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Synthesis and molecular orbital calculations of some benzo-substituted macrocyclic diamides and their corresponding macrocyclic dithiodiamides

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Abstract—A new series of benzo-substituted macrocyclic diamides were prepared by nucleophilic reaction of the appropriate dipotassium salts with the corresponding bis(halo) compounds in refluxing DMF. Treatment of the novel macrocyclic diamides with Lawesson's reagent in refluxing toluene led to the formation of the corresponding macrocyclic dithiodiamides in good yields. Molecular orbital calculations were performed at the semi-empirical level AM1 on some of the studied macrocycles. Thermodynamic functions show that the most stable structures in gas phase that have internal amine groups are less in energy than the other ones that have internal carbonyl groups. The solvent polarity does not appreciably affect the stability trend of the three conformers of each compound due to their comparable dipole moments. A complete and thorough survey of proton affinity (PA) and proton detachment energies (PDE) on each of the possible sites has been performed.

1. Introduction

Among the different areas of supramolecular chemistry, the synthesis and complexing properties of crown compounds have been a subject of intensive exploration.[1–7] Since Pedersen[8,9] reported the synthesis and complexing properties of crown ethers, the influence of structure variation within such ligands has received much attention.[10] One such structural variation is the replacement of oxygen with nitrogen and/or sulfur.[7,11] Another is the development of functional groups in the macrocyclic receptors. For example, insertion of an amide group in the ring of the macrocyclic crown ether has been reported to affect the binding properties and selectivity of macrocyclic compounds with metal cations[12,13] as well as organic molecules.[14–16] This effect is due to the dual ligating behavior of the amide O and N atoms,[12,17] in addition to the greater negative character displayed by the oxygen of amides than that of ether and ester functionalities. Recently Kumar and co-workers have reported that diamide-ester macrocyclic compounds showed extraordinary Ag^+ binding strength with a remarkable selectivity for Ag^+ over other metal ions.[18–20] Gokel and co-workers have found that diaza-18-crown-6 derivatives with amide groups in their side arms exhibit extraordinary Ca^{2+} binding strength and remarkable selectivity for Ca^{2+} over Na^+,[21] while a number of synthetic cyclopeptides are K^+ or Ca^{2+} ionophores.[22] Moreover macrocyclic amides are precursors in the preparation of azacrown ethers and cryptands.[1,7,23] Furthermore, some diamide-containing macrocycles have been utilized as new catalysts.[24] However, most conclusions relating the above activities to structural factors are qualitative due to the absence of systematic studies on the electronic properties and bonding characteristics of these macrocycles. The use of quantum chemical methods in studying the electronic structure of various macrocycles is a recent topic in the literature. The hydrogen bonding,[25] tautomerism,[26] cation complexation,[27–30] and many other properties were theoretically studied. For the understanding of these interactions, the estimation of relative energies, which characterize thermodynamic stabilities of possible conformers and tautomers is very important both in theoretical studies and in the investigation of the chemical reactivity of macrocycles.

In connection with these findings, we report here on the synthesis of a series of novel benzo-substituted macrocyclic diamides with expected useful binding properties. Another aim of this work is to pinpoint those structural factors that underlie the bonding characters of those macrocyclic diamides. To achieve this goal, the relative stability and abundance of various conformers of those macrocyclic diamides, the geometrical features of the most stable conformer, and their proton affinities and proton detachment energies are computed.

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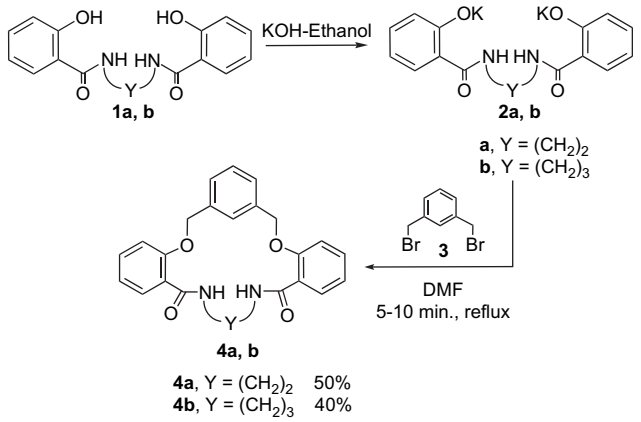
2. Results and discussions

2.1. Synthesis

Previously[31] we reported the synthesis of tribenzo-substituted macrocyclic diamides **4a**,**b** by reacting the appropriate dipotassium salts **2a**,**b** (obtained from the corresponding bis(phenols) **1a**,**b** upon treatment with ethanolic KOH) with 1,3-bis(bromomethyl)benzene **3** in refluxing DMF (Scheme 1).[31]



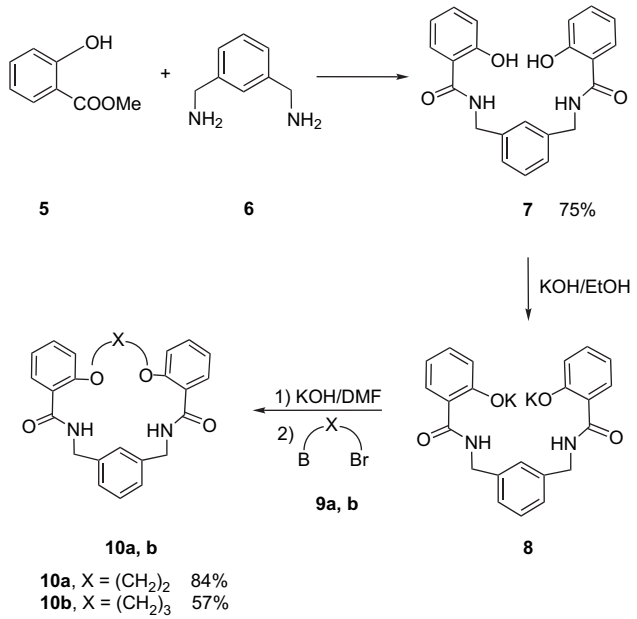
Scheme 1.

In this study we intended to make structure variations within the ligand **4** aiming at improving their binding properties. These structure variations involve the number of donor atoms in the macrocyclic ring, their relative positions, and the size of the chelating rings. These factors, together with the flexibility and the shape of the coordinating moiety, were reported to play an important role in controlling the selective binding of charged or neutral species.[32]

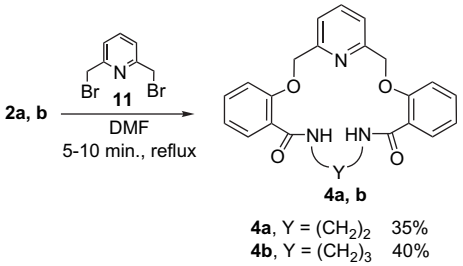
At first we studied an alteration of the arrangement of the donor atoms in macroring **4** by attachment of the 1,3-xylyl unit to the amide group. For this purpose, the bis(phenol) **7** was chosen as a key intermediate and could be readily obtained in 75% yield by reacting methyl salicylate **5** with 1,3-bis(aminomethyl)benzene **6**. Treatment of **7** with ethanolic KOH afforded the corresponding dipotassium salt **8**. Reaction of **8** with each of 1,2-dibromoethane **9a** and 1,3-dibromopropane **9b** in boiling DMF led to the formation of the novel macrocyclic diamides **10a**,**b** in 84% and 57% yields, respectively (Scheme 2).

We also studied another structure variation of ligand **4** by the insertion of additional donor atoms into the macrocycles to increase their binding abilities. In this respect, we recently reported[31] the incorporation of pyridine ring as a subcyclic unit in the macrocyclic ring. This could be successfully achieved in our laboratory by reacting the dipotassium salts **2a**,**b** with 2,6-bis(bromomethyl)pyridine **11** in refluxing DMF to give the pyridino-macrocycles **12a**,**b** in good yields. Such nitrogen containing heterocycles provide rigidity and are able to participate in complexation through their soft donor atoms (Scheme 3).[31]

The insertion of additional donor atoms to ligand **4** as a pendant arm by exchange of the 1,3-xylyl unit with a 2-hydroxy



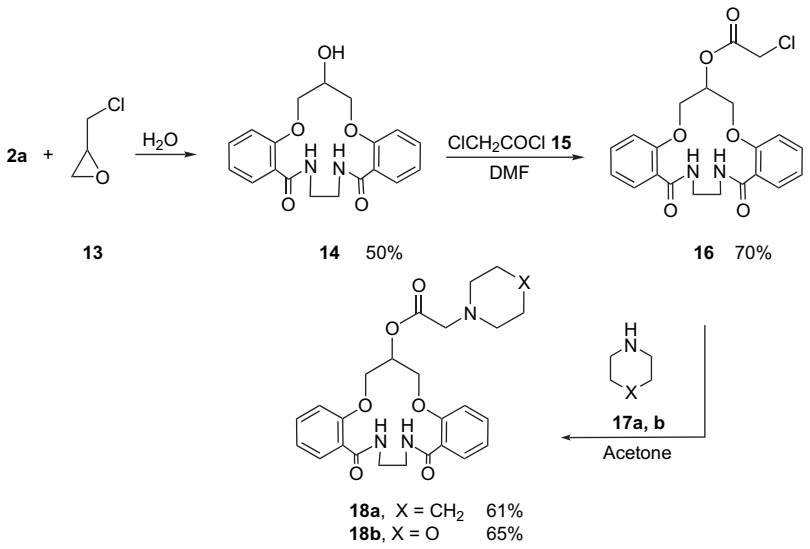
Scheme 2.



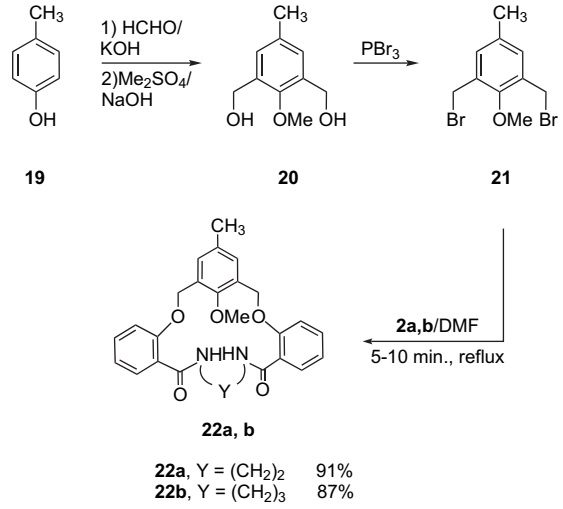
Scheme 3.

propyl group has also been investigated (cf. Scheme 4).[33] Firstly we synthesized the macrocyclic diamide with pendant hydroxyl group **14** by reacting the potassium salt **2a** with epichlorohydrin **13** in aqueous media. Acylation of the hydroxy group of compound **14** with 2-chloroacetylchloride **15** in DMF gave the corresponding chloroacetoxy macrocycle **16**. Subsequent reaction of **16** with piperidine **17a** and morpholine **17b** in acetone afforded the corresponding lariat macrocycles **18a**–**c**.

Our study was extended to include the synthesis of modified derivatives of **4** with additional donor atoms. The dibromo compound **21** serves as starting material for the synthesis of novel macrocycles with one 4-methylanisole group incorporated into the ring system by substitution in the 2,6 positions. Thus, reaction of **21** with the dipotassium salts **2a**,**b** in refluxing DMF afforded **22a**,**b** in 91% and 87% yields, respectively. Compound **21** was obtained from *p*-cresol **19** by first formylation in the presence of base to give the corresponding dihydroxymethyl derivative followed by selective methylation with dimethyl sulfate to give the diol **20**. The two hydroxymethyl groups of the latter were converted with PBr_3 to the bromomethyl derivative **21** in quantitative yield (Scheme 5).[34,35]



Scheme 4.



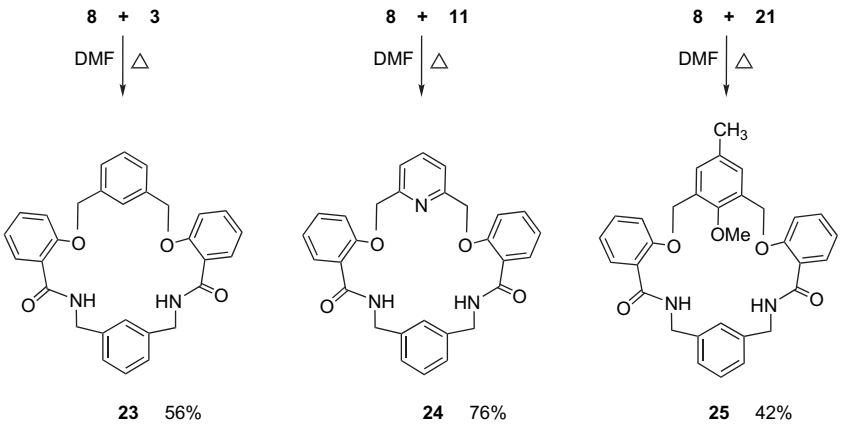
Scheme 5.

We also studied the insertion of an additional 1,3-xylyl unit into the macrocyclic rings **10**, **12**, and **22** instead of the ethylene or the propylene moiety. Our object was to study the effect of rigidity provided by these groups on the ability of the ligands to form stable complexes compared to other macrocyclic analogues.

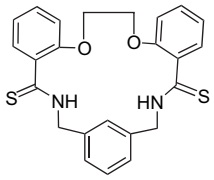
Thus, the macrocyclic diamides **23**–**25** could be obtained in 56%, 76%, and 42% yields, respectively, by the reaction of the dipotassium salts **8** with **3**, **11**, and **21**, respectively, in refluxing DMF (Scheme 6).

The novel macrocyclic diamides, now available, led us to study their possible transformation to other functionalized derivatives. Thioamides are known to be weaker hydrogen-bond acceptors and stronger acids than amides.[36,37] For these reasons, thioamides are attractive groups for the construction of anion hosts. Thioamide groups were recently successfully introduced into macrocyclic systems by us and some research groups.[31,38–43] The novel macrocyclic dithiodiamides **26** and **27a**,**b** were prepared in 70–72% yields upon treatment of each of the macrocyclic diamides **10a** and **22a**,**b** with Lawesson's reagent in refluxing toluene.

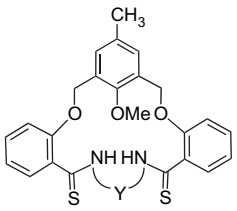
The macrocyclic dithiodiamides **28a**,**b** and **29a**,**b** were recently synthesized by Elwahy and Abbas[31] by thiation of the corresponding macrocyclic diamides under similar conditions.



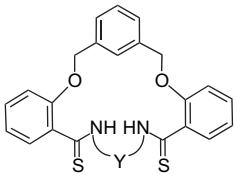
Scheme 6.



26 70%

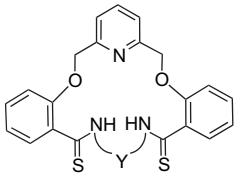


27a, Y = $(CH_2)_2$ 71%
27b, Y = $(CH_2)_3$ 72%



28a, b

28a, Y = $(CH_2)_2$ 50%
28b, Y = $(CH_2)_3$ 44%



29a, b

29a, Y = $(CH_2)_2$ 72%
29b, Y = $(CH_2)_3$ 70%

The enthalpy change ΔH for this process is calculated using Eq. 2.

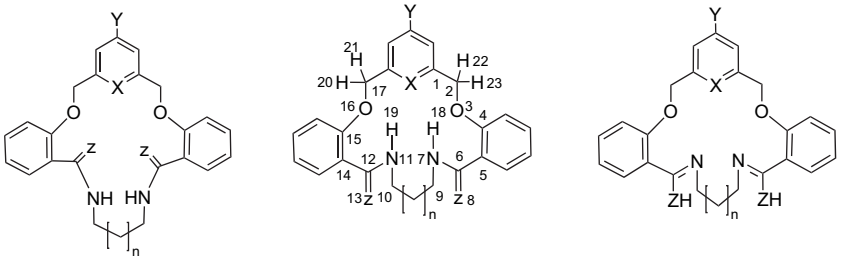
$$\Delta H = \Delta E + \Delta \mathrm{ZPE} + \Delta \mathrm{TC} \quad (2)$$

Here, ΔZPE and ΔTC are the difference in zero point energy and thermal correction of the same two conformers. Finally, the corresponding free energy change ΔG can be evaluated using Eq. 3.

$$\Delta G = \Delta H - T\Delta S \quad (3)$$

T is the absolute temperature and ΔS is the entropy difference.

2.2.1. Energy and stability. Compound **4a** can exist in three conformer structures two of them (A and B) are according to the rotation of its subsystem (O═C–NH–) around the single C–C bonds, and the third one (C) to the position of the hydrogen atom (keto⇆enol tautomerism). (The orientation and numbering system used through this part is shown in Figure.)



A **B** **C**

no.	Z	X	Y	n
4a (28a)	O, (S)	CH	H	0
4b (28b)	O, (S)	CH	H	1
12a (29a)	O, (S)	N	H	0
22a (27a)	O, (S)	C-OMe	Me	0
22b (27b)	O, (S)	C-OMe	Me	1

2.2. Molecular orbital calculations

Although using ab initio methods to generate molecular geometries is well established,[44] large size molecules are time-consuming problems. For these problems, semi-empirical methods are essential.[45,46] Theoretical calculations were carried out at the restricted Hartree–Fock level (RHF) using AM1[47] semi-empirical SCF-MO method, incorporated in the MOPAC 7.0 program.[48] Each structure was fully optimized without any constrains to a gradient of 0.01 using eigenvector following method (EF) at the precise level. The nature of each structure was tested using force field calculations, the stationary points are those without imaginary frequency. Thermodynamic properties, ΔH_f, ΔS, and ΔG were also calculated using the following equations.

The energy difference ΔE between any two conformers 1 and 2 is given by Eq. 1.

$$\Delta E = E_1 - E_2 \quad (1)$$

E_1 and E_2 are the total energies of the two conformers.

The three forms of this compound were found to represent stationary points in their potential energy surface. No imaginary frequencies were obtained in force calculations. Table 1 shows the relative total energies ΔE of the studied series. The results show that conformer B is the most stable one and structure A has 28.4 kcal/mol more than B. The enol form C is found to be only 22.2 kcal/mol more than its keto form (B) therefore, in the gas phase the order of relative stabilities of the three structures is

$$B > C > A$$

The higher stability of form (B) is attributed to the electrostatic interactions between the negatively charged etheric oxygen atoms (−0.234 and −0.225) and the two positive amide hydrogen atoms (NH) (+0.234 and +0.232). The calculated O···H distances are 2.335 and 2.192 Å, Table 2. On the other hand, the existence of nonbonding interactions and the repulsion forces between the two oxygen atoms O3 and O8 and the other pairs O13 and O16 lead to the instability of conformer A. Table 1 contains the thermodynamic functions that govern the above conversions. The free energy changes ΔG

Table 1. Relative energies ΔE (kcal/mol), dipole moment μ (D), entropy S (cal/K/mol), zero point energy ZPE (kcal/mol), thermal correction TC (kcal/mol), enthalpy change ΔH (kcal/mol), and free energy change ΔG (kcal/mol) of different conformers of the studied series

Property	Conformer	**4a** (**28a**)	**12a** (**29a**)	**22a** (**27a**)	**4b** (**28b**)	**22b** (**27b**)
ΔE	A	28.18 (38.87)	57.04 (23.78)	— (—)	3.75 (20.24)	22.77 (60.72)
	B	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	C	22.36 (11.36)	25.47 (18.56)	28.18 (9.44)	22.46 (11.09)	23.67 (9.53)
μ	A	5.41 (8.30)	4.36 (6.12)	— (—)	2.08 (2.39)	1.21 (0.57)
	B	7.62 (4.12)	8.65 (9.53)	15.38 (9.87)	5.80 (5.19)	6.97 (7.30)
	C	6.86 (6.63)	5.42 (8.37)	8.25 (10.22)	6.42 (6.21)	8.91 (9.66)
S	A	166.1 (172.2)	157.8 (167.0)	— (—)	176.8 (174.8)	187.6 (181.1)
	B	175.7 (179.5)	163.7 (178.1)	186.4 (187.1)	182.2 (186.4)	191.1 (184.3)
	C	178.6 (183.6)	169.2 (182.2)	187.9 (190.4)	180.0 (187.3)	187.8 (197.7)
ZPE	A	268.4 (267.5)	262.8 (260.1)	— (—)	288.5 (285.1)	309.1 (304.7)
	B	270.3 (266.7)	263.2 (259.5)	291.2 (287.6)	288.6 (284.9)	309.4 (306.7)
	C	269.6 (263.4)	266.2 (256.2)	290.7 (284.4)	288.4 (281.8)	308.9 (302.5)
TC	A	15.9 (16.1)	15.2 (16.0)	— (—)	16.3 (16.9)	17.5 (18.0)
	B	16.4 (16.6)	15.5 (16.5)	17.9 (18.2)	16.5 (16.5)	17.7 (18.5)
	C	16.6 (17.1)	15.8 (16.9)	18.0 (18.5)	17.0 (17.7)	18.5 (19.3)
ΔH	B–A	25.8 (39.2)	56.3 (29.7)	— (—)	3.5 (20.6)	22.3 (58.2)
	B–C	22.1 (8.6)	28.8 (15.7)	27.8 (6.5)	22.8 (9.2)	24.0 (6.1)
ΔG	B–A	28.1 (41.4)	58.1 (33.0)	— (—)	5.1 (24.1)	23.3 (59.2)
	B–C	21.3 (7.4)	27.2 (14.5)	27.4 (5.5)	22.1 (8.9)	24.1 (2.1)

Table 2. Some selected bond lengths (Å) for the studied compounds, form (B), calculated at the AM1 level

Parameter	**4a** (**28a**)	**12a** (**29a**)	**22a** (**27a**)	**4b** (**28b**)	**22b** (**27b**)
C1–C2	1.492 (1.492)	1.511 (1.510)	1.493 (1.443)	1.439 (1.493)	1.492 (1.492)
C2–O3	1.441 (1.441)	1.435 (1.436)	1.431 (1.431)	1.442 (1.443)	1.443 (1.443)
C4–O3	1.389 (1.390)	1.383 (1.384)	1.389 (1.385)	1.388 (1.388)	1.390 (1.391)
C4–C5	1.491 (1.485)	1.493 (1.484)	1.492 (1.482)	1.494 (1.484)	1.494 (1.484)
C5–N7	1.378 (1.361)	1.378 (1.362)	1.380 (1.362)	1.376 (1.361)	1.376 (1.358)
C5–O8(S)	1.250 (1.595)	1.250 (1.598)	1.252 (1.602)	1.251 (1.599)	1.250 (1.600)
C9–N7	1.436 (1.439)	1.435 (1.439)	1.440 (1.442)	1.438 (1.441)	1.440 (1.443)
C9–C10	1.454 (1.543)	1.545 (1.542)	1.538 (1.537)	1.526 (1.525)	1.529 (1.525)
C10–N11	1.436 (1.440)	1.435 (1.439)	1.438 (1.440)	1.437 (1.361)	1.435 (1.441)
C12–N11	1.386 (1.365)	1.379 (1.363)	1.376 (1.359)	1.379 (1.362)	1.376 (1.360)
C12–O13(S)	1.251 (1.600)	1.250 (1.599)	1.252 (1.602)	1.251 (1.600)	1.251 (1.602)
C12–C14	1.493 (1.483)	1.493 (1.483)	1.493 (1.493)	1.493 (1.484)	1.493 (1.438)
C15–O16	1.386 (1.382)	1.383 (1.384)	1.390 (1.390)	1.382 (1.383)	1.382 (1.383)
C17–O16	1.493 (1.439)	1.455 (1.434)	1.493 (1.392)	1.439 (1.441)	1.438 (1.392)
O3–CH22	2.110 (2.100)	2.102 (2.104)	2.100 (2.102)	2.008 (2.108)	2.092 (2.090)
O3–CH23	2.100 (2.090)	2.090 (2.087)	1.990 (1.993)	2.083 (2.085)	2.100 (2.100)
O3–NH18	2.335 (2.413)	2.343 (2.379)	2.235 (2.262)	2.241 (2.300)	2.241 (2.336)
O16–NH18	2.192 (2.210)	2.280 (2.322)	2.258 (2.268)	2.237 (2.263)	2.280 (2.290)
O16–CH20	2.098 (2.114)	2.072 (2.062)	2.097 (2.097)	2.105 (2.109)	2.104 (2.083)
O16–CH21	2.092 (2.080)	2.120 (2.126)	2.094 (2.092)	2.083 (2.086)	2.085 (2.106)

for the two conversions B to A or C are 28.1 and 21.3 kcal/mol, which are highly positive indicating the predominance of the B form. The three conformers, A, B, and C, are high polar and have comparable dipole moments, Table 1. Consequently, equivalent stabilization in polar solvents is expected and thus their relative abundance and stability in solution should not appreciably differ to that in the gas phase.

Replacement of the benzene ring in compound **4a** by a pyridine ring to produce compound **12a** does not affect the stability trend of the various conformers. Table 1 shows the AM1 results for such compound and indicates only the change of the values of the stability differences. In compound **22a** the substitution by the bulky $-OCH_3$ group in the *ortho* position of the benzene ring retards the rotation of (CONH) group. Therefore, only B and C conformers are theoretically detected at this level. The nonbonding interactions between the $-OCH_3$ and C═O groups and also the steric factor that disables the existence of A. On the other hand, structure C has 28.2 kcal/mol higher energy than its keto form (B).

The above retarding interactions, electrostatic, nonbonding, and steric factors, can be diminished by elongation of the hydrocarbon part, i.e., increase of ring size as in case of **4b** and **22b**. The three conformers of **4b** were optimized to the best and least energy structure by the same method; the results are collected in Table 1. The results show, comparing to compound **4a**, the increase of stability of conformer A relative to the B form. The energy difference between the two forms becomes only 3.75 kcal/mol compared with 28.1 kcal/mol in the case of compound **4a**. The relative stabilities of structures A and C are changed in order where the A form is found to be more stable than the C form by 18.73 kcal/mol, i.e., the order of stability is B>A>C this means that the two forms A and B may exist in an

equilibrium gaseous mixture. On increasing the ring size in compound **22b**, the difference in stability between A and B forms is only 22.8 kcal/mol while that between B and the enol form C is only 23.7 kcal/mol.

The thione isomers, **28a**, **29a**, **27a**, **28b**, and **27b**, have the same conformational and structural features as those for keto forms. The thio analogues stabilize the C form more than the enol one, Table 1. ΔG values for C forms of **28a**, **29a**, and **27b** are small indicating their higher abundance relative to B than in the case of their keto analogues.

2.2.2. Gas-phase acidities. In solution, the studied macrocycles may act as a base through proton abstraction on the carbonyl oxygen, amine nitrogen or the etheric oxygen, forming a positive species. They may also act as an acid by the loss of amine (B) proton or enol hydroxyl (C) protons forming a negative ion. The proton affinity PA or the proton detachment energy PDE of an acid may be defined as for a gas phase reaction $A^-+H^+=AH$.

$$\mathrm{PDE} = -\Delta E_{\mathrm{o}}^{\mathrm{el}} - \Delta\mathrm{ZPE} - \Delta C_{\mathrm{P}}\mathrm{d}t \quad (4)$$

where $\Delta E_{\mathrm{o}}^{\mathrm{el}}$ is the electronic energy difference $[E(A^-)-E(AH)]$; ΔZPE is the zero point energy difference; ZPE(A^-)−ZPE(AH), and ΔC_{P} is the difference of constant pressure molar heat capacities.

$$C_{\mathrm{P}}(H^+) + C_{\mathrm{P}}(A^-) - C_{\mathrm{P}}(HA) \quad (5)$$

This term is neglected due to its small contribution since A^- and AH have the same number of rotational degrees of freedom. ZPEs of A^- and AH are small comparing to E^{el}, therefore PDE can be reduced to the first term only.

For each molecule under investigation, the proton can attach to three different centers, i.e., carbonyl oxygen, etheric oxygen, and amino nitrogen. In the following part, the PA for each center is calculated to find out the most probable center of basicity and compares it with the expected experimental results.

In this section a complete and through survey of PA and PDE on each of the possible sites of the studied compounds has been performed to select the most probable site in the case of each one. The PA and PDE values for the studied series are summarized in Table 3. The net charges collected in Table 4 show that the most negative centers in the most stable tautomer are the oxygen (sulfur) and nitrogen atoms of the amide group. The difference between the charges on the two atoms is only 0.01 while the etheric oxygen has much less negative charge. Therefore, it is expected that the protonation is favored at the amide or thioamide groups. Table 3 shows the PA energies calculated at the three centers, which show that protonation is more energetically favored on the amide oxygen or nitrogen atoms. This is attributed to the lone pair of electrons of the oxygen (sulfur) and nitrogen atoms possessing more directional character and being less strictly hindered as compared to those of O3.

The investigated macrocyclic diamides or their dithoamides can act as acids and they possess the tendency to lose the amide proton from N7 or O8(S8). In conformer B, the PDE(N7) is greater than PDE(O8) by 11–13 kcal/mol and by 5–9 kcal/mol over PDE(S8) in conformer C, which means the deprotonation of conformer C is energetically favored. Since the alkylation position depends on the relative activity and nucleophilicity of NH, OH, and SH it is expected that monoalkylation occurs at S- before N- due to the higher acidity of SH than NH.

2.2.3. Geometry. The geometrical parameters of the most stable conformers (A, B, and C) of the studied compounds are collected in Table 2 and represented in Figure 1. All

Table 3. Proton affinity (PA) and proton detachment (PDE) energies (kcal/mol) for the studied compounds calculated using AM1 method

Property	**4a** (**28a**)	**12a** (**29a**)	**22a** (**27a**)	**4b** (**28b**)	**22b** (**27b**)
PA(O3)	−199.64 (−133.40)	−136.85 (−144.90)	−143.06 (−178.48)	−144.21 (−150.65)	−142.14 (−178.25)
PA(O8)	−227.70 (−195.50)	−167.21 (−195.50)	−188.83 (−180.87)	−172.04 (−175.72)	−174.43 (−178.48)
PA(N7)	−224.48 (−158.24)	−171.12 (−173.76)	−184.00 (−166.06)	−166.06 (−178.94)	−172.96 (−172.50)
PDE(N7)	257.60 (276.46)	284.05 (281.06)	298.31 (282.67)	300.61 (273.70)	298.31 (277.38)
PDE(O8)	243.34 (272.32)	273.01 (275.31)	287.27 (270.25)	289.57 (266.80)	286.81 (270.71)

Table 4. Ionization potential (eV), electron affinity (eV), energy gap (eV), and charge density at some atoms of the studied compounds, form B

Parameter	**4a** (**28a**)	**12a** (**29a**)	**22a** (**27a**)	**4b** (**28b**)	**22b** (**27b**)
O3	−0.243 (−0.246)	−0.217 (−0.219)	−0.217 (−0.218)	−0.238 (−0.242)	−0.235 (−0.239)
N7	−0.365 (−0.277)	−0.968 (−0.277)	−0.361 (−0.281)	−0.370 (−0.280)	−0.361 (−0.274)
O8(S)	−0.373 (−0.228)	−0.379 (−0.237)	−0.379 (−0.247)	−0.380 (−0.241)	−0.379 (−0.249)
N11	−0.368 (−0.288)	−0.362 (−0.284)	−0.357 (−0.267)	−0.366 (−0.280)	−0.368 (−0.279)
O13(S)	−0.379 (−0.234)	−0.378 (−0.236)	−0.384 (−0.256)	−0.384 (−0.242)	−0.385 (−0.256)
O15	−0.225 (−0.226)	−0.213 (−0.270)	−0.233 (−0.237)	−0.226 (−0.237)	−0.210 (−0.214)
H18	0.234 (0.238)	0.241 (0.240)	0.245 (0.253)	0.242 (0.245)	0.240 (0.249)
H19	0.232 (0.239)	0.238 (0.245)	0.250 (0.253)	0.236 (0.240)	0.240 (0.248)
H20	0.091 (0.1)	0.093 (0.095)	0.09 (0.089)	0.091 (0.087)	0.090 (0.094)
H21	0.99 (0.09)	0.111 (0.102)	0.12 (0.122)	0.088 (0.093)	0.100 (0.110)
H22	0.092 (0.095)	0.092 (0.098)	0.10 (0.087)	0.095 (0.097)	0.080 (0.082)
H23	0.093 (0.094)	0.103 (0.113)	0.09 (0.095)	0.088 (0.089)	0.087 (0.092)
μ, D	7.62 (8.78)	8.65 (9.53)	8.01 (8.99)	5.80 (5.193)	7.65 (7.30)
I.P, eV	9.393 (8.333)	9.329 (8.250)	9.402 (8.200)	9.47 (8.323)	9.340 (8.180)
E.A., eV	−0.262 (−0.677)	−0.611 (−0.709)	−0.426 (−0.693)	−0.308 (−0.632)	−0.384 (−0.696)
ΔE_{g}, eV	9.131 (7.656)	9.940 (7.541)	8.976 (7.507)	9.162 (7.691)	8.956 (7.484)

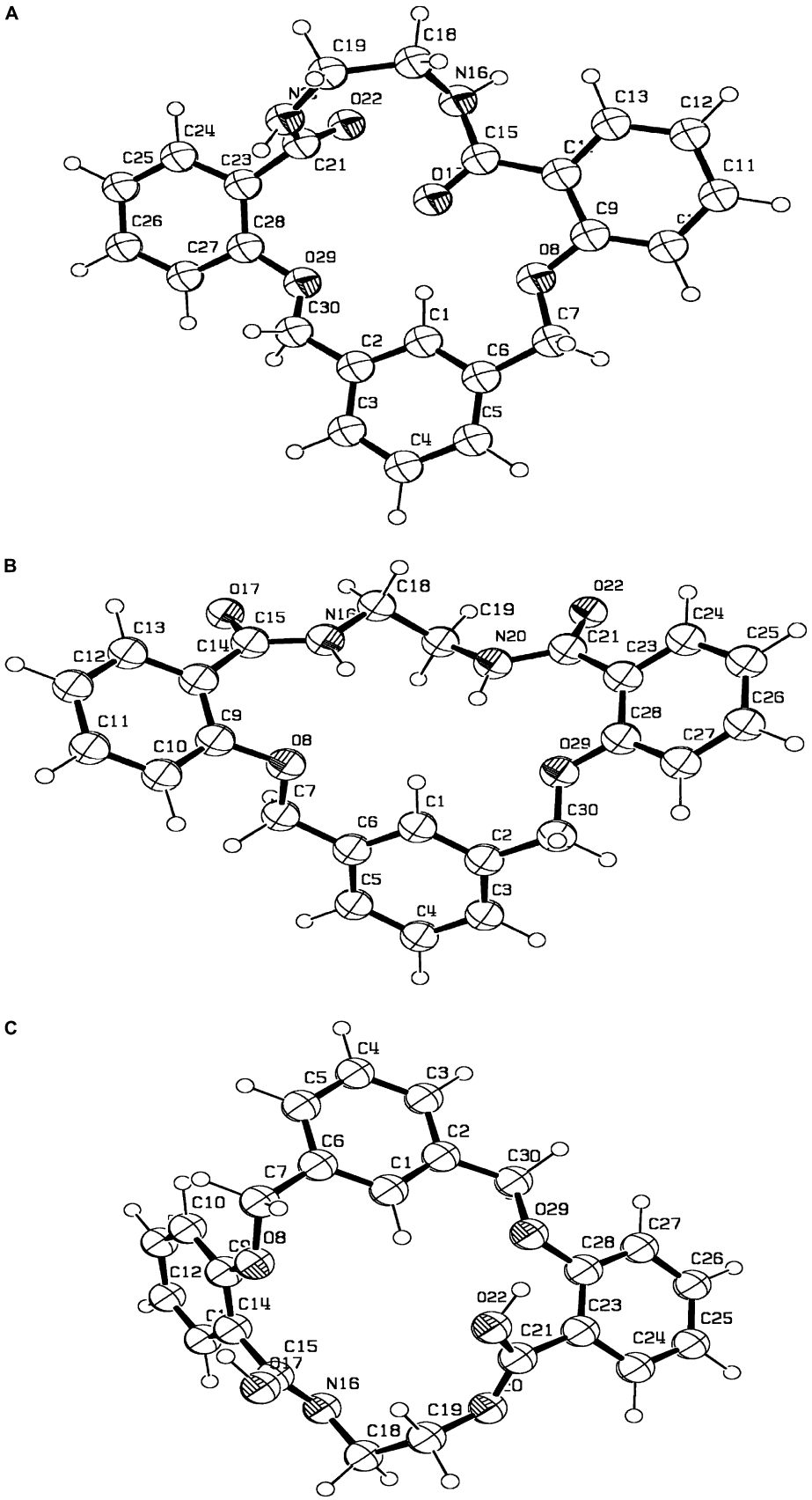


Figure 1. Optimized geometry of the three forms (A, B, and C) of **4a**.

studied compounds are nonplanar. The results show that the lengths of the same bonds are nearly identical, the difference is only ±0.005 Å. This is explained by the weak interactions between different parts in the same molecule. Thus, the effect of the $–OCH_3$ group or pyridyl moiety on the geometry of the corresponding compounds is negligible. The variation of different bond angles and dihedral angles is attributed to avoid the steric and nonbonding interactions.

In compounds **4a** and **12a**, the two hydrogen atoms H_{35} and H_{36} are equivalent with respect to interactions with different atoms in their vicinity as indicated by O···H distances, the C–H bond length and their atomic charges, Tables 2 and 4. In the case of compound **4a**, the difference between $O\cdots H_{35}$ and $O\cdots H_{36}$ lengths is only 0.01 Å, the same value is found in case of $O_8\cdots H_{50}$ and $O_8\cdots H_{51}$, while the two hydrogen pairs have atomic charges of 0.099 and 0.093, respectively. The same results were also found for compound **12a** and the thio derivatives, Tables 2 and 4. On the other hand, in the case of compound **22a** the bulky $–OCH_3$ group disturbs this equivalence, which is reflected by different O···H distances (2.10 and 1.99 Å), i.e., one H atom becomes more attracted to both the etheric and methoxy oxygen atoms, Table 2. The calculated atomic charges on both atoms become 0.12 and 0.09, respectively. As the ring size increases, for compounds **4b** and **22b**, this effect disappears (Fig. 2). The two hydrogen atoms are now equally affected by the two oxygen atoms, which appear as nearly equal $O_8\cdots H$ distances and atomic charges. This means that the strain caused by $O–CH_3$ group decreased as the ring size increases. Experimentally, the 17-membered macrocycles **22a** and **27a** show geminal coupling and nonequivalence in all OCH_2 protons in their ^1H NMR spectra. The multiplicity of the $ArCH_2O$ proton chemical shift in the ^1H NMR spectra of these macrocycles indicated that they are evidently present in one stable conformer or as slow (on the time scale of NMR) interconverting conformers. Evidence for the existence of macrocycle **22a** entirely as one stable nonconvertible conformer comes from ^{13}C NMR data (cf. Section 4).

This indicated that the CH_3O group could not pass through the center of their macroring rapidly enough on the instrument's time scale at ambient temperature to provide equivalent environments for these methylene protons.

On the other hand, equivalent magnetic environments were observed for all four $–OCH_2–$ protons in compounds **22b**, **23**–**25**, and **27b** at ambient temperature indicating rapid conformational exchange in these macrocycles.

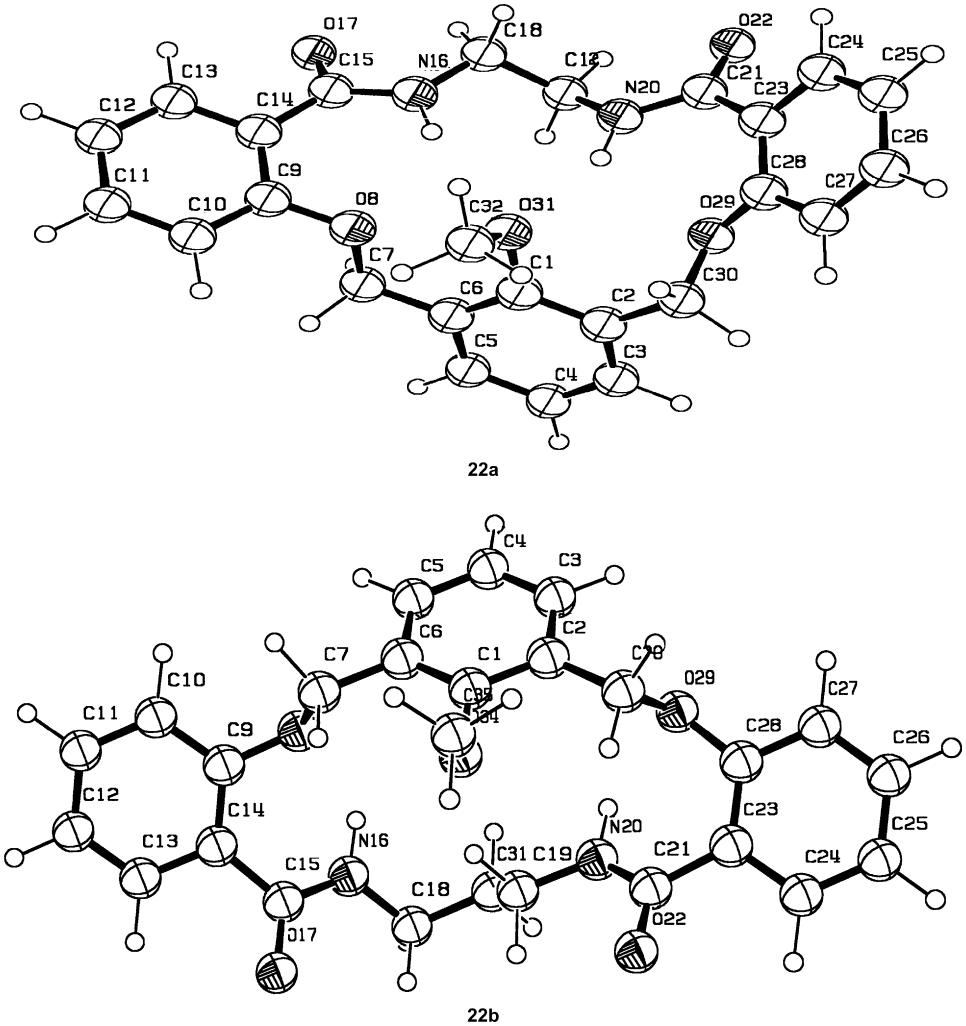


Figure 2. Optimized geometry of compounds **22a**,**b**.

3. Conclusion

In conclusion, we prepared a new series of macrocyclic diamides and their corresponding macrocyclic dithiodiamides by making structure variations within some previously prepared derivatives. These structure variations involve an alteration of the arrangement of the donor atoms in the macroring as well as insertion of additional donor atoms and aromatic moieties into the macrocyclic rings. We expect this should improve the binding abilities of the new macrocycles compared to their corresponding precursors. The new synthesized macrocycles offer an advantage of their easy synthesis on a large scale in a simple procedure from inexpensive starting materials. A study of the complexing properties of the new macrocycles will be described in detail when the work is completed.

The theoretically studied diamide macrocyles show that the structures having an internal –NH group are more stable than the form with an internal CO group. The same trend is also found for the dithioamides. The increase of ring size relatively stabilizes the latter conformer. The PA energies calculated at the three centers show that protonation is more energetically favored on the amide oxygen or nitrogen atoms compared with the etheric oxygen. The PDE values show that monoalkylation occurs at S- before N- due to the higher acidity of SH than NH.

4. Experimental

4.1. General

All melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin–Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian Mercury 300 (300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR) spectrophotometer and chemical shifts are given in parts per million from TMS. Mass spectra were recorded on a GC–MS QP1000 EX (70 eV) or MS 5988 (15 eV) spectrometers. Elemental analyses were carried out at the Microanalytical Centre, Cairo University.

4.1.1. 1,3-Bis(2-hydroxybenzoylaminomethyl)benzene (7). A mixture of 1,3-bis(2-aminomethyl)benzene (**5**, 10 mmol) and methyl 2-hydroxy-benzoate (**6**, 20 mmol) was heated on a steam bath for 1 h. The reaction mixture was allowed to cool to room temperature and then poured over crushed ice (50 g). The solid obtained was collected and crystallized from methanol to give colorless crystals of **7** (75%), mp 166 °C; IR (cm^{-1}) 3275–3400 (OH, NH), 1619 (C═O); MS (EI): *m/z* 376 (M$^+$, 20%), 255 (36%), 181 (5.8%), 135 (24.8%), 119 (100%); ^{1}H NMR (DMSO) δ 4.51 (s, 4H, CH_2NH), 4.88 (br, 2H, NH), 6.82–7.92 (m, 12H, ArH's), 9.47 (br, 2H, OH). Anal. Calcd for $C_{22}H_{20}N_2O_4$ (376.41): C, 70.20; H, 5.36; N, 7.44. Found: C, 70.40; H, 5.30; N, 7.70.

4.2. Preparation of the potassium salt (8)

To a solution of KOH (1.14 g, 10 mmol) in methanol (10 ml) was added the bisphenol **7** (5 mmol). The mixture was stirred at room temperature for 10 min. The solvent was then removed in vacuo. The remaining solid was triturated with dry ether, collected, dried, and used in the next step without further purification.

4.3. Synthesis of macrocycles 10a,b, 22a,b, and 23–25

General procedure: A solution of the appropriate potassium salts of **2a**,**b** and **8** (10 mmol) and the appropriate dihalo compounds **3**, **9a**,**b**, **11**, and **21** (10 mmol) in DMF (20 ml) was heated under reflux for 10 min during which time KCl precipitated. The solvent was then removed in vacuo and the remaining material was washed with water (50 ml) and purified by crystallization from the proper solvent to give compounds **10a**,**b**, **22a**,**b**, and **23**–**25**.

4.3.1. Macrocycle 10a. With the use of the general procedure **8** and **9a** gave crude **10a**, which was crystallized from ethanol as colorless crystals (84%), mp 262 °C; IR (cm^{-1}) 3301 (NH), 1639 (C═O); MS (EI): *m/z* 402 (M$^+$, 67.5%), 357 (3.1%), 284 (32.9%), 266 (43.4%), 164 (35.9%), 121 (100%), 91 (30.8%); ^{1}H NMR (DMSO) δ 4.52 (s, 4H, CH_2NH), 4.61 (s, 4H, OCH_2), 7.01–7.75 (m, 12H, ArH's), 8.66 (br, 2H, NH). Anal. Calcd for $C_{24}H_{22}N_2O_4$ (402.45): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.80; N, 6.70.

4.3.2. Macrocycle 10b. With the use of the general procedure **8** and **9b** gave crude **10b**, which was crystallized from methanol/water (1:1) as colorless crystals (57%), mp 218–220 °C; IR (cm^{-1}) 3399 (NH), 1644 (C═O); MS (EI): *m/z* 416 (M$^+$, 92%), 298 (58.8%), 255 (25.7%), 161 (25.7%), 121 (100%); ^{1}H NMR (DMSO) δ 2.04 (quintet, 2H, J=6.9 Hz, CH_2CH_2O), 4.20 (t, 4H, J=6.6 Hz, OCH_2), 4.48–4.50 (m, 4H, CH_2NH), 7.04–7.82 (m, 12H, ArH's), 8.44 (br, 2H, NH). Anal. Calcd for $C_{25}H_{24}N_2O_4$ (416.48): C, 72.11; H, 5.80; N, 6.73. Found: C, 71.80; H, 5.60; N, 6.90.

4.3.3. Macrocycle 22a. With the use of the general procedure **2a** and **21** gave crude **22a**, which was crystallized from ethanol as colorless crystals (91%), mp 290 °C; IR (cm^{-1}) 3399 (NH), 1641 (C═O); MS (EI): *m/z* 446 (M$^+$, 1.8%), 404 (109%), 310 (8.4%), 233 (37.4%), 204 (8.1%), 148 (100%), 133 (65.9%); ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3H, CH_3), 3.48–3.54 (m, 4H, NCH_2), 5.30 (d, 2H, J=11.4 Hz, OCH_2), 5.38 (d, 2H, J=11.4 Hz, OCH_2), 7.01–7.88 (m, 10H, ArH's), 8.32 (br, 2H, NH); ^{13}C NMR δ 20.06 ($CH_3C_6H_2$), 39.75 (CH_2NH), 60.98 (OCH_3), 66.81 (CH_2O), 113.66, 120.98, 122.13, 129.01, 131.20, 132.50, 133.11, 133.49, 155.85, 156.13 (ArC's), 164.68 (C═O). Anal. Calcd for $C_{26}H_{26}N_2O_5$ (446.51): C, 69.94; H, 5.87; N, 6.27. Found: C, 70.20; H, 5.60; N, 6.20.

4.3.4. Macrocycle 22b. With the use of the general procedure **2b** and **21** gave crude **22b**, which was crystallized from ethanol as colorless crystals (87%), mp 243–248 °C; IR (cm^{-1}) 3378 (NH), 1656 (C═O); MS (EI): *m/z* 460 (M$^+$, 2.9%), 385 (1.3%), 311 (11.2%), 282 (13.8%), 162 (15.8%), 148 (72.6%), 121 (100%); ^{1}H NMR (DMSO) δ 1.40 (br s, 2H, CH_2CH_2NH), 2.32 (s, 3H, $CH_3C_6H_2$), 3.14–3.16 (m, 4H, CH_2NH), 3.79 (s, 3H, OCH_3), 5.21 (br s, 4H, OCH_2), 7.08–7.86 (m, 10H, Ar's), 8.14 (br, 2H, NH); ^{13}C NMR (DMSO) δ 20.1 ($CH_3C_6H_2$), 29.23 (CH_2CH_2NH), 36.01 (CH_2NH), 61.65 (OCH_3), 67.78 (OCH_2), 113.67, 121.17, 172.73, 128.82, 130.65, 132.44, 133.65, 133.81, 155.89, 156.46,

164.45 (C=O). Anal. Calcd for $C_{27}H_{28}N_2O_5$ (460.53): C, 70.42; H, 6.13; N, 6.08. Found: C, 70.10; H, 6.40; N, 6.10.

4.3.5. Macrocycle 23. With the use of the general procedure **8** and **3** gave crude **23**, which was crystallized from ethyl acetate/*n*-pentane (3:1) as colorless crystals (56%), mp 226 °C; IR (cm^{-1}) 3394 (NH), 1648 (C=O); MS (EI): *m/z* 478 (M^+, 8.4%), 358 (57.7%), 223 (19.4%), 196 (11.5%), 121 (100%), 104 (82.4%); ^1H NMR (DMSO) δ 4.39–4.41 (m, 4H, CH_2NH), 5.22 (s, 4H, OCH_2), 7.03–7.96 (m, 16H, ArH's), 8.56 (s, 2H, NH). Anal. Calcd for $C_{30}H_{26}N_2O_4$ (478.55): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.10; H, 5.20; N, 5.60.

4.3.6. Macrocycle 24. With the use of the general procedure **8** and **11** gave crude **24**, which was crystallized from ethanol as colorless crystals (76%), mp 268 °C; IR (cm^{-1}) 3392 (NH), 1643 (C=O); MS (EI): *m/z* 479 (M^+, 18.8%), 358 (95.41%), 313 (7.3%), 226 (72.8%), 121 (100%); ^1H NMR (DMSO) δ 4.40 (s, 4H, CH_2NH), 8.49 (br, 2H, NH). Anal. Calcd for $C_{29}H_{25}N_3O_4$ (479.54): C, 72.64; H, 5.26; N, 8.76. Found: C, 72.60; H, 5.40; N, 9.10.

4.3.7. Macrocycle 25. With the use of the general procedure **8** and **21** gave crude **25**, which was crystallized from butanol as colorless crystals: (42%), mp>300 °C; IR (cm^{-1}) 3382 (NH), 1647 (C=O); MS (EI): *m/z* 491 (M^++1, 1.35%), 402 (8.1%), 376 (7.9%), 255 (15.9%), 162 (8.4%), 121 (100%); ^1H NMR (DMSO) δ 2.26 (s, 3H, $CH_3C_6H_2$), 3.45 (s, 3H, OCH_2), 4.33 (s, 4H, CH_2NH), 5.06 (s, 4H, OCH_2), 7.05–7.99 (m, 14H, ArH's), 8.23 (br, 2H, NH). Anal. Calcd for $C_{32}H_{30}N_2O_3$ (490.61): C, 78.34; H, 6.16; N, 5.71. Found: C, 78.30; H, 6.30; N, 5.60.

4.4. Synthesis of the macrocyclic dithiodiamides 26 and 27a,b

General procedure: To a boiling solution of **10a** and **22a**,**b** (10 mmol) in toluene (30 ml) was added Lawesson's reagent (8.1 g, 20 mmol). The reaction mixture was heated under reflux for 3 h. After cooling the yellow precipitate was collected and crystallized from DMF/H_2O to give yellow crystals of **26** and **27a**,**b**, respectively.

4.4.1. Macrocycle 26. With the use of the general procedure **10a** gave **26** as yellow crystals (70%), mp 240–242 °C; IR (cm^{-1}) 3320 (NH), 1550 (C=S); MS (EI): *m/z* 434 (44.6), 402 (54%), 368 (5%), 313 (9.5%), 266 (28.6%), 239 (12.6%), 164 (31%), 137 (100%); ^1H NMR (DMSO) δ (s, 4H, CH_2O), 4.93 (s, 4H, CH_2NH), 6.97–7.95 (m, 12H, ArH's), 10.55 (br, 2H, NH). Anal. Calcd for $C_{24}H_{22}N_2O_2S_2$ (434.59): C, 66.33; H, 5.10; N, 6.45; S, 14.76. Found: C, 66.60; H, 4.90; N, 6.40.

4.4.2. Macrocycle 27a. With the use of the general procedure **22a** gave **27a** as yellow crystals (71%), mp 266 °C; IR (cm^{-1}) 3296 (NH), 1524 (C=S); MS (EI): *m/z* 478 (M^+, 17.4%), 445 (27.34%), 411 (4.49%), 325 (8.9%), 266 (33.8%), 178 (100%), 133 (83.1%); ^1H NMR (DMSO) δ 2.27 (s, 3H, $CH_3C_6H_2$), 3.78 (s, 3H, OCH_3), 3.93 (s, 4H, NCH_2), 5.12 (d, 2H, J=11.1 Hz, OCH_2), 5.32 (d, 2H, J=10.8 Hz, OCH_2), 6.95–7.73 (m, 10H, ArH's), 9.89 (br, 2H, NH). Anal. Calcd for $C_{26}H_{26}N_2O_3S_2$ (478.64): C, 65.25; H, 5.48; N, 5.85; S, 13.40. Found: C, 65.40; H, 5.80; N, 5.80.

4.4.3. Macrocycle 27b. With the use of the general procedure **22b** gave **27b** as yellow crystals (72%), mp 274 °C; IR (cm^{-1}) 3323 (NH), 1546 (C=S); MS (EI): *m/z* 492 (M^+, 11.1%), 459 (75.5%), 427 (7.1%), 340 (4.5%), 266 (44.2%), 192 (60.4), 137 (100%), 105 (96.8%); ^1H NMR (DMSO) δ 1.43 (br s, 2H, CH_2CH_2NH), 2.30 (s, 3H, $CH_3C_6H_2$), 3.54 (br s, 4H, CH_2NH), 3.76 (s, 3H, OCH_3), 5.06 (s, 4H, OCH_2), 7.0–7.71 (m, 10H, ArH's), 9.87 (br, 2H, NH). Anal. Calcd for $C_{27}H_{28}N_2O_3S_2$ (492.67): C, 65.83; H, 5.73; N, 5.69. Found: C, 65.60; H, 5.60; N, 5.90.

References and notes

1. Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929–972.
2. Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475–4515.
3. Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Azacrown Macrocycles*; Taylor, E. C., Ed.; The Chemistry of Heterocyclic Compounds; John Wiley & Sons: New York, NY, 1993; Vol. 51.
4. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721–2085.
5. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529–2586.
6. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L.; Tarbet, B. J. *Chem. Rev.* **1992**, *92*, 1261–1354.
7. Elwahy, A. H. M. *J. Heterocycl. Chem.* **2003**, *40*, 1–23.
8. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
9. Pedersen, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 386–391.
10. *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Elsevier: Oxford, 1996; Vol. 1.
11. Pioget, T.; Duriez, M. C.; Picard, C.; Cazaux, L.; Tisnes, P. *Tetrahedron* **1992**, *48*, 4359–4368.
12. Irie, S.; Yamamoto, M.; Kishikawa, K.; Kohmoto, S.; Yamada, K. *Synthesis* **1995**, 1179–1182.
13. Wu, S. L.; Franklin, S. J.; Raymond, K. N.; Horrocks, W. D. *Inorg. Chem.* **1996**, *35*, 162–167.
14. Fujita, T.; Lehn, J.-M. *Tetrahedron Lett.* **1988**, *29*, 1709–1712.
15. Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101–109.
16. Mitchell, M. C.; Cawley, A.; Kee, T. P. *Tetrahedron Lett.* **1995**, *36*, 287–290.
17. Wipf, P.; Venkatraman, S.; Miller, C. P.; Geib, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1516–1518.
18. Kumar, S.; Singh, R.; Singh, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 363–364.
19. Kumar, S.; Kaur, N.; Singh, H. *Tetrahedron* **1996**, *52*, 13483–13492.
20. Kumar, S.; Kaur, N.; Singh, H. *Tetrahedron Lett.* **1996**, *37*, 2071–2072.
21. Trafton, J. E.; Li, C.; Mallen, J.; Miller, S. R.; Nakano, A.; Schall, O. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1266–1268.
22. Ozeki, E.; Kimura, S.; Lmanishi, Y. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1743–1748.
23. For a review on Cryptands see: Dietrich, B. *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon: New York, NY, 1996; pp 153–212.

24. Sharghi, H.; Massah, A. R.; Eshgi, H.; Niknam, K. *J. Org. Chem.* **1998**, *63*, 1455–1461.
25. Shagidullin, R.; Chernova, A.; Bazhanova, Z.; Lii, J.; Kataev, V.; Katsyuba, S.; Reznik, V. *J. Mol. Struct.* **2004**, *707*, 1–9.
26. Takemura, H.; Sako, T. *Tetrahedron Lett.* **2005**, *46*, 8169–8172.
27. Ayako, F.; Keiko, T.; Shojiro, O.; Shinji, T. *J. Mol. Struct. (Theochem)* **2003**, *620*, 49–63.
28. Johansson, P.; Abrahamsson, E.; Jacobsson, P. *J. Mol. Struct. (Theochem)* **2005**, *717*, 215–221.
29. Keypour, H.; Khanmohammadi, H.; Wainwright, K. P.; Taylor, M. R. *Inorg. Chim. Acta* **2004**, *357*, 1283–1291.
30. Keypour, H.; Khanmohammadi, H.; Wainwright, K. P.; Taylor, M. R. *Inorg. Chim. Acta* **2005**, *358*, 247–256.
31. Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **2000**, *56*, 885–895.
32. Brooker, S. *Coord. Chem. Rev.* **2001**, *222*, 33–56.
33. Abbas, A. A.; Elwahy, A. H. M.; Ahmed, A. A. M. *J. Heterocycl. Chem.* **2005**, *42*, 93–101.
34. Ito, K.; Ohba, Y.; Sone, T. *Heterocycles* **1999**, *51*, 2203–2212.
35. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.
36. Zielinski, T.; Jurczak, J. *Tetrahedron* **2005**, *61*, 4081–4089.
37. Lee, H.-J.; Choi, Y.-S.; Lee, K.-B.; Park, J.; Yoon, C.-J. *J. Phys. Chem. A* **2002**, *106*, 7010–7017.
38. Alien, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Crystallogr., Sect. B* **1997**, *53*, 680–695.
39. Inoue, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2003**, *44*, 5167–5169.
40. Hossain, A.; Kang, S. O.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 5043–5045.
41. Coles, S. J.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Warriner, C. N. *Supramol. Chem.* **2004**, *16*, 469–486.
42. Ibrahim, Y. A.; Elwahy, A. H. M. *Sulfur Lett.* **1993**, *17*, 45–65.
43. Elwahy, A. H. M.; Masaret, Gh. S. *J. Heterocycl. Chem.* **2004**, *41*, 711–715.
44. Pople, J. A. *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; McGraw-Hill: New York, NY, 1986; Vol. 4.
45. Berthier, G. *Adv. Quantum Chem.* **1974**, *8*, 183–203.
46. De Brouckere, G. *Adv. Chem. Phys.* **1978**, *37*, 203–304.
47. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
48. Stewart, J. J. P. *MOPAC 6.0 Quantum Chemistry Program Exchange*; University of Indiana: Bloomington, IN, 1990.