CROWN AND AZACROWN ETHERS WITH PENDANT ADENINE GROUP*

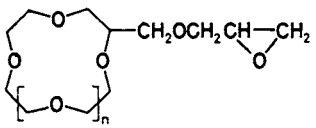
Petr HOLÝ, Martin BĚLOHRADSKÝ, Ivan STIBOR, Juraj KOUDELKA, David ŠAMAN, Jana HODAČOVÁ, Antonín HOLÝ and Jiří ZÁVADA

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

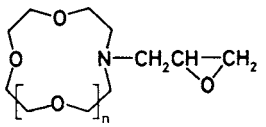
Received April 25th, 1987

Base-catalyzed oxirane ring-opening reaction of 4,5-epoxy-2-oxapentyl crown ethers *Ia—Ie* and N-(2,3-epoxy-1-propyl) azacrown ethers *IIa—IIc* with adenine affords mixtures of corresponding adenin-9-yl, adenin-3-yl and adenin-7-yl derivatives (*IIIa—IIIe*, *IVa—IVe*, *Va—Ve*, *VIa—VIc*, *VIIa—VIIc* and *VIIIa—VIIIc*) respectively, separable by liquid chromatography. Structure of the individual isomers was assigned on basis of ^{1}H and ^{13}C NMR spectroscopy. Complexation of the prevailing (adenin-9-yl) isomers *IIIa—IIIe* and *VIa—VIc* with sodium ion was measured potentiometrically in 99% methanol and the calculated stability constants were compared with corresponding data from related homologous series of crown and azacrown ethers *IXa—IXe*, *Xa—Xe*, *XIa—XIc* and *XIIa—XIIc* differing in pendant group.

In the preceding paper[1] we have shown that reaction of 4,5-epoxy-2-oxapentyl crown ethers *Ia—Ie* and N-(2,3-epoxy-1-propyl) azacrown ethers *IIa—IIc* with amines provides access to a variety of macrocyclic multisite ligands with β-hydroxyamine pendant groups. As a complement to the synthetic study we have now examined reaction of the epoxy-compounds *Ia—Ie* and *IIa—IIc* with adenine. Adenine is an



Ia-Ie, (*n* = 1-5)

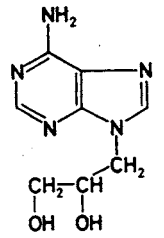


IIa-IIc, (*n* = 1-3)

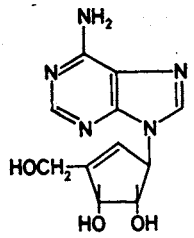
ambident nitrogen nucleophile and the course of oxirane ring opening in *Ia—Ie* and *IIa—IIc* represents a problem of some interest on its own right. Furthermore, adenine may afford additional ligation site for a selective complexation of metal ions. Last but not least, possible biological activity of adenine–crown ether conjugates arose our interest. Potent antiviral activity has been recently discovered in several acyclic[2-4] and carbocyclic[5,6] adenosine analogues bearing some structural

* Part VIII in the series Chemistry of Multidentate Ligands; Part VII: Collect. Czech. Chem. Commun. *52*, 2961 (1987).

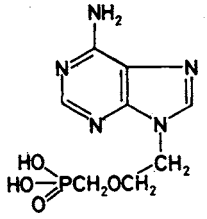
semblance with products of the present reaction. There is also an increased interest in adenine derivatives as potential modulators[7] of adenine receptors in cellular membranes.



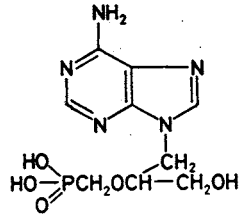
(*S*)-DHPA (ref.[2])



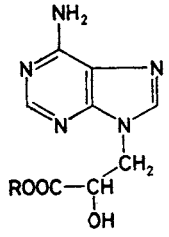
Neplanocin A (ref.[5])



PMEA (ref.[4])



HPMPA (ref.[4])



AHPA esters (ref.[3])

EXPERIMENTAL

Analytical samples were dried in a rotating film at 60°C/1 Pa for 60 h. ^{1}H and ^{13}C NMR spectra were measured in FT mode on Varian XL-200 (at 200 MHz for ^{1}H) in hexadeuteriodimethyl sulphoxide (Aldrich Chemical; 99·9% ^{2}H) and the spectra were referred to central peak of solvent signal (2·5 ppm in ^{1}H and 39·7 ppm in ^{13}C NMR spectra). Mass spectra were measured on AEI MS 902 spectrometer with a double focusation. Potentiometric measurements were

carried out on Radelkis digital OP-208/1 pH-meter with Crytur sodium ion selective electrode (Monokrystaly, Turnov) and Ag/AgCl/LiCl as the reference. Thin layer chromatography (TLC) was performed on Kieselgel GF_{254} Merck (eluent $CHCl_3$–CH_3OH–aq. NH_4OH) or on alumina Woelm TLC (eluent $CHCl_3$–CH_3OH) using UV absorption and Draggendorff's reagent[8] for detection. Preparative liquid chromatography was carried out on alumina (Reanal neutral, Brockmann activity II) employing $CHCl_3$–CH_3OH (99 : 1—95 : 5) as eluent. HPLC analyses were carried out using Knauer modular instrument with UV detector at 267 nm (Lichrosorb RP 18 — 7 μm; 100 × 4 mm column with a precolumn; CH_3OH–H_2O–$(C_2H_5)_3N$ eluent, 25 : 100 : 0·1—50 : 100 : 0·1 gradient).

Reaction of Epoxides *Ia—Ie* and *IIa—IIc* with Adenine

A mixture of adenine (270 mg; 2 mmol), an appropriate epoxide (2·2 mmol), and anhydrous potassium carbonate (2·8 mg; 0·02 mmol) in dimethylformamide (15 ml) was heated under stirring at 70—80°C until adenine disappeared (20—40 h; TLC monitoring). The solvent was distilled off *in vacuo* and the residue was subjected to a column chromatography. Yields and elemental analyses of the main products (adenin-9-yl isomers) are in Table I. The ^1H, ^{13}C NMR, and mass spectra are summarized in Tables II—V.

TABLE I

Adenin-9-yl derivatives *III* and *VI*: yields and elemental analyses

Compound	Yield[a] %	Formula (mol. weight)	Calculated/found		
			% C	% H	% N
IIIa	70	$C_{17}H_{27}N_5O_6$ (397·4)	51·37 51·04	6·85 6·80	17·62 17·08
IIIb	52	$C_{19}H_{31}N_5O_7$ (441·5)	51·69 51·34	7·08 7·07	15·87 15·57
IIIc	61	$C_{21}H_{35}N_5O_8$ (485·5)	51·95 51·74	7·27 7·31	14·43 14·12
IIId	51	$C_{23}H_{39}N_5O_9$ (529·6)	52·16 52·13	7·42 7·35	13·23 12·98
IIIe	45	$C_{25}H_{43}N_5O_{10}$ (573·6)	52·34 52·47	7·55 7·47	12·21 11·80
VIa	72	$C_{16}H_{26}N_6O_4$ (366·4)	52·44 52·06	7·15 7·09	22·94 22·58
VIb	54	$C_{18}H_{30}N_6O_5$ (410·5)	52·67 52·43	7·37 7·43	20·48 19·83
VIc	58	$C_{20}H_{34}N_6O_6$ (454·5)	52·85 52·61	7·54 7·46	18·49 18·47

[a] From column chromatography.

TABLE II

Adenine derivatives *III*—*VIII*: mass spectra

Compound[a]	*m/z* (r.i.)
IIIa	M^+ = 397 (5), 178 (100), 193 (83), 178 (58), 45 (53), 149 (44), 87 (44), 148 (36), 136 (36), 135 (36), 218 (25)
IIIb	M^+ = 441 (5), 178 (100), 193 (50), 87 (48), 45 (48), 149 (38), 136 (29), 208 (26), 148 (26), 135 (23), 252 (17)
IIIc	M^+ = 485 (4), 178 (100), 45 (58), 193 (46), 192 (42), 149 (38), 136 (38), 87 (33), 148 (31), 208 (27), 135 (27)
IIId	M^+ = 529 (4), 178 (100), 193 (46), 45 (43), 87 (39), 192 (38), 149 (33), 136 (30), 208 (27), 179 (25), 176 (25)
IIIe	45 (100), 135 (54), 59 (54), 57 (54), 178 (49), 87 (48), 136 (46), 148 (45), 73 (45), 191 (31)
IVa	M^+ = 397 (1), 45 (100), 87 (70), 178 (55), 105 (48), 175 (44), 149 (37), 136 (30), 208 (28), 135 (28), 193 (15)
IVb	M^+ = 441 (4), 178 (100), 45 (78), 136 (69), 252 (67), 149 (67), 135 (61), 208 (45), 87 (43), 179 (37), 250 (35)
IVc	M^+ = 485 (4), 45 (100), 178 (71), 87 (51), 136 (38), 149 (36), 193 (33), 192 (27), 135 (27), 208 (24), 148 (24)
IVd	M^+ = 529 (6), 178 (100), 136 (64), 252 (55), 208 (45), 149 (45), 45 (41), 135 (30), 250 (27), 179 (25), 87 (25)
IVe	M^+ = 579 (1), 45 (100), 178 (60), 87 (53), 136 (51), 149 (36), 89 (35), 135 (31), 208 (29), 252 (25), 250 (15)
Va	M^+ = 397 (2), 45 (100), 178 (72), 87 (48), 149 (46), 136 (39), 135 (38), 208 (30), 193 (26), 148 (26), 192 (22)
Vb	M^+ = 441 (4), 45 (100), 178 (94), 87 (65), 135 (58), 136 (56), 149 (46), 252 (42), 208 (31), 89 (27), 250 (21)
Vc	M^+ = 485 (1), 45 (100), 87 (80), 178 (48), 149 (36), 89 (36), 135 (32), 136 (30), 252 (26), 179 (24), 148 (22)
Vd	M^+ = 529 (4), 178 (100), 45 (65), 87 (47), 193 (42), 192 (37), 149 (33), 208 (27), 179 (26), 252 (24), 89 (24)
Ve	M^+ = 575 (0·5), 45 (100), 87 (62), 89 (53), 59 (38), 135 (33), 57 (31), 178 (29), 58 (24), 136 (22)
VIa	$M^+ - H_2O$ = 348 (3), 178 (100), 135 (66), 148 (60), 100 (57), 56 (51), 44 (51), 149 (43), 136 (37), 108 (31), 214 (29)
VIb	$M^+ + 1$ = 411 (0·5), 56 (100), 232 (76), 178 (76), 178 (76), 57 (65), 100 (50), 233 (47), 149 (45), 70 (37), 58 (34), 258 (31)

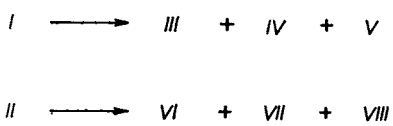
TABLE II
(*Continued*)

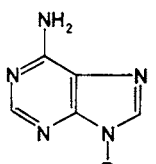
Compound[a]	*m/z* (r.i.)
VIc	$M^+ + 1$ = 455 (0·4), 276 (100), 178 (37), 277 (22), 56 (12), 302 (11), 45 (11), 179 (10), 100 (10), 124 (9), 136 (8)
VIIa	$M^+ + 1$ = 367 (1), 178 (100), 214 (89), 56 (55), 45 (35), 149 (32), 189 (28), 135 (27), 100 (27), 126 (14), 108 (12)
VIIb	$M^+ + 1$ = 411 (1), 232 (100), 178 (64), 258 (38), 149 (29), 135 (22), 45 (22), 56 (21), 233 (17), 262 (14), 100 (13)
VIIc	$M^+ + 1$ = 455 (1), 276 (100), 179 (83), 302 (43), 277 (21), 56 (21), 45 (20), 149 (16), 100 (13), 135 (12), 124 (9)
VIIIa	$M^+ - H_2O$ = 348 (0·6), 56 (100), 57 (94), 100 (93), 188 (88), 83 (85), 144 (56), 55 (53), 158 (40), 58 (35)
VIIIc	188 (100), 178 (43), 214 (24), 100 (19), 56 (15), 189 (14), 45 (11), 158 (9), 135 (9), 149 (8)

[a] Compounds *IVa*, *IVc*–*IVe*, *Va*–*Ve*, *VIIa*–*VIIc*, *VIIIa*, and *VIIIc* were measured in form of chromatographically enriched isomer mixtures.

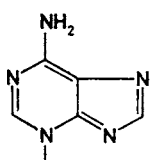
RESULTS AND DISCUSSION

Reaction of the macrocyclic epoxides *Ia*–*Ie* as well as *IIa*–*IIc* with adenine was carried out in dimethylformamide under catalytic action of anhydrous potassium carbonate. A nearly quantitative conversion of the educts into products occured at elevated temperature.

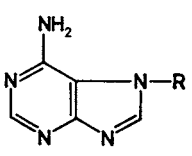




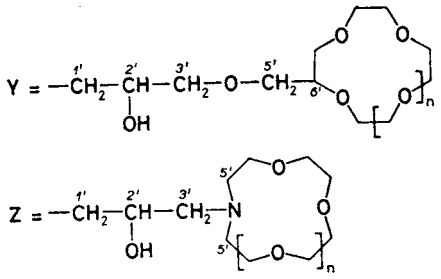
IIIa–*IIIe*, (R = Y; *n* = 1–5)
VIa–*VIc*, (R = Z; *n* = 1–3)



IVa–*IVe*, (R = Y; *n* = 1–5)
VIIa–*VIIc*, (R = Z; *n* = 1–3)



Va–*Ve*, (R = Y; *n* = 1–5)
VIIIa–*VIIIc*, (R = Z; *n* = 1–3)



Three isomeric products were invariably found in the reaction mixture and these were assigned (*vide infra*) structures of adenin-9-yl, adenin-3-yl, and adenin-7-yl derivatives shown above. It was found that the former positional isomer prevails always in the reaction over the latter two in ratio approximately 6 : 1, irrespective of structure and ring size of the starting crown. Thus formation of the individual isomers appears to depend primarily upon electron density on the alternative reaction sites in the adenine nucleophile. Qualitatively similar prevalence of adenin-9-yl isomers was observed earlier in reaction of adenine with other glycidylethers[9], where however formation of the minor adenin-7-yl isomers was not noted.

Only incomplete separation of the positional isomers could be attained by liquid chromatography on preparative as well as on analytical scale owing to small differences in retention times following always the order *III* < *IV* < *V* and *VI* < *VII* < *VIII*. Pure adenin-9-yl isomers *IIa*–*IIe* and *VIa*–*VIc* were isolated by a column chromatography on alumina in 40–65% yields, the remaining portion being co-eluted with the slower components. The complementary adenin-3-yl and adenin-7-yl isomers were accordingly obtained merely in form of enriched chromatographic fractions; these however sufficed for an structure assignment by NMR spectroscopy.

Assignment of Structure of the Adenine Derivatives III–VIII *by* ^{1}H *and* ^{13}C NMR *Spectroscopy.*

A common feature of ^{1}H NMR spectra of all the adenine derivatives investigated in this study is presence of three signals in the aromatic region, a broad signal corresponding to protons in the macroring (CH_2—O δ 3·4–3·5; CH_2—N δ 2·7), and signals due to the aliphatic junction between the adenine and crown moieties (CH_2—OH δ 3·95; CH_2—N δ 4·05 and 4·25; CH_2—O δ 3·4–3·5). It indicates that structure of all the obtained products is in accord with the proposed formulae.

A closer examination of the proton signals in the aromatic regions shows (Table III) that chemical shifts for the individual positional isomers in any investigated triad *III*–*V* or *VI*–*VIII* differ each from the other markedly. Tentative assignment of structure for the individual isomers could be made on basis of the observed differences, since available evidence from other substituted adenines[10–14] strongly

suggests (Table VI) that a simple relationship exists between magnitude of chemical shift of adenine protons and the substituent position.

Independent structure assignment could be drawn on basis of ^{13}C NMR spectroscopy, the chemical shifts for adenine grouping being in the individual position isomers again distinctly different (Tables IV and V). A correlation of the observed values with available literature analogies (Table VI) confirmed in full the structure assignment based on ^{1}H NMR.

The Effect of Pendant Group and Ring Size on Complexation of Adenin-9-yl Isomers III *and* VI *with Sodium Ion*

As a part of our interest in complexation of alkali metal salts with macrocyclic ligands[15,16] we have performed a customary study of complexing ability of the

TABLE III

^{1}H NMR chemical shifts of compounds *III*— *VIII* in hexadeuteriodimethyl sulphoxide

Compound[a]	H-2	H-8	NH_2
IIIa	8·04 s	8·13 s	7·17 s
IVa	8·22 s	7·78 s	7·93 s
Va	8·18 s	8·15 s	6·85 s
IIIb	8·04 s	8·13 s	7·17 s
IVb	8·24 s	7·82 s	8·01 s
IIIc	8·04 s	8·12 s	7·17 s
Vc	8·17 s	8·16 s	6·87 s
IIId	8·04 s	8·13 s	7·17 s
IVd	8·28 s	7·76 s	7·87 s
Vd	8·18 s	8·15 s	6·87 s
IIIe	8·04 s	8·13 s	7·19 s
IVe	8·21 s	7·78 s	7·91 s
Ve	8·18 s	8·15 s	6·85 s
VIa	8·07 s	8·13 s	7·17 s
VIIa	8·24 s	7·78 s	7·94 s
VIIIa	8·18 s	8·17 s	6·90 s
VIb	8·06 s	8·13 s	7·18 s
VIIb	8·24 s	7·77 s	7·93 s
VIc	8·07 s	8·14 s	7·21 s
VIIc	8·23 s	7·76 s	7·90 s
VIIIc	8·16 s	8·16 s	6·84 s

[a] Compounds *IVa*, *IVb*, *IVd*, *IVe*, *Va*, *Vc*, *Vd*, *Ve*, *VIIa*, *VIIb*, *VIIc*, *VIIIa*, and *VIIIc* were measured in form of chromatographically enriched isomer mixtures.

TABLE IV

^{13}C NMR chemical shifts of compounds *IIIa–IIIe, IVa, IVb, IVe, Va, Vb, Ve* in hexadeuteriodimethyl sulphoxide

Carbon	*IIIa*	*IVa*	*Va*	*IIIb*	*IVb*	*IIIc*	*IIId*	*IIIe*	*IVe*	*Ve*
C-2	152·45 d	150·91 d	152·20 d	152·51 d	151·39 d	152·44 d	152·67 d	152·42 d	151·74 d	152·77 d
C-4	149·92 s	149·60 s	159·79 s	149·92 s	149·73 s	149·90 s	150·09 s	149·96 s	149·83 s	159·81 s
C-5	118·81 s	118·64 s	112·10 s	118·79 s	119·28 s	118·78 s	118·91 s	118·82 s	119·71 s	112·34 s
C-6	156·08 s	154·97 s	152·20 s	156·12 s	154·97 s	156·07 s	156·15 s	156·02 s	155·14 s	152·47 s
C-8	141·91 d	145·34 d	146·87 d	141·88 d	145·34 d	141·84 d	142·43 d	142·09 d	144·86 d	147·18 d
C-1′	46·70 t	53·11 t	49·57 t	46·66 t	53·09 t	46·68 t	46·97 t	46·79 t	53·12 t	49·83 t
C-2′	67·81 d	66·72 d	66·73 d	67·81 d	66·74 d	67·81 d	68·16 d	67·94 d	66·78 d	67·07 d
C-3′	73·35 t	73·43 t	72·50 t	73·34 t	73·44 t	73·33 t	73·51 t	73·38 t	73·44 t	72·54 t
C-4′	69·57 t	69·51 t	69·01 t	69·45 t	69·35 t	69·13 t	69·50 t	69·36 t	69·29 t	69·47 t
C-5′[a]	77·96 d	77·86 d	77·87 d	78·00 d	77·90 d	77·79 d	78·19 d	78·07 d	77·96 d	78·11 d

[a] Remaining crown carbons: in *IIIa* 71·23 t, 71·16 t, 70·53 t, 70·32 t, 70·27 t, 70·19 t, 69·91 t; in *IVa* 71·21 t, 71·08 t, 70·46 t, 70·24 t, 70·19 t, 70·11 t, 69·85 t; in *Va* 71·30 t, 71·00 t, 70·49 t, 70·23 t, 70·13 t, 69·86 t, 69·49 t; in *IIIb* 71·32 t, 70·88 t, 70·44 t, 70·24 t, 70·07 t, 69·99 t, 69·96 t, 69·92 t (2 C); in *IVb* 71·24 t, 70·81 t, 70·34 t, 70·13 t, 69·93 t (2 C), 69·87 t, 69·81 t (2 C); in *IIIc* 71·10 t, 71·00 t, 70·34 t, 70·30 t, 70·13 t (3 C), 70·06 t (2 C), 70·02 t (2 C); in *IIId* 71·34 t, 71·27 t, 70·90 t, 70·80 t, 70·50 t (8 C), 70·41 t; in *IIIe* 71·17 t, 70·65 t, 70·58 t, 70·31 t (9 C), 70·26 t (3 C); in *IVe* 71·11 t, 70·58 t, 70·50 t, 70·23 t (9 C), 70·18 t (3 C); in *Ve* 71·27 t, 71·10 t, 70·77 t, 70·72 t, 70·42 t (8 C), 70·22 t (3 C).

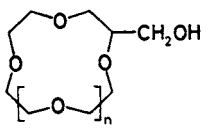
TABLE V

^{13}C NMR chemical shifts of compounds *VI*, *VII*, *VIIIa*, and *VIIIc* in hexadeuteriodimethyl sulphoxide

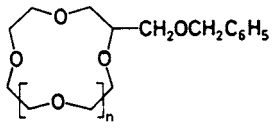
Carbon	*VIa*	*VIIa*	*VIIIa*	*VIb*	*VIIb*	*VIc*	*VIIc*	*VIIIc*
C-2	152·42 d	151·99 d	152·10 d	152·38 d	152·02 d	152·48 d	152·14 d	152·08 d
C-4	149·89 s	149·96 s	159·78 s	149·90 s	150·01 s	149·98 s	150·01 s	—[a]
C-5	118·74 s	120·12 s	111·93 s	118·76 s	120·17 s	118·82 s	120·30 s	111·81 s
C-6	156·08 s	155·15 s	152·10 s	156·07 s	155·18 s	156·13 s	155·19 s	152·08 s
C-8	141·78 d	144·57 d	146·75 d	141·86 d	144·69 d	142·00 d	144·53 d	146·71 d
C-1′	47·37 t	53·93 t	50·54 t	47·57 t	54·16 t	47·73 t	53·95 t	50·68 t
C-2′	67·41 d	66·45 d	68·74 d	67·51 d	66·80 d	67·73 d	66·54 d	68·99 d
C-3′	59·63 t	59·54 t	58·83 t	60·14 t	60·20 t	59·47 t	59·61 t	58·94 t
C-5′[b]	55·43 t	55·32 t	55·19 t	55·49 t	55·57 t	55·03 t	55·33 t	55·23 t

[a] Not determined; [b] remaining crown carbons: in *VIa* 69·50 t (2 C), 69·69 t (2 C), 70·42 t (2 C); in *VIIa* 68·80 t (2 C), 69·58 t (2 C), 70·28 t (2 C); in *VIIIa* 69·56 t (4 C), 70·09 t (2 C); in *VIb* 69·33 t (2 C), 69·59 t (2 C), 69·84 t (2 C), 70·28 t (2 C); in *VIIb* 69·45 t (2 C), 69·55 t (2 C), 69·76 t (2 C), 70·20 t (2 C); in *VIc* 69·44 t (2 C), 69·84 t (2 C), 70·12 t (2 C), 70·28 t (2 C); in *VIIc* 69·60 t (2 C), 69·68 t (2 C), 70·28 t (2 C), 70·40 t (2 C); in *VIIIc* 69·73 t (2 C), 69·94 t (2 C), 69·98 t (2 C), 70·18 t (2 C).

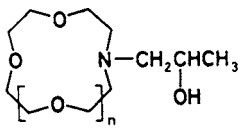
adenin-9-yl substituted crowns and azacrowns *IIIa–IIIe* and *VIa–VIc* in respect to sodium cation. Stability constants K_s corresponding to 1 : 1 metal–ligand complex formation were determined potentiometrically in 99% methanol employing sodium ion selective electrode. In order to assess the effect of the adenine group upon complexation, we have included in the potentiometric study several related series of macrocyclic ligands differing in pendant group. The adenin-9-yl derivatives *IIIa–IIIe* were compared with the hydroxymethyl[17] derivatives *IXa–IXe*, benzyloxymethyl[17] derivatives *Xa–Xe*, and 4,5-epoxy-2-oxapentyl[17] derivatives *Ia–Ie*. The adenin-



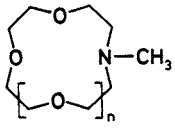
IXa–IXe, ($n = 1-5$)



Xa–Xe, ($n = 1-5$)



XIa–XIc, ($n = 1-3$)



XIIa–XIIc, ($n = 1-3$)

TABLE VI

Characteristic values of ^1H and ^{13}C NMR chemical shifts of substituted adenines in hexadeuteriodimethyl sulphoxide

Atom	Chemical shifts for substitution in position		
	3[a,b]	7[c,d]	9[d,e]
H-2	8·32 s	8·55 s	8·04 s
H-8	7·76 s	8·21 s	8·14 s
NH_2	—[f]	6·99 bs	7·18 bs
C-2	147·8 d	153·8 d	153·9 d
C-4	147·5 s	161·3 s	148·8 s
C-5	110·3 s	111·4 s	121·0 s
C-6	153·2 s	152·8 s	157·1 s
C-8	144·4 d	145·4 d	141·3 d

[a] Data from ref.[10]; [b] data from ref.[11]; [c] data from ref.[12]; [d] data from ref.[13]; [e] data from ref.[14]; [f] value was not reported.

-9-yl derivatives *VIa–VIc* were similarly compared with the corresponding methyl derivatives *XIa–XIc* and with the 2-hydroxypropyl derivatives *XIIIa–XIIIc*. The results are summarized in Tables VII and VIII.

As inspection of Tables VII and VIII shows, ring size is the dominant factors which controls complex stability in all the investigated series, irrespective of pendant group. The observed order of complex stability $12 < 15 < 18 > 21 \sim 24$ is in accord with the principle of best fit between macroring cavity and metal ion diameter which is known to govern complexation behaviour of unsubstituted crown[18,19].

A closer examination of Tables VII and VIII show that only subtle differences exist among the compared pendant groups. It suggests that adenin-9-yl group does not contribute significantly to complexation of sodium ion with the ligands *IIIa–IIIe*

TABLE VII

Stabilities of 1 : 1 complexes between sodium ion and functionalized crown ethers *III*, *I*, *IX*, and *X* determined in 99% methanol: the effect of ring size and pendant group on stability constant (K_s)

Homologue (ring size)	K_s, 1 mol^{-1}			
	III	*I*	*IX*	*X*
a (12)	36	13	37	—[a]
b (15)	664	1 100	890	1 120
c (18)	6 490	7 590	4 560	6 610
d (21)	75	78	144	65
e (24)	133	141	159	151

[a] Not determined.

TABLE VIII

Stabilities of 1 : 1 complexes between sodium ion and functionalized azacrown ethers *VI*, *XI*, and *XII* in 99% methanol: the effect of ring size and pendant group on stability constant (K_s)

Homologue (ring size)	K_s, 1 mol^{-1}		
	VI	*XI*	*XII*
a (12)	170	110	330
b (15)	1 350	2 570	4 470
c (18)	15 600	6 100	20 420

and *VIa*–*VIc* regardless of the macroring size. This does not come much as a surprise since adenine is known to provide a soft[20,21] ligation site which is not convenient for hard sodium cation; a more pronounced effect of the adenine group may be expected in complexation with softer, *e.g.*, transition metal ions.

REFERENCES

1. Bělohradský M., Holý P., Stibor I., Závada J.: Collect. Czech. Chem. Commun. *52*, 2961 (1987).
2. DeClercq E., Descamps J., DeSomer P., Holý A.: Science *200*, 563 (1978).
3. DeClercq E., Holý A.: J. Med. Chem. *28*, 282 (1985).
4. DeClercq E., Holý A., Rosenberg I., Sakuma T., Balzarini J., Maudgal P. C.: Nature *323*, 464 (1986).
5. DeClercq E.: Antimicrob. Agents Chemother. *28*, 84 (1985).
6. Robins R. K.: Chem. Eng. News *64*, 28 (1986).
7. Daly J. W.: J. Med. Chem. *25*, 197 (1982).
8. Trezl L., Bako P., Fenichel L., Rusznak I.: J. Chromatogr. *269*, 40 (1983).
9. Ueda N., Kawabata T., Takemoto K.: J. Heterocycl. Chem. *8*, 827 (1971).
10. Miyaki M., Shimizu B.: Chem. Pharm. Bull. *18*, 1446 (1970).
11. Seela F., Hasselmann D.: Chem. Ber. *113*, 2043 (1980).
12. Montgomery J. A., Thomas H. J.: J. Am. Chem. Soc. *87*, 5442 (1965).
13. Akhrem A. A., Mikhailopulo I. A., Abramov A. F.: Org. Magn. Reson. *12*, (1979).
14. Holý A.: Collect. Czech. Chem. Commun. *48*, 1910 (1983).
15. Závada J., Pechanec V., Kocián O.: Collect. Czech. Chem. Commun. *48*, 2509 (1983).
16. Závada J., Pechanec V., Zajíček J., Stibor I., Vítek A.: Collect. Czech. Chem. Commun. *50*, 1184 (1985).
17. Bělohradský M., Stibor I., Holý P., Závada J.: Collect. Czech. Chem. Commun. *52*, 2500 (1987).
18. Pedersen C. J.: J. Am. Chem. Soc. *89*, 7017 (1967).
19. Izatt R. M., Bradshaw J. S., Nielsen S. A., Lamb J. D., Christensen J. J.: Chem. Rev. *85*, 271 (1985).
20. Martin R. B.: Acc. Chem. Res. *18*, 32 (1985).
21. Tu A. T., Heller M. J. in the book: *Metal Ions in Biological Systems* (H. Siegel, Ed.), Vol. 1, Chapt. 1. Dekker, New York 1974.

Translated by the author (J.Z.).