Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

Synthesis, metal ion complexation and antibacterial activities of some thiapodands with lipophilic amide and ester end groups

Muhammad Ashram [a], Shehadeh Mizyed [b], Wael Zereini [c] & Abdel Monem Rawashdeh [b]

[a] Chemistry Department, Mutah University, Mutah, Al-Karak, Jordan

[b] Chemistry Department, Yarmouk University, Irbid, Jordan

[c] Department of Biological Sciences, Mutah University, Mutah, Al-Karak, Jordan

Published online: 18 Sep 2012.

To cite this article: Muhammad Ashram, Shehadeh Mizyed, Wael Zereini & Abdel Monem Rawashdeh (2012) Synthesis, metal ion complexation and antibacterial activities of some thiapodands with lipophilic amide and ester end groups, Journal of Sulfur Chemistry, 33:5, 561-571, DOI: 10.1080/17415993.2012.716843

To link to this article: http://dx.doi.org/10.1080/17415993.2012.716843

Journal of Sulfur Chemistry
Vol. 33, No. 5, October 2012, 561–571

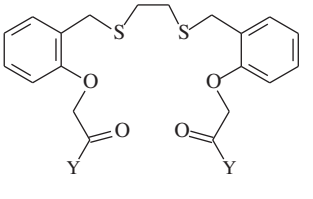
Synthesis, metal ion complexation and antibacterial activities of some thiapodands with lipophilic amide and ester end groups

Muhammad Ashram[a]*, Shehadeh Mizyed[b], Wael Zereini[c] and Abdel Monem Rawashdeh[b]

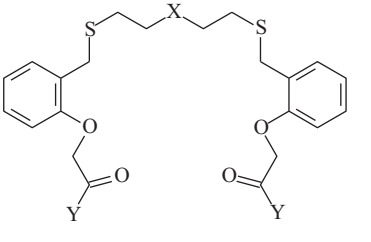
[a]*Chemistry Department, Mutah University, Mutah, Al-Karak, Jordan;* [b]*Chemistry Department, Yarmouk University, Irbid, Jordan;* [c]*Department of Biological Sciences, Mutah University, Mutah, Al-Karak, Jordan*

(*Received 9 June 2012; final version received 26 July 2012*)

A series of acyclic analogues of thiacrown ethers (podands) **7**–**12** with lipophilic amide and ester end groups were synthesized in high yield and in a simple way. Their transition metal ions complexation was studied using a conductometric method in acetonitrile at 25°C. Podands **7** and **11** showed a continuous decrease in the molar conductances in their complexation with Ag^{+}, Cu^{2+}, Cd^{2+}, Hg^{2+}, Zn^{2+} and Pb^{2+} which begins to level off at a mole ratio of 1:1 podand to metal indicating the formation of a stable 1:1 complexes. On the other hand, podand **9** also showed the formation of 1:1 complexes with above metal cations except with Hg^{2+} ion, which formed a 1:2 podand-to-metal ratio complex. An influence of end groups on metal ion selectivity is evident. Podands having ethoxy end groups (podands **8**, **10** and **12** exhibit pronounced metal ion selectivity over podands having amino end groups (podands **7**, **9** and **11**). Compounds **10** and **12** with dithiaethylene units and ethoxy end groups provide the best selectivity for Hg^{2+} and Ag^{+} ions. These results suggest that podands **10** and **12** could be useful for the selective removal of Hg^{2+} and Ag^{+} ions from industrial waste that may contain a variety of toxic heavy and transition metal ions. The *in vitro* antibacterial activity of the investigated compounds was tested against several microorganisms such as *Bacillus subtilis* (ATCC 6633), *Micrococcus luteus* (ATCC 10240), *Staphylococcus aureus* (ATCC 43300), *Escherichia coli* (ATCC 25922) and *Enterobacter aerogenes* (ATCC 13048). The antibacterial activity of podand **10** is significant for *M. luteus* and *B. subtilis* compared with other podands under investigation.



7 $Y=N(C_2H_5)_2$
8 $Y=OC_2H_5$



9 $X=S;Y=N(C_2H_5)_2$
10 $X=S;Y=OC_2H_5$
11 $X=O;Y=N(C_2H_5)_2$
12 $X=O;Y=OC_2H_5$

Keywords: thiapodands; transition metals; stability constant; conductivity; antibacterial activity

*Corresponding author. Email: ashram_1961@yahoo.com

ISSN 1741-5993 print/ISSN 1741-6000 online

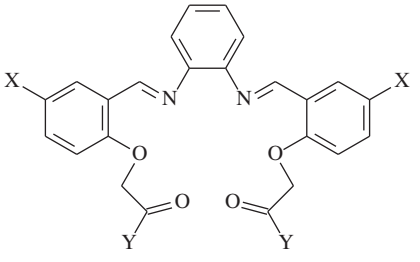
http://dx.doi.org/10.1080/17415993.2012.716843
http://www.tandfonline.com

1. Introduction

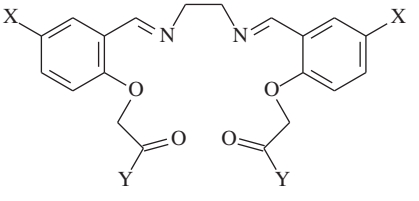
Acyclic analogues of crown ethers (podands) have received an important amount of interest by research groups. Due to their low cost production, saving ring formation step(s) and their ability to complex metal cations, anions and neutral guests, podands have became a significant type of host in host–guest chemistry. A large number of podands with different end groups, chain length and ligation atoms have been synthesized and their complexation properties were studied (*1–6*). Several studies have focused on the determination of the selectivity and efficiency of the podand-mediated extraction or transport of metal ions (*4–6*). Some of the crown ethers and their noncyclic analogues proved to have different biological activities (*7–9*).

The stability and selectivity of the podands toward metal ions depend on several variables such as chain length, identities of hetero-ligation atoms among the chain, the end groups and the type of metal ions (*10–15*).

Previously, we have investigated the complexation of some transition metal cations (Ag^{+}, Cu^{2+}, Cd^{2+}, Hg^{2+}, Zn^{2+} and Pb^{2+}) by two series of acyclic Schiff-base podands **1–6** with lipophilic amide and ester end groups (Scheme 1) (*15*). The two series of podands show weak to good complexation ability with poor selectivity toward metal cations studied. It was also found that there was no large difference in the stability constants whether the Schiff-base podands ended

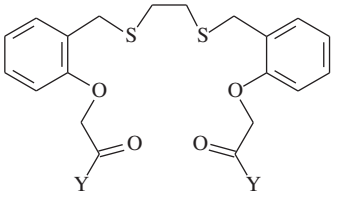


1 X = H; Y = OC_2H_5
2 X = H; Y = $N(C_2H5)_2$
3 X = Br; Y = $N(C2H_5)_2$

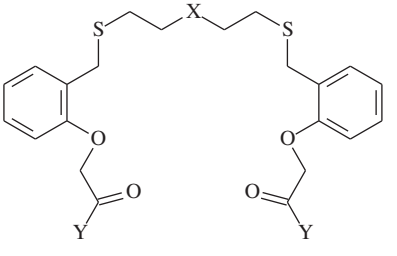


4 X = H; Y = OC_2H_5
5 X = H; Y = $N(C_2H5)_2$
6 X = Br; Y = $N(C_2H_5)_2$

Scheme 1. Acyclic Schiff-base podands **1–6**.



7 Y = $N(C_2H_5)_2$
8 Y = OC_2H_5



9 X = S; Y = $N(C_2H_5)_2$
10 X = S; Y = OC_2H_5
11 X = O; Y = $N(C_2H_5)_2$
12 X = O; Y = OC_2H_5

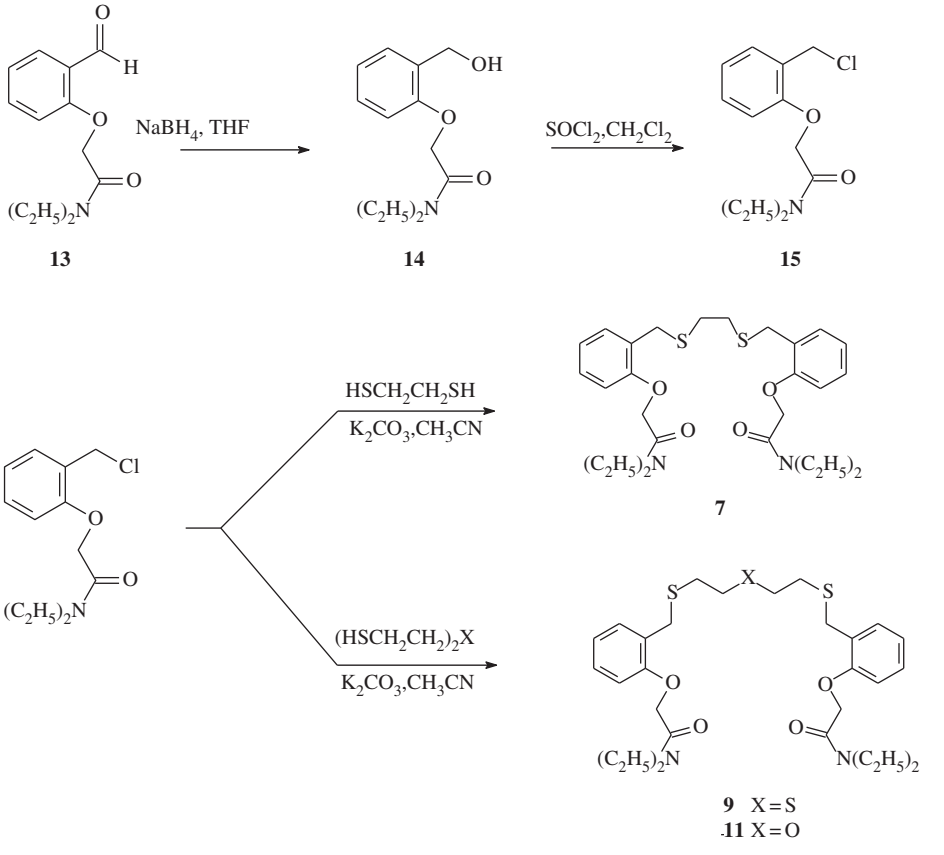
Scheme 2. The synthesized acyclic thiacrown ethers **7–12**.

with ester groups or ended with amino groups. To further probe the end group and the chain length with different ligation hetero-atom effects, two series of podands with sulfur atoms embedded in the chain and with lipophilic amide and ester end groups were synthesized (Scheme 2) and their complexation with the above transition metal cations was studied using a conductometric method in acetonitrile (AN) at 25°C in addition to their antibacterial activity.

2. Results and discussion

2.1. *Synthesis*

The synthesis of podands **7**, **9** and **11** was carried out in the same manner as the synthesis of **8**, **10** and **12** (Schemes 3) (*15*). Treatment of **13** with two equivalents of $NaBH_4$ in THF at 0–5°C produce compound **14** in more than 90% yield as an oily product. Treatment of **14** with freshly distilled $SOCl_2$ in dry CH_2Cl_2 at 5 °C for 15 min produce **15** in about 90% yield as an oily product. When two equivalents of compound **15** were treated with one equivalent of ethane 1,2-dithiol or bis(2-mercaptoethyl)sulfide or bis(2-mercaptoethyl) ether in the presence of one equivalent of K_2CO_3 in refluxing anhydrous AN for 24 h, podands **7**, **9** and **11** were produced, respectively, in high yields. Compounds **7**, **9** and **11** were fully characterized by ^1H, ^{13}C NMR, infrared (IR) spectroscopy and elemental analysis.



Scheme 3. The synthesis of acyclic thiacrown ethers **7**, **9** and **11**.

2.2. *Complexation studies*

In this study, the conductometric method was used to

(1) establish the stoichiometry of the complexes formed between transition metals Ag^{+}, Cu^{2+}, Cd^{2+}, Hg^{2+}, Zn^{2+} and Pb^{2+} and podands **7**–**12**.
(2) determine the stability constants of the formed complexes using a simplex program (*16*–*22*). The variation of molar conductivity Λ with $[L]_T/[M]_T$ for complexes of podands **7**–**12** and metal cations mentioned above in AN were studied at 25°C. $[L]_T$ and $[M]_T$ denote the total concentrations of podands and metal cations, respectively. The resulting molar conductance–mole ratio plots are shown in Figure 1 as an example. The addition of podand **10** to metal cation solutions causes a continuous decrease in the molar conductance that begins to level off at a mole ratio 1 of podand-to-metal ion indicating the formation of stable 1:1 complexes. Anomalous behavior was observed in the complexation of other podands with metal cations studied. Regarding **9**-Hg^{2+} complex, the addition of podand **9** to Hg^{2+} salt solution indicates that the change in the slope of the conductometric titration curve are observed at a ligand:metal ratio of 0.5 which means the formation of 1:2 complex. To confirm the 1:2 complexation ratio obtained by conductivity measurements, the complexation between ligand **9** and Hg^{2+} was studied using Job's plot (Figure 2). This figure shows that a maxima of about 0.25 is obtained indicating 1:2 ligand-to-metal ratio. Furthermore, the complexation is also verified by changes in the ^{1}H NMR chemical shifts of the podands under investigation. The addition of Hg^{2+} ion to podand **9** in CD_3CN resulted in a chemical shift change for the benzylic protons of about 0.25 ppm. A complete complexation study using NMR will be published in due course. From these experimental results, we deduce that the sulfur atoms of the bis(thiaethylene) unit spacer, the oxygen atoms of the carbonyl groups and the nitrogen atoms of the amino amide groups are participants in the coordination with Hg^{2+} ion. The contribution of the carbonyl groups in the coordination is confirmed from the change in IR stretching of these groups upon complexation as shown in Figure 3. Replacement of amino end groups in podand **9** by ethoxy end groups in podand **10** gave 1:1 ligand-to-Hg^{2+} complexes indicating that the oxygen atoms of the ethoxy groups do not participate in the interaction with the Hg^{2+} ion. This result is consistent with a poor association of Hg^{2+} ion (soft ion) and oxygen atoms (hard atoms) according to hard and soft acid-base theory (*23*).

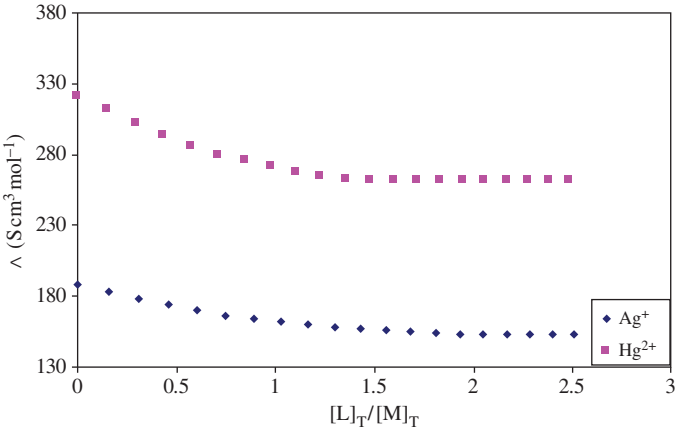


Figure 1. Molar conductance–mole ratio plots for **10** and metal cations in CH_3CN at 25°C.

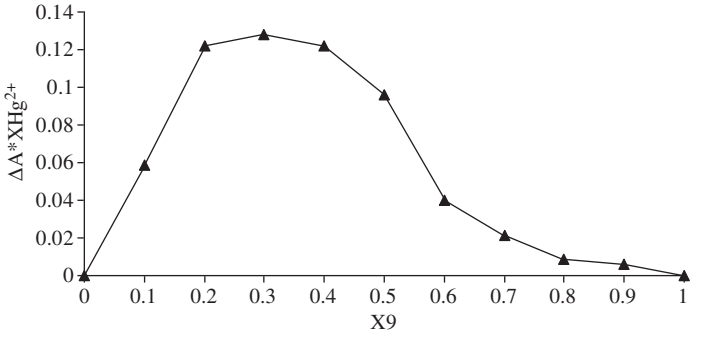


Figure 2. Job's plot of the complex of compound **9** with Hg^{2+} metal cation in CH_3CN at 25°C.

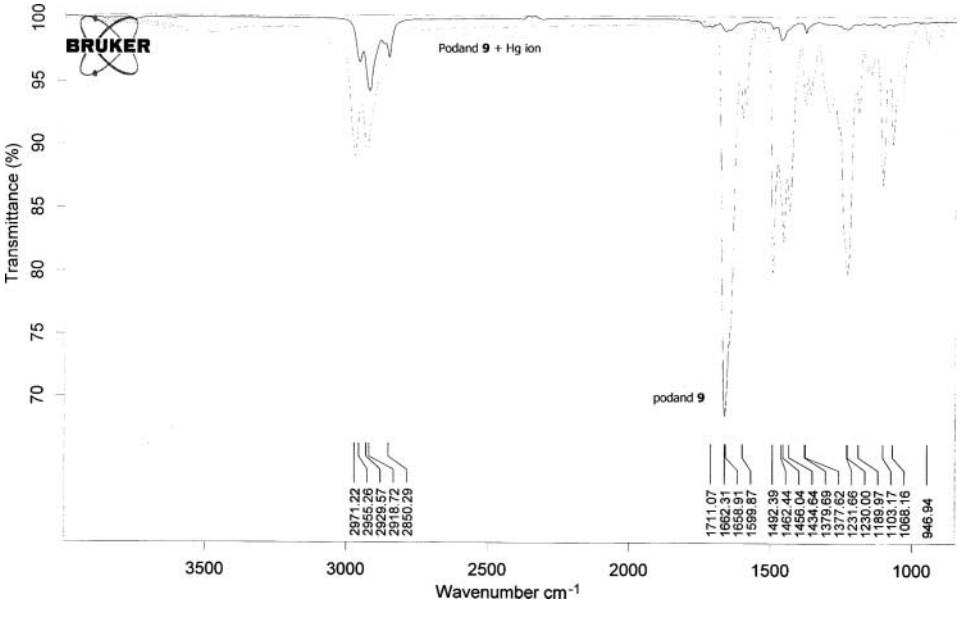


Figure 3. The change in IR stretching of carbonyl groups of **9** upon complexation with Hg^{2+}.

When a ligating agent complexes with a specific metal ion, many factors influence the stability constants such as the radius of metal ion, the identity of the donor atoms and a macrocyclic effect which involves the dimensional compatibility between the macrocycle and the size of the metallic cation. As shown in Table 1, the order of stability constant of podands-Ag^+ is **9**>**11**>**7** when the end group is the amino group and **10**>**12**>**8** when the end group is the ethoxy group. From these observations, we can conclude the following:

(a) The cavity size of podands that contain bis(thiaethylene) unit spacer (**9**, **10**, **11** and **12**) is more flexible and, therefore, it has the ability to adopt a suitable orientation and wrap around the metal ion to form more stable complexes with Ag^+ comparing to more rigid cavities of podands **7** and **8** that contain the monothiaethylene unit spacer. Indeed, when quantum mechanical calculations were performed using the GAUSSIAN03 program package (*24*), they show that

Table 1. Log K_{assoc} for complexation of Ag^+, Cu^{2+}, Cd^{2+}, Hg^{2+}, Zn^{2+} and Pb^{2+} and with podands **7**–**12** in AN at 25°C.

Compound	Ag^+	Cu^{2+}	Cd^{2+}	Hg^{2+}	Zn^{2+}	Pb^{2+}
7	4.42 ± 0.11	6.57 ± 0.16	5.76 ± 0.14	5.38 ± 0.13	6.67 ± 0.17	7.71 ± 0.19
8	2.77 ± 0.07	3.38 ± 0.08	[a]	5.24 ± 0.12	[a]	[a]
9	5.24 ± 0.12	6.33 ± 0.16	6.67 ± 0.15	(2:1)[b]	5.00 ± 0.12	6.86 ± 0.17
10	4.76 ± 0.11	[a]	[a]	5.43 ± 0.14	[a]	[a]
11	5.00 ± 0.11	5.14 ± 0.12	5.71 ± 0.13	5.76 ± 0.17	4.43 ± 0.11	5.38 ± 0.11
12	3.95 ± 0.09	[a]	[a]	4.95 ± 0.12	[a]	[a]

Notes: [a]No change in molar conductance was observed.
[b]The data cannot be fitted in equation.

the podand **9** complex with Ag^+ has wrapped itself around the ion and formed a square planar complex (Figure 4) with an S–Ag distance of 2.57 Å. Podand **7** in its complex with Ag^+ formed a tetrahedral complex (Figure 5) with an S–Ag distance of 2.67 Å. Comparing those distances with the typical S–Ag distance which is 2.50 Å shows that the former is more stable (*25*).

(b) Replacement of one sulfur atom in bis(thiaethylene) unit space by one oxygen atom causes a decrease in stability constants. Compare stability constants of **9** and **11**, and **10** and **12**.

(c) Replacement of amino end groups by ethoxy end groups causes a decrease in stability constants. Compare stability constants of **7** and **8**, **9** and **10**, and **11** and **12**. This tendency is also observed for the stability constants of the complexes **7**-Hg^{2+} and **8**-Hg^{2+}, and **7**-Cu^{2+} and **8**-Cu^{2+}. These results give clear evidence that the nature of the end groups takes part in determining the value of stability constants.

Figure 4. Speculated structure for **9**-Ag complex showing square planar arrangement.

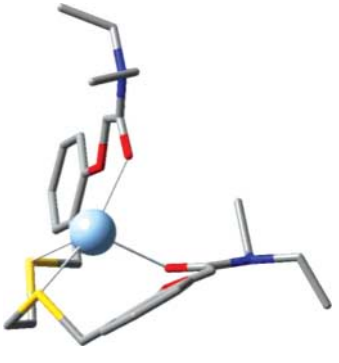


Figure 5. Predicted structure for **7**-Ag complex with tetrahedral geometry.

An influence of end groups on metal ion selectivity is evident. As shown in Table 1, podands having ethoxy end groups (podands **8**, **10** and **12**) exhibit pronounced metal ion selectivity over podands having amino end groups (podands **7**, **9** and **11**). Among the three podands **8**, **10** and **12**, podands **10** and **12** exhibit the highest Hg^{2+} and Ag^{+} ion selectivity. These results suggest that podands **10** and **12** could be useful for the selective removal of Hg^{2+} and Ag^{+} ions from industrial waste which may contains a variety of toxic heavy and transition metal ions.

2.3. *Antibacterial activity*

The synthesized podands showed weak to moderate activities against Gram-positive bacteria, especially *Micrococcus luteus*. Compounds **10** and **12** revealed a very weak activity against *B. subtilis.* The multidrug-resistant *Staphylococcus aureus* and Gram-negative bacteria were resistant to the applied test substances. The bioactivity of these compounds is shown in Tables 2 and 3.

It is clear that these compounds were selectively active against *M. luteus*. Compound **10** was the most potent bioactive agent against *M. luteus* in agar diffusion test (Figure 6). Although some of these compounds exhibit antibacterial activities at concentrations more than 100 $\mu g\,ml^{-1}$ (*i.e.* **7** and **8**), their minimum inhibitory concentration (MIC) values were around or even lower than that concentration with a static effect. Such finding may be attributed to their low diffusion ability in the agar plate test and their lipophilic nature. As shown in Table 3, the potency of these compounds to inhibit *M. luteus* growth increased when there are more than two sulfur atoms present in the bridge. Moreover, sulfur containing podand esters are 4–8-fold more active than the amide ones.

The activity of these compounds could be attributed to their ability to bind and complex with metal ions in the cell that may disturb the ionic homeostasis in the bacterial cells or inhibit the activities of some crucial bacterial enzymes. Such findings are in agreement with the results of Federova *et al.* (*8*). They noticed an increase in the tuberculostatic activity of the oxygen containing crown esters upon going from cyclic crowns to their acyclic analogs and that their activity exceeds the amino analogs (*8*). In addition, Tochtrop *et al.* (*26*) reported that the presence of sulfur atoms as ligating sites in a podand makes it more lipophilic and increase its efficiency to extract and transport cations.

Table 2. Bioactivity of the synthesized compounds against the susceptible bacterial strains.

	Micrococcus luteus ($\mu g\,disc^{-1}$)			*Bacillus subtilis* ($\mu g\,disc^{-1}$)		
Compound	100	300	500	100	300	500
7	–	11	11	–	–	–
9	13	15	16	–	–	–
11	12	15	15	–	–	–
8	–	–	10	–	–	–
10	23	25	25	–	8	9
12	12	14	14	–	9	10

Note: –, No activity.

Table 3. MIC of the synthesized compounds in the serial dilution assay with the susceptible bacterial strains.

	MIC ($\mu g\,ml^{-1}$)						
Organisms	**7**	**9**	**11**	**8**	**10**	**12**	St
Micrococcus luteus	125s	31.5s	31.5s	31.5s	3.9s	3.1s	<0.4
Bacillus subtilis	–	–	–	–	–	–	<0.4

Note: St, streptomycin; s, bacteriostatic; –, >1000 $\mu g\,ml^{-1}$.

Figure 6. Inhibition zones indicating the activity of compound **10** against *M. luteus*. Left zone: 50 μg disc^{-1}, right zone: 100 μg disc^{-1}.

3. Conclusion

A series of podands in which the length of ethereal linkage connecting the two benzo-moieties is varied to contain mono- and dithiaethylene units with different ending groups were synthesized in a simple way and in high yields. A conductometric titration technique was used to determine the stability constants in AN at 25°C and the *L*:*M* mole ratio for the complexation of podands **7**, **8**, **9**, **10**, **11** and **12** with Ag^+, Cu^{2+}, Cd^{2+}, Hg^{2+}, Zn^{2+} and Pb^2 ions. Podands **10** and **12** with dithiaethylene units and ethoxy end groups provide the best selectivity for Hg^{2+} and Ag^+ ions. The antimicrobial activity of these podands was tested. Podand **10** shows a significant activity for *M. luteus* and *B. subtilis* compared with other podands.

4. Experimental

Melting points are uncorrected and obtained on electrothermal melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on 300 and 50 MHz NMR spectrometers, respectively. Unless otherwise noted, samples were dissolved in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS used as internal standard. Elemental analyses (C, H, N and S) were performed on Euro elemental analysis 3000 from Euro Vector S.P.A. SN 8910. All reagents were of analytical grade and used without further purification. Ethane 1,2-dithiol or bis(2-mercaptoethyl)sulfide or bis(2-mercaptoethyl) ether were obtained from Aldrich; salicylaldehyde was from Lancaster; ethyl bromoacetate from Merck and anhydrous potassium carbonate from SureChem. The solvents were used without further purification.

The following salts were purchased from the companies indicated: $AgNO_3$ (Degussa), $Cu(ClO_4)_2{\cdot}6H_2O$ (Aldrich), $Pb(ClO_4)_2{\cdot}3H_2O$ (Aldrich), $Zn(ClO_4)_2{\cdot}6H_2O$ (Aldrich), $Cd(ClO_4)_2$ (Aldrich) and $Hg(ClO_4)_2.xH_2O$ (Aldrich). For the conductivity measurements, AN was used after fractional distillation. The conductivity of the CH_3CN was less than 1×10^{-7} S cm^{-1}. Solutions having metal ion concentrations of approximately 1.0–1.1 $\times$ 10^{-4} M were prepared by dissolving a known mass of each salt in the respective solvent. These solutions were also used as solvents for preparing the thiapodand solutions with concentrations of approximately 1.5–1.6 $\times$ 10^{-3} M. The description of the conductometer and the details of the conductance measurements have been given previously (*16*). Compounds **8**, **10**, **12** and **13** were prepared according to the literature procedures (*15*, *17*).

4.1. *Synthesis*

4.1.1. *Synthesis of O-(N,N-diethylacetamidooxy)benzyl alcohol (14)*

To a solution of **13** (0.51 g, 2.12 mmol) in THF (10 ml) was added $NaBH_4$ (0.16 g, 4.24 mmol) at 0–5°C. The reaction was stirred for 15 min and then for 45 min at room temperature. The reaction mixture was quenched by adding 2 ml of cold water, followed by aqueous 5% HCl until the solution become acidic to pH paper. The mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give **14** as a colorless oil in 95% yield; ^{1}H NMR δ_H 1.14 (t, $J = 6$ Hz, 3H, NCH_2CH_3), 1.20 (t, $J = 6$ Hz, 3H, NCH_2CH_3), 3.41 (q, $J = 6$ Hz, 4H, NCH_2CH_3), 4.68 (s, 2H), 4.70 (s, 2H), 6.81 (d, $J = 4$ Hz, 1H), 6.93 (t, $J = 6$ Hz, 1H), 7.20–7.25 (m, 2H); ^{13}C NMR δ_C 12.86, 14.42, 40.19, 41.28, 60.5, 67.67, 111.2, 121.23, 128.11, 128.24, 129.61, 136.50, 168.51.

4.1.2. *Synthesis of O-(N,N-diethylacetamidooxy)benzyl chloride (15)*

To a solution of **14** (0.45 g, 1.9 mmol) in dry CH_2Cl_2 (30 ml) at 0°C was added freshly distilled $SOCl_2$ (0.28 ml, 3.8 mmol). The reaction mixture was stirred at 0°C for 15 min and then was quenched by adding 20 ml of cold water. The organic layer was washed with water until the aqueous layer was neutral to pH paper. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give **15** as a colorless oil in 92% yield; ^{1}H NMR δ_H 1.13 (t, $J = 6$ Hz, 3H, NCH_2CH_3), 1.20 (t, $J = 6$ Hz, 3H, NCH_2CH_3), 3.39 (q, $J = 6$ Hz, 4H, NCH_2CH_3), 4.69 (s, 2H), 4.71 (s, 2H), 6.79 (d, $J = 4$ Hz, 1H), 6.90 (t, $J = 6$ Hz, 1H), 7.20–7.30 (m, 2H); ^{13}C NMR δ_C 12.84, 14.42, 40.15, 41.26, 41.61, 67.72, 113.62, 120.66, 125.90, 128.15, 128.65, 135.58, 167.54.

4.1.3. *General procedure for synthesis of acyclic thiacrown ether podands **7**, **9** and **11***

In a 100 ml one-necked flask equipped with a magnetic stirrer bar and a reflux condenser, the chloride amide compound **15** (0.75 g, 2.94 mmol), ethane 1,2-dithiol or bis(2-mercaptoethyl)sulfide or bis(2-mercaptoethyl) ether (1.47 mmol) and anhydrous K_2CO_3(0.41 g, 2.94 mmol) were mixed in anhydrous CH_3CN (50 ml). The mixture was refluxed for 24 h. The mixture was filtered and the filtrate was evaporated to dryness. The ^{1}H NMR and ^{13}C NMR, IR analysis and elemental analysis measured for the obtained products are consistent very well with the corresponding acyclic thiacrown ether podand formula.

4.1.4. *1,2-Bis[2-(N,N-diethylacetamidooxy)thiabenzyl]ethane **7***

Pale brown semi-solid (92%); Fourier transform infrared spectroscopy (FT-IR) (KBr, cm^{-1}): 1659 [$CON(C_2H_5)_2$]; ^{1}H NMR ($CDCl_3$): δ 1.13 (t, $J = 8$ Hz, 6H, CH_2CH_3), 1.19 (t, $J = 6$ Hz, 6H, CH_2CH_3), 2.68 (s, 4H, SCH_2CH_2S), 3.40 (q, $J = 6$ Hz, 8H, CH_2CH_3), 3.80 (s, 4H, CH_2Ph), 4.71 (s, 4H, OCH_2CO), 6.86 (d, $J = 6$ Hz, 2H), 6.91–6.94 (m, 2H), 7.17–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 12.86, 14.42, 30.08, 31.22, 40.06, 41.03, 67.77, 112.21, 121.39, 127.26, 128.41, 130.46, 156.32, 167.88. Anal. Calcd for $C_{28}H_{40}N_2S_2O_4$ (%): C 63.13, H 7.57, N 5.26, S 12.04; found (%):C 63.01, H 7.44, N 5.19, S 11.97.

4.1.5. *1,5-Bis[2-(N,N-diethylacetamidooxy)thiabenzyl]-3-thiapentane **9***

Pale yellow oil (89%); FT-IR (KBr, cm^{-1}): 1658 [$CON(C_2H_5)_2$]; ^{1}H NMR ($CDCl_3$): δ 1.15 (t, $J = 8$ Hz, 6H, CH_2CH_3), 1.21 (t, $J = 6$ Hz, 6H, CH_2CH_3), 2.67 (m, 8H, $(SCH_2CH_2)_2S$), 3.41

(q, $J = 6$ Hz, 8H, CH_2CH_3), 3.83 (s, 4H, CH_2Ph), 4.73 (s, 4H, OCH_2CO), 6.87 (d, $J = 6$ Hz, 2H), 6.94 (m, 2H), 7.19–7.27 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 12.89, 14.45, 30.33, 31.43, 31.79, 40.29, 41.38, 67.78, 112.24, 121.45, 127.19, 128.49, 130.50, 156.05, 166.89. Anal. Calcd for $C_{30}H_{44}N_2S_3O_4$ (%): C 60.78, H 7.48, N 4.73, S 16.22; found (%):C 60.63, H 7.39, N 4.85, S 16.09.

4.1.6. *1,5-Bis[2-(N,N-diethylacetamidooxy)thiabenzyl]-3-oxapentane **11***

Pale yellow oil (95%); FT-IR (KBr, cm^{-1}): 1657 [$CON(C_2H_5)_2$]; ^{1}H NMR ($CDCl_3$): δ 1.15–1.20 (m, 12H, CH_2CH_3), 2.66 (t, $J = 5$ Hz, 4H, $SCH_2CH_2OCH_2CH_2S$), 3.42 (q, $J = 6$ Hz, 4H), 3.58 (t, $J = 6$ Hz, 4H, $SCH_2CH_2OCH_2CH_2S$), 3.84 (s, 4H, CH_2Ph), 4.73 (s, 4H, OCH_2CO), 6.88 (d, $J = 6$ Hz, 2H), 6.92–6.96 (m, 2H), 7.18–7.23 (m, 2H), 7.27–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 12.84, 14.42, 30.68, 30.81, 31.09, 40.31, 41.44, 67.88, 70.44, 112.21, 121.37, 127.31, 128.34, 130.56, 156.04, 167.02. Anal. Calcd for $C_{30}H_{44}N_2S_2O_5$ (%): C 62.47, H 7.69, N 4.86, S 11.12; found (%): C 62.53, H 7.49, N 4.91, S 11.18.

4.2. *In vitro antibacterial activity*

The antibacterial activity of these compounds was determined by measuring the inhibition zones in agar diffusion test and calculating the MIC by serial dilution assay as described earlier (*27*). Streptomycin was used as a positive control.

The tested microorganisms were *B. subtilis* (ATCC 6633), *M. luteus* (ATCC 10240), *S. aureus* (ATCC 43300), *Escherichia coli* (ATCC 25922) and *Enterobacter aerogenes* (ATCC 13048). The applied concentrations on the blank 6 mm disks were 100, 300 and 500 μg ml^{-1}.

Acknowledgements

We thank Deanship of the Academic Research at Mutah University and Scientific Research for financial support.

References

(1) Korn, T.E.; Tsvetkov, E.N. *Russ. Chem. Rev.* **1990,** *59* (3), 283–298.
(2) Shahrisa, A.; Banaei, A. *Molecules* **2001,** *9,* 721–727.
(3) Li, H.; Zheng, Q.; Han, C. *Analyst* **2001,** *135* (6), 1360–1364.
(4) Jyothish, K.; Zhang, W. *Angew. Chem. Int. Ed.* **2011,** *50* (15), 3435–3438.
(5) Cherkasov, R.A.; Vasil'ev, R.I.; Garifzyanov, A.R.; Talan, A.S. *Russ. J. Gen. Chem.* **2008,** *78* (6), 1167–1171.
(6) Atwood, J.L. *Encyclopedia of Supramolecular Chemistry*; Marcel Dekker: New York, 2004.
(7) Ghosh, K.; Sarker, A.R.; Ghorai, A.; Ghosh, U. *New J. Chem.* **2012,** *36,* 1231–1245.
(8) Federova, O.V.; Mordovskoi, G.G.; Rusinor, G.L.; Zueva, M.N.; Ovchinnikova, I.G. *Pharm. Chem. J.* **1996,** *30,* 611–612.
(9) Khalili, N.S.A.M. *Eur. J. Med. Chem*. **2010,** *45,* 5265–5277.
(10) Zhang, D.; Crawford, J.D.; Bartsch, R.A. *J. Incl. Phenom. Macrocycl. Chem.* **2011,** *70,* 205–216.
(11) Ohki, A.; Kim, J.S.; Suzuki, Y.; Hayashita, T.; Maeda, S. *Talanta* **1997,** *44,* 1131–1135.
(12) Elshani, S.; Wai, C.M.; Natale, N.R.; Bartsch, R.A. *Tetrahedron* **1999,** *55,* 9425–9438.
(13) Kim, J.S.; Cho, M.H.; Lee, S.C.; Pang, H.P.; Lee, J.H.; Ohki, A. *Talanta* **1999,** *49,* 69–75.
(14) Kim, S.K.; Cho, M.H.; Cho, J.H.; Lee, J.H.; Bartsch, R.A.; Lee, Y.I.; Kim, H. *Talanta* **2000,** *51,* 99–105.
(15) Mizyed, S; Ashram, M. *J. Incl. Phenom. Macrocycl. Chem.* **2011,** *70,* 135–142.
(16) Ashram, M.; Al-Jaafreh, E. *J. Incl. Phenom. Macrocycl. Chem*. **2008,** *62,* 75–80.
(17) Ashram, M. *J. Chem. Soc. Perkin Trans.* **2002,** *2,* 1662–1668.
(18) Tawarah, K.M.; Mizyed, S.A. *J. Incl. Phenom. Macrocycl. Chem*. **1988,** *6,* 583–591.
(19) Tawarah, K.M.; Khasawnah, M.A.; Mizyed, S.A. *J. Incl. Phenom. Macrocycl. Chem.* **2005,** *51,* 143–148.
(20) Tawarah, K.M.; Mizyed, S.A. *J. Solution Chem*. **1989,** *18,* 387–401.
(21) Mizyed, S.A.; Ashram, M. *Z. Naturforsch*. **2005,** *6a,* 424–428.
(22) Ashram, M.; Bqaeen, M.; Mizyed, S. *J. Incl. Phenom. Macrocycl. Chem*. **2010,** *67,* 81–84.
(23) Pearson, R.G. *J. Am. Chem. Soc*. **1963,** *85,* 3533–3539.

(24) Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery Jr., J.A.; Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; Pople, J.A. *Gaussian 03 Revision D 01*; Gaussian Inc.: Wallingford, CT, 2004.
(25) Cordero, B.; Gómez, V.; Platero-Prats, A.E.; Revés, M.; Echeverría, J.; Cremades, E.; Barragán, F.; Alvarez, S. *Dalton Trans.* **2008,** *21,* 2832–2838.
(26) Tochtrop, G.P.; Sadhukhan, A.; Koner, R.R.; Ghosh, S. *Tetrahedron* **2009,** *65,* 10515–10534.
(27) Alshahateet, S.F.; Al-Zereini, W.A.; Alghezawi, N.M. *J. Chem. Cryst.* **2011,** *41,* 1807–1811.