 297 and 393, respectively, were cyclized products, one of which was *N*-trifluoroacetylated (mass 393) and the other one was not (mass 297).

The mixture was resolved by preparative TLC yielding two fractions. The major one (32% yield) had a parent peak at *m*/*z* 297. Its IR spectrum indicated the presence of a secondary aromatic amine (single peak at 3319 cm^{-1}). There was also a strong peak at 843 cm^{-1}, which indicated a 1,4-disubstituted aromatic ring,[17] while the two strong peaks at 731 and 689 cm^{-1} in the starting azide, indicative of a monosubstituted benzene ring, were no longer present, showing that intramolecular cyclization had occurred. The parent ion peak at *m*/*z* 297 corresponds to $C_{19}H_{23}NS$, as expected for the intramolecular cyclization product **8**.

The structure of the major cyclized product was determined by NMR spectroscopy. The most distinguishing feature of this major product was that the two phenyl rings were now both 1,4-disubstituted, as indicated by the presence of three doublets in the aromatic regions: two of these doublets [δ 7.29 (d, J = 8.5 Hz); 6.93 (d, J = 8.3 Hz)] integrated for two protons each, and the other [δ 7.09 (dd, J = 8.3, 8.5 Hz)] represented four protons. The last doublet was actually a doublet of doublets, as seen from an expanded spectrum. An NH group was indicated by the ^{1}H NMR spectrum [δ 3.80 (bs, 1H), D_2O exchange]. Those features strongly suggest that the new bond was formed between the nitrogen atom and the para-position of the thiophenyl ring to give **8**. In addition, all the aliphatic protons absorbed at higher fields than in the uncyclized compound. Eight protons were found to have the chemical shifts below 1.0 ppm and, in particular, two protons resonated at 0.17 ppm. This phenomenon suggested that they were part of a strained ring that caused the shift to higher field. The unusually high chemical shifts for some protons could be explained if these were located above the phenyl ring, thus being strongly shielded by the aromatic ring current. This seems to be confirmed by the global minimum energy

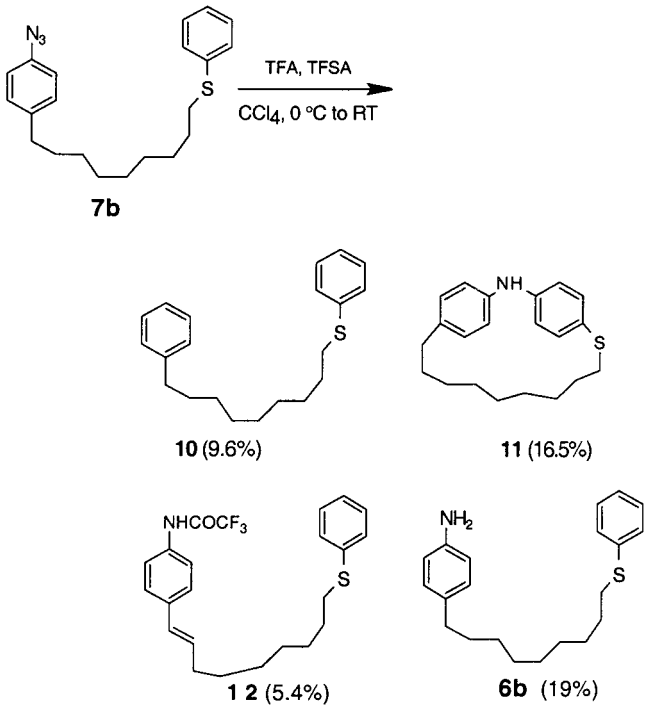
(17) Bellamy, L. J. *The Infrared Spectra of Complex Molecules*; John Wiley & Sons. New York, 1958; p 64.

conformation of macrocycle **8** as calculated using MMX (Figure 7). It can be seen that some of the protons are indeed in the shielding cone of the aromatic rings. The benzylic protons resonate at higher fields than those in azide **7a**, probably because the aryl groups are twisted in a different orientation in the macrocycle.

The trifluoroacetylated macrocycle **9** could not be obtained pure owing its formation in very low yield, while the hydrogen-abstraction product was identical (GC−MS, ^{1}H NMR) with amine **6a**.

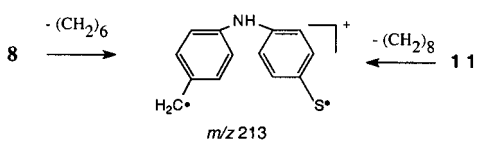
Acid-catalyzed decomposition of 1-(4-azidophenyl)-9-phenylthiononane (**7b**) (Scheme 4) under the same conditions as used for **7a** gave mainly four components, as indicated by GC−MS. One component had a parent ion peak at *m*/*z* 325, and another had one at *m*/*z* 421. The first is the desired macrocycle, and the second is a trifluoroacetylated derivative thereof. The third was the hydrogen-abstraction product (*m*/*z* 327, same fragmentation pattern as **6b**), and the fourth had a parent ion peak at *m*/*z* 312 with a base peak at *m*/*z* 110.

Scheme 4



The mixture was resolved by preparative TLC into four fractions. The first (R_f = 0.85) (ca. 9.6% yield) had a parent ion peak at *m*/*z* 312. The base peak at *m*/*z* 110 indicated that the unmodified phenylthio group was still present, suggesting that deamination had occurred to give 1-phenyl-9-phenylthiononane (**10**). The second fraction (R_f = 0.52) gave a parent ion (also the base peak) at *m*/*z* 325, which corresponds to the desired macrocycle (**11**), $C_{21}H_{27}NS$ (16.5% yield). The second most abundant peak was at *m*/*z* 213, which was also observed with macrocycle **8** (Scheme 5). Microanalysis indicated the presence of a small amount of contaminant (possibly inorganic since no peaks could be attributed to it in the spectral data).

Scheme 5



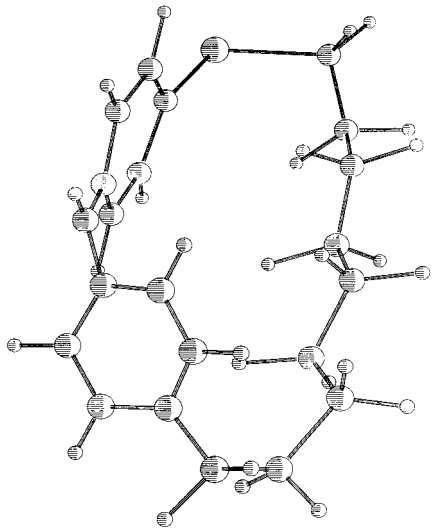


Figure 8. MMX force field calculated global minimum energy conformation of **11**.

Assignment of structure **11** was also supported by its ^{1}H NMR spectrum. Three aromatic proton peaks were present: two 2H doublets [δ 7.27 (d, J = 8.5 Hz), 6.93 (d, J = 8.3 Hz)] and a 4H doublet of doublets [δ 7.03−7.10 (dd, J = 8.3, 8.5 Hz)] indicated that both aryl rings were 1,4-disubstituted. Again, all the aliphatic protons resonated at higher fields than those of the open chain compounds. For example, the two α-methylene protons of **11** resonated at 2.55−2.60 ppm, compared with 2.67−2.93 ppm for amine **7b**; also there are two protons present at 0.66 ppm for **11**, compared with 1.27 ppm for amine **7b**. The aliphatic protons are not as shielded as those in **8**, probably owing to the longer chain length allowing greater flexibility. MMX computation of **11** (Figure 8) confirms that these protons are further removed from the face of the aromatic rings than the corresponding ones in **8**.

The third fraction (R_f = 0.40) was a mixture whose major component had a molecular weight of 421, and it was first assumed that this was the *N*-trifluoroacetylated macrocycle. This was not the case, however, since the mass spectral base peak had *m*/*z* 110, corresponding to C_6H_5SH. One possible structure is **12,** which could be formed as shown in Scheme 6.

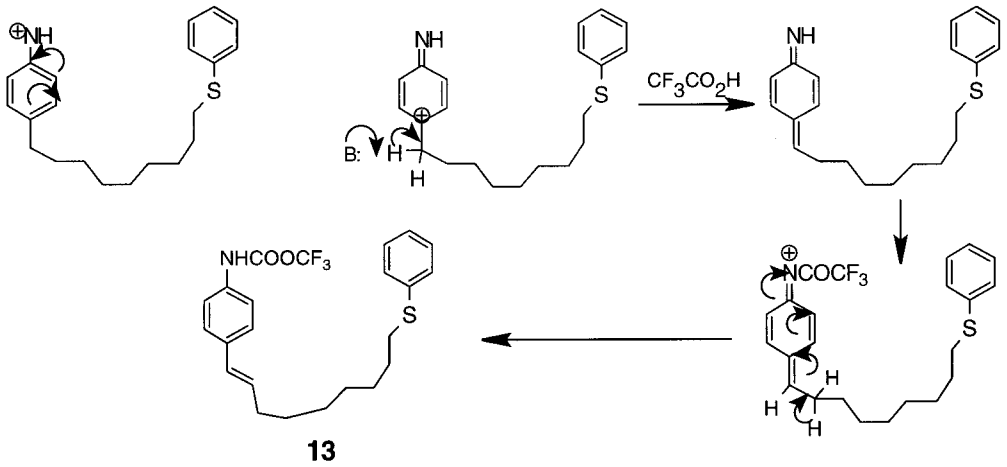
The last fraction (R_f = 0.32) was the hydrogen-abstraction product (**6b**) (GC, GC−MS, NMR) formed in 19% yield.

In conclusion, simple MMX calculations have, once again, been shown to predict the global minimum energy conformations of compounds **1** and **2** in solution, and the corresponding nitrenium ions have undergone intramolecular cyclization to give macrocycles **8** and **11**, albeit in modest yields. The bent conformations of **1** and **2** are probably owing to edge to face attractive aromatic interactions between the electron-poor and the electron-rich terminal aryl groups, which is overcome by crystal packing forces in the solid state.

Experimental Section

General Information. Reactions were conducted either under a dry N_2 atmosphere or in air, as specified. THF was distilled from sodium benzophenone ketyl under a nitrogen

Scheme 6



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atmosphere. Super-dry ethanol was prepared according to the procedure described in Vogel's "Textbook of Practical Organic Chemistry."[17] Benzene, toluene, and diethyl ether were dried over sodium wire. For chromatography, distilled petroleum ether (bp 40−60 °C), hexane, and EtOAc were used. All other solvents and reagents were used directly without further purification, unless otherwise noted. Organic solvents were recovered using a rotary evaporator (water aspirator).

Column chromatography was carried out with Aldrich silica gel (70−230 mesh) or Fisher Scientific basic alumina (80−200 mesh). Thin-layer chromatography was carried out using commercially available aluminum plates coated with a 0.25 mm layer of silica gel containing a 254 nm fluorescent indicator. Preparative TLC was carried out on glass plates (20 × 20 cm) coated with a 1 mm layer of Aldrich silica gel, Merck, TLC grade 7749, with gypsum binder and fluorescent indicator. Flash chromatography was carried out using Universal Adsorbents Inc. silica gel 32−63 (40 μm).

MMX force field calculations were carried out by using PCMODEL (Pi v.4.1) from Serena Software, Bloomington, IN.

The NMR spectra were run on a Bruker AC300 instrument. 2D NOESY spectra were run in either $CDCl_3$ or CH_3CN solution, as specified in the Discussion or in the Experimental Section, with an internal TMS standard. The spectra were acquired in the phase-sensitive TPPI mode: 2K × 1024 FID's of 16 scans over sweep widths of 2262 Hz for compound **1**, 1992 Hz for compound **6a**, 2762 Hz for compound **2**, and 2008 Hz for compound **6b**, with a recycle delay of 2.0 s, and collected at room temperature. The mixing time (τ_m) was 1.0 s. Data were processed in the F_2 dimension with a Gauss function and F_1 dimension with a 45° shifted sine function, and zero filled to 2k × 2k prior to Fourier transformation and phase correction. The spectra were symmetrized prior to plotting.

6-Phenylthiohexyl Bromide (3a). In a 250 mL three-necked round-bottom flask connected to a condenser, a thermometer, and a dropping funnel was placed sodium hydroxide (10 g) in water (90 mL). To this solution was added 1,6-dibromohexane (12 g, 49 mmol) in benzene (50 mL), and tetrabutylammonium bromide (16.1 g, 48 mmol). The solution was heated to 48 °C, and thiophenol (5.7 g, 52 mmol) in benzene (100 mL) was then added dropwise over a period of 12 h. The mixture was stirred at that temperature for 6 h. The reaction mixture was cooled and the organic layer separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with water and dried (Na_2SO_4). Filtration and evaporation of the solvent gave a semisolid crude product (14.1 g), which was purified by chromatography on a column of silica gel. Elution with petroleum ether (bp 40−60 °C) afforded pure **3a** as a colorless liquid (56%). GC−MS (70 eV): *m*/*z* 272 (274) ($M^{\bullet+}$). Anal. Calcd for $C_{12}H_{17}BrS$: C, 52.75; H, 6.27. Found: C, 52.87; H, 6.27.

Ethyl [2-(4-Nitrophenyl)-8-phenylthio]octanoate (4a). Sodium hydride (0.78 g, 19.5 mmol, 60% suspension in mineral oil) was suspended in DMF (40 mL), the suspension was cooled to 0 °C under a nitrogen atmosphere, ethyl 4-nitrophenylacetate (4.06 g, 19.4 mmol) in DMF (40 mL) was added dropwise over a period of 1 h, and stirring continued for 2 h. Bromide **3a** (1.76 g, 6.45 mmol) in DMF (40 mL) was then added dropwise over a period of 1 h, and the resulting suspension was stirred at 0 °C for 1 h, gradually brought to room temperature (RT) over a period of 2 h, and kept there for 45 h. The reaction mixture was quenched with water, and the mixture was evaporated to dryness. The residue was then extracted with ethyl acetate, and the organic phase was washed with water and dried (Na_2SO_4). The filtered solution was decolorized with activated carbon for 1 h at room temperature. Filtration and evaporation of the solvent afforded a red-brown oily liquid (4.85 g). Unreacted starting material was removed by bulb−bulb distillation at ≤160 °C/1.5 mmHg. The residue was purified by chromatography on silica gel using 20% EtOAc in hexane as eluant, to give **1** as a pale yellow solid (0.23 g, 11%), mp 61−63 °C (see synthesis of authentic sample below) and the desired **4a** an oil (1.99 g, 77%). IR (KBr): 1740 (CO_2Et) (s), 1528 (s), 1353 (NO_2) cm^{-1} (s). ^1H NMR ($CDCl_3$): δ 7.26−7.24 (m, 4H), 7.14−7.19 (m, 1H), 3.37−3.42 (t, 2H), 2.89−2.94 (t, 2H), 1.82−1.87 (m, 2H), 1.64−1.68 (m, 2H), 1.45 (bs, 4H). GC−MS (70 eV): *m*/*z* 401 ($M^{\bullet+}$). Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78. Found: C, 65.71; H, 6.82.

2-(4-Nitrophenyl)-8-phenylthiooctanoic Acid (5a). Ester **4a** (1.96 g, 4.89 mol) was dissolved in 10% NaOH solution (8 mL) and ethanol (1 mL). The mixture was boiled under reflux for 2 h. The ethanol was evaporated, and 10% HCl solution (15 mL) was added. The precipitated acid was filtered, washed with water, and dried at 70 °C to give **5a** (1.8 g, 100%) as a yellow-red solid, mp 97−98 °C (from hexane/CH_2Cl_2). Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21. Found: C, 64.47; H, 6.29.

1-(4-Nitrophenyl)-7-phenylthioheptane (1). Acid **5a** (1.77 g, 4.75 mol) was dissolved in quinoline (7 mL), and copper chromite (91.5 mg) was added. The mixture was heated under reflux for 2.5 h in an oil bath kept at 210−220 °C. It was then cooled, treated with 10% HCl (23 mL), and stirred for 2 h. The aqueous solution was extracted with diethyl ether (3 × 50 mL), and the combined organic layers were washed with 10% HCl and water and then dried (Na_2SO_4). Silica gel (40−140 mesh) column chromatography of the crude product [petroleum ether (bp 40−60 °C)/EtOAc, 95:5 v/v] gave **1** (1.14 g, 73%), mp 61−63 °C (from hexane/CH_2Cl_2), identical with the byproduct obtained from **4a** above. IR: (KBr) 1505 (s), 1338 (NO_2) cm^{-1} (s). ^1H NMR ($CDCl_3$): δ 8.12−8.14 (d, 2H, J = 8.47 Hz), 7.24−7.31 (m, 6H), 7.16−7.18 (m, 1H), 2.88−2.93 (t, 2H), 2.67−2.72 (t, 2H), 1.62−1.64 (m, 4H), 1.18−1.42 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 150.62, 146.24, 136.88, 129.10, 128.85, 128.79, 125.67, 123.55, 35.78, 33.51, 30.82, 28.97, 28.87, 28.56. GC−MS (70 eV): *m*/*z* 329 ($M^{\bullet+}$). Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04. Found: C, 69.31; H, 7.03.

1-(4-Aminophenyl)-7-phenylthioheptane (6a). To compound **1** (0.78 g, 2.37 mmol) in methanol (80 mL) was added

hydrazine hydrate (2.4 mL) and Raney Ni (1.5 mL). The suspension was heated under reflux for 3 h. The methanol was evaporated, the residue was extracted with diethyl ether, and the solution was washed with water and dried (Na_2SO_4). Filtration and evaporation of the solvent afforded crude product (0.70 g). GC−MS indicated it was the desired product containing a small amount of 4-heptylaniline (produced by the cleavage of the carbon sulfur bond). The pure product **6a** (mp 49−51 °C) (85%) (from CH_2Cl_2) was obtained after silica gel column chromatography using EtOAc/petroleum ether (bp 40−60 °C) (1:4 v/v). IR (KBr): 3383 (NH_2) (m), 3300 (NH_2) cm^{-1} (w). ^1H NMR ($CDCl_3$): δ 7.23−7.32 (m, 4H), 7.11−7.16 (m, 1H), 6.93−6.96 (d, 2H, J = 8.29 Hz), 6.58−6.61 (d, 2H, J = 8.35), 2.86−2.91 (t, 2H), 2.44−2.49 (t, 2H), 1.51−1.67 (m, 4H), 1.35,1.42 (m, 2H), 1.26−1.32 (m, 4H). ^{13}C NMR: δ 150.62, 146.24, 136.88, 129.10, 128.85, 128.79, 125.67, 123.55, 35.78, 33.51, 30.82, 28.97, 28.87, 28.56. GC−MS (70 eV): m/z 299 ($M^{\bullet+}$). Anal. Calcd for $C_{19}H_{25}NS$: C, 76.20; H, 8.41. Found: C, 76.15; H, 8.43.

1-(4-Azidophenyl)-7-phenylthioheptane (7a). Amine **6a** (100 mg, 0.33 mmol) was dissolved in hot dilute HCl (0.68 mL of concentrated HCl in 3.4 mL of H_2O). The mixture was placed in an ice-bath and cooled to <5 °C and treated with $NaNO_2$ (45 mg) in H_2O (5.6 mL). After stirring for 1.5 h, NaN_3 (45 mg) in H_2O (5.6 mL) was added and the solution was stirred for 1.5 h. It was extracted with ethyl acetate, and the combined organic layers were washed with water and dried ($MgSO_4$). Filtration and solvent evaporation, followed by silica gel column chromatography (hexane) gave **7a** (77 mg, 71%) as a white solid, mp 44.5−45.5 °C. IR (KBr): 2095 (N_3) cm^{-1} (s). GC−MS (70 eV): m/z 299, 190, 146, 123, 106, 77 (no parent ion observed). Anal. Calcd for $C_{19}H_{23}N_3S$: C, 70.10; H, 7.14. Found: C, 69.95; H, 7.05.

Acid-Catalyzed Decomposition of 1-(4-Azidophenyl)-7-phenylthioheptane (7a). Azide **7a** (76 mg, 0.23 mmol) was dissolved in carbon tetrachloride (7 mL) at 0 °C under a nitrogen atmosphere. Trifluoroacetic acid (1.5 mL) and trifluoromethanesulfonic acid (TFSA) (2 drops) were then added dropwise to the solution, which was stirred at 0 °C for 0.5 h and then at room temperature for 24 h. The solution was basified with saturated aqueous sodium bicarbonate, and the CCl_4 layer was separated. The aqueous phase was extracted with methylene chloride, the combined organic layers were washed with saturated aqueous $NaHCO_3$ and then with water and dried (Na_2SO_4). The residue was resolved by preparative TLC (hexane/EtOAc, 9:1 v/v) to give 4,4′-heptylenethiodiphenylamine (**8**) as a white solid, mp 127−128 °C (22 mg, 32%). IR (KBr): 3319 (NH) cm^{-1} (m). ^1H NMR ($CDCl_3$): δ 7.29 (d, 2H, J = 8.5 Hz), 7.09 (dd, 4H, J = 8.3, 8.5 Hz), 6.93 (d, 2H, J = 8.3 Hz), 3.80 (bs, 1H, D_2O exchange), 2.54 (t, 2H, J = 7.2 Hz), 2.40 (t, 2H, J = 7.3 Hz), 1.25−1.36 (m, 2H), 0.81−0.89 (m, 4H), 0.45−0.53 (m, 2H), 0.19−0.24 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 150.90, 147.97, 139.54, 136.27, 129.76, 124.49, 124.33, 36.79, 34.69, 32.48, 29.68, 28.99, 28.59, 26.18. GC−MS (70 eV): m/z 297 ($M^{\bullet+}$). Anal. Calcd for $C_{19}H_{23}NS$: C, 76.70; H, 7.81. Found: C, 76.54; H, 7.82. Two additional products were detected by GC−MS: the hydrogen-abstraction product **6a** (12%), identical with the authentic sample, and a product assumed to be the *N*-trifluoroacetylated macrocycle (**9**): GC−MS (70 eV) m/z 393 ($M^{\bullet+}$), 354, 284, 226, 200, 150, 110, 77.

9-Phenylthiooctyl Bromide (3b). In a 250 mL three-necked round-bottom flask connected to a condenser, a thermometer, and a dropping funnel was placed sodium hydroxide (6.9 g) in water (62 mL). To this solution was added 1,8-dibromooctane (9.5 g, 34.9 mmol) in benzene (34 mL) and tetrabutylammonium bromide (11.1 g, 34.4 mmol). The solution was heated to 48 °C, and thiophenol (4.1 g, 37.3 mmol) in benzene (100 mL) was then added dropwise over a period of 21 h. The mixture was stirred at that temperature for 4.5 h. The reaction mixture was cooled and the organic layer separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water, and dried (Na_2SO_4). Filtration and evaporation of the solvent gave a semisolid crude product (11.1 g), which was purified by chromatography on a column of silica gel. Elution with petroleum ether (bp 40−60 °C) afforded pure **3b** as a colorless liquid, bp 140−160 °C/1 mmHg (47%). GC−MS (70 eV): m/z 300(302) ($M^{\bullet+}$). Anal. Calcd for $C_{14}H_{21}BrS$: C, 55.81; H, 7.03. Found: C, 56.01; H, 7.00.

Ethyl [2-(4-Nitrophenyl)-10-phenylthio]decanoate (4b). Sodium hydride (1.99 g, 49.8 mmol, 60% suspension in mineral oil) was suspended in dry DMF (102 mL), the suspension was cooled to 0 °C under a nitrogen atmosphere, and ethyl 4-nitrophenylacetate (10.41 g, 49.8 mmol) in DMF (102 mL) was added dropwise with stirring over a period of 1 h. Stirring was continued for 2 h, and bromide **3b** (5.0 g, 16.6 mmol) in DMF (102 mL) was then added over a period of 1 h. The resulting suspension was stirred at 0 °C and the temperature gradually raised to room temperature over the course of 2 h and kept there for 46 h. The reaction was quenched with water and the solvent evaporated. The residue was extracted with ethyl acetate, and the organic phase was washed with water and dried (Na_2SO_4). The filtered solution was decolorized with activated charcoal for 1 h at room temperature. Filtration and evaporation of the solvent afforded a red-brown oily liquid (11.7 g). Most of the unreacted starting material was removed by bulb−bulb distillation at ≤160 °C/1.5 mmHg. The residue was purified by chromatography on silica gel using 20% EtOAc in hexane as eluant, to give the desired ester **4b** as an oil (5.39 g, 76%). IR (KBr): 1736 (C═O) cm^{-1} (s). GC−MS (70 eV): m/z 429 ($M^{\bullet+}$). Anal. Calcd for $C_{24}H_{31}NO_4S$: C, 67.09; H, 7.29. Found: C, 67.01; H, 7.22. Additionally, compound **2** was isolated as a pale yellow solid (0.53 g, 9%), mp 53−54 °C. IR (KBr): 1512 (NO_2) (s), 1343 (NO_2) cm^{-1} (s). ^1H NMR ($CDCl_3$): δ 8.11−8.14 (d, 2H, J = 8.7 Hz), 7.24−7.33 (m, 6H), 7.12−7.18 (m, 1H), 2.88−2.93 (t, 2H), 2.67−2.72 (t, 2H), 1.60−1.69 (m, 4H), 1.36−1.43 (m, 2H), 1.29 (bs, 8H). ^{13}C NMR ($CDCl_3$): δ 150.73, 146.21, 136.97, 129.10, 128.77, 125.60, 123.52, 35.81, 33.52, 30.90, 29.28, 29.05, 28.72. GC−MS (70 eV): m/z 357 ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{27}NO_2S$: C, 70.54; H, 7.63. Found: C, 70.52; H, 7.62.

2-(4-Nitrophenyl)-10-phenylthiodecanoic Acid (5b). Ester **4b** (4.7 g, 11 mol) was dissolved in aqueous 5% NaOH solution (19.1 mL) and ethanol (2.73 mL) and boiled under reflux for 2 h. The ethanol was then evaporated, and 10% HCl solution (30 mL) was added to precipitate the carboxylic acid. The product was filtered, washed with water, and dried at 70 °C to give **5b** (4.4 g, 100%) as a yellow-red solid, mp 61−63 °C. IR (KBr): 1705 (CO_2H) (s),1518 (NO_2) (s), 1346 (NO_2) cm^{-1} (s). Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.80; H, 6.79. Found: C, 65.90; H, 6.83.

1-(4-Nitrophenyl)-9-phenylthiononane (2). Acid (**5b**) (4.4 g) was dissolved in quinoline (17 mL), and copper chromite (0.24 g) was added. The mixture was heated under reflux in an oil bath kept at 210−220 °C for 3 h. The mixture was cooled, treated with 10% HCl (50 mL), and stirred for 2 h. The solution was extracted with diethyl ether and the combined organic layers were washed with 10% HCl and then with water and dried (Na_2SO_4). Silica gel (40−140 mesh) column chromatography of the crude product [petroleum ether (bp 40−60 °C)/EtOAc, 95:5, v/v] gave **2** (2.82 g, 72%) as a pale yellow solid with the same physical and spectroscopic data as reported above.

1-(4-Aminophenyl)-9-phenylthiononane (6b). To nitro compound **2** (0.687 g, 1.92 mmol) in ethanol (10 mL) was added glacial acetic acid (1.25 mL) and iron powder (0.54 g). The suspension was heated under reflux for 6.5 h under a nitrogen atmosphere (monitored by TLC). Water (40 mL) was added, and the mixture was extracted with diethyl ether. The solution was washed with saturated aqueous sodium bicarbonate solution and water and then dried (Na_2SO_4). Filtration and evaporation of the solvent afforded pure **7b** (0.626 g, 99.5%), mp 55−56 °C. IR (KBr): 3408 (m), 3340 cm^{-1} (w) (NH_2). ^1H NMR ($CDCl_3$): δ 7.24−7.33 (m, 4H), 7.13−7.18 (m, 1H), 6.95−6.97 (d, 2H, J = 8.22 Hz), 6.60−6.63 (d, 2H, J = 8.25 Hz), 3.53 (bs, 2H), 2.88−2.93 (t, 2H), 2.46−2.51 (t, 2H), 1.61−1.66 (m, 2H), 1.57−1.59 (m 2H), 1.40 (bs, 2H), 1.27 (bs, 8H). GC−MS (70 eV): m/z 327 ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{29}NS$: C, 76.99; H, 8.94. Found: C, 76.88; H, 8.88.

1-(4-Azidophenyl)-9-phenylthiononane (7b). Amine **6b** (160 mg, 0.49 mmol) was dissolved in warm 20% HCl (10 mL).

The mixture was cooled to below 5 °C and treated with $NaNO_2$ (100 mg) in H_2O (5 mL). After the solution was stirred for 1.5 h, NaN_3 (100 mg) in H_2O (5 mL) was added dropwise and the resulting solution stirred for 2 h. It was then extracted with ethyl acetate, and the combined organic layers were washed with water and dried (Na_2SO_4). The crude product was purified by silica gel column chromatography (hexane) to give **7b** (71 mg, 65%) as a white solid, mp 43−45 °C: IR (KBr): 2115 cm^{-1} (s) (N_3). GC−MS (70 eV): *m*/*z* 327, 252, 207, 123, 106, 77. Anal. Calcd for $C_{21}H_{27}N_3S$: C, 71.33; H, 7.71. Found: C, 71.46; H, 7.73.

Acid-Catalyzed Decomposition of 1-(4-Azidophenyl)-9-phenylthiononane (7b). Azide **7b** (36 mg, 0.10 mmol) was dissolved in carbon tetrachloride (4 mL) at 0 °C under a nitrogen atmosphere. Trifluoroacetic acid (0.75 mL) and trifluoromethanesulfonic acid (TFSA) (3 drops) were then added to the solution, which was stirred at 0 °C for 0.5 h and then at room temperature for 24 h. It was basified with saturated sodium bicarbonate, and the CCl_4 layer was separated. The aqueous phase was extracted with methylene chloride. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and then water and dried (Na_2SO_4). Filtration and evaporation of the solvent afforded a mixture whose GC−MS indicated the presence of mainly four components: one component gave a parent ion peak at *m*/*z* 325, and one gave a parent ion peak at *m*/*z* 421. One of the other two components was definitely the hydrogen-abstraction product because of its formula weight (with a parent ion peak at *m*/*z* 327) and the fact that it exhibited the same fragmentation pattern as did amine **6b**. The last component had a parent ion peak at *m*/*z* 312, with a base peak at *m*/*z* 110. The mixture was resolved by preparative TLC. Elution with ethyl acetate−hexane (1:9, v/v) gave four fractions. The first fraction (R_f 0.85) was compound **10** (9.6%): parent ion peak at *m*/*z* 312. The second fraction afforded impure (as indicated by the C, H microanalysis) macrocycle **11** (16.5%). ^{1}H NMR ($CDCl_3$): δ 7.27 (d, 2H, J = 8.5 Hz), 7.08 (dd, 4H, J = 8.3, 8.5 Hz), 6.93 (d, 2H, J = 8.3 Hz), 2.55−2.60 (m, 4H), 1.45 (m, 2H), 1.25−1.28 (m, 4H), 1.09−1.17 (m, 2H), 0.95−1.02 (m, 2H), 0.75−0.81 (m, 4H), 0.66 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 134.44, 129.67, 124.86, 121.23, 35.58, 34.83, 30.72, 29.49, 29.32, 29.14, 28.59, 28.31, 26.50. GC−MS (70 eV): *m*/*z* 325, 282, 227, 213, 181, 152, 91, 77. Anal. Calcd for $C_{21}H_{27}NS$: C, 77.47; H, 8.38. Found: C, 73.56; H, 8.07. The third fraction afforded a mixture that had a major component **12** in about 5.4% yield. GC−MS (70 eV): *m*/*z* 421 ($M^{\bullet+}$), 352, 312, 242, 200, 123, 110 (100%), 91, 77, 65. The last fraction afforded the hydrogen-abstraction product **6b** (19%). ^{1}H NMR ($CDCl_3$): δ 7.24−7.33 (m, 4H), 7.13−7.18 (m, 1H), 6.95−6.97 (d, 2H, J = 8.22 Hz), 6.60−6.63 (d, 2H, J = 8.25 Hz), 3.53 (bs, 2H), 2.88−2.93 (t, 2H), 2.46−2.51 (t, 2H), 1.61−1.66 (m, 2H), 1.57−1.59 (m, 2H), 1.40 (bs, 2H), 1.27 (bs, 8H). GC−MS (70 eV): *m*/*z* 327 ($M^{\bullet+}$), 210, 164, 123, 106, 77, 55.

Acknowledgment. We are grateful for support from the NSF-INT (Grant No. 9304094), and we thank NATO (Grant 930536) for partial support of this work.

Supporting Information Available: 2D NOESY spectra of compounds **1**, **2**, **6a**, and **6b** in deuteriochloroform solution. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991139Z