Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **23:** 195–201, 1995.

Novel Monoaza- and Diazacrown Ethers Incorporating Sugar Units and Their Extraction Ability towards Picrate Salts

PÉTER BAKÓ and LÁSZLÓ TÖKE*
Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, Müegyetem rkp. 3. Hungary.

(Received: 12 July 1995; in final form: 1 November 1995)

Abstract. A number of new 15- and 1 8-membered ring aza-crown (**4**, **5**, **8–13**, **17**, **18**) and lariat ethers (**6**, **7**) incorporating glucose or galactose units have been synthesized in good yields by a simple route. Their extracting abilities were measured with Li^+, Na^+, K^+ and NH_4^+ cations. The substituents at the nitrogen atom and the type of monosaccharide affected this property significantly.

Key words: Chiral crown ethers, extraction ability, aza-crown ethers, lariat ethers.

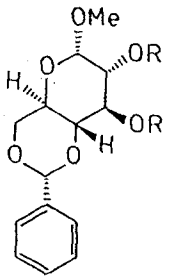
1. Introduction

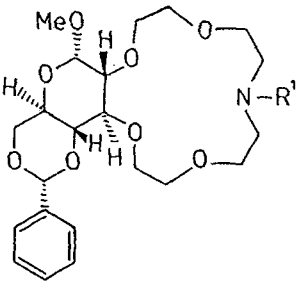
Asymmetric carbon–carbon bond forming reactions catalyzed by chiral crown ethers have recently attracted a great deal of attention [1–4]. The design of efficient catalysts for asymmetric induction has been a recent focus in synthetic organic chemistry. Many optically active crown ethers have been synthesised from monosaccharides. Carbohydrates including glucosides and galactosides as the source of chirality have been incorporated in crown ethers by Stoddart *et al.* [5–7]. Chiral monoaza- and diaza-crown ethers and cryptands containing monosaccharides have also been prepared [8–14].

Nitrogen atoms and side arms (among others side arms with heteroatoms) were built into the macrorings to enhance and regulate the cation binding properties as well as the lipophilicity. The latter compounds with heteroatoms, named lariat ethers or armed crown ethers, are known to display encapsulated complexation, high lipophilic character and unique guest specificity via macroring – side arm cooperativity [15–17].

In this paper we report the efficient synthesis of 15-membered monoazacrown ethers having different pendant arms (alkyl and aryl substituents) on the nitrogen atom (**4**, **5**, **8–11**, **17**, **18**) or functionalized pendant arms (lariat ethers: **6**, **7**) and 18-membered diazacrown ethers (**12**, **13**) from methyl-4,6-*O*-benzylidene-α-D-glucopyranoside and galactopyranoside.

* Author for correspondence.





1 R = H

2 R = $(CH_2)_2O(CH_2)_2Cl$

3 R = $(CH_2)_2O(CH_2)_2I$

4 R^1 = butyl

5 R^1 = decyl

6 R^1 = CH_2CH_2OH

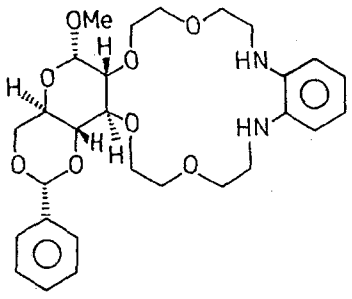
7 R^1 = CH_2COOCH_3

8 R^1 = cyclohexyl

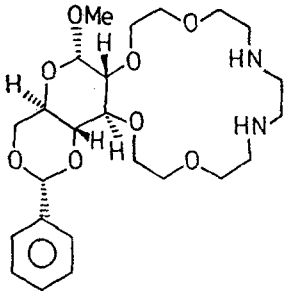
9 R^1 = benzyl

10 R^1 = Ph

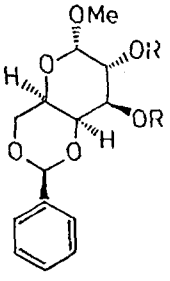
11 R^1 = α-naphthyl

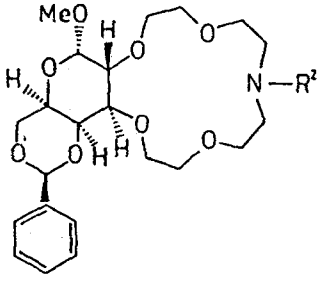


12



13





14 R = H

15 R = $(CH_2)_2O(CH_2)_2Cl$

16 R = $(CH_2)_2O(CH_2)_2I$

17 R^2 = benzyl

18 R^2 = decyl

Scheme 1.

Table I. Characterisation data of compounds and extraction of alkali metal and ammonium picrates for crown ethers **4–13**, **17** and **18**.

Comp.	Yield[a] (%)	$[\alpha]_D^{20}$ $CHCl_3$ $c = 1$	M.p. °C	Extractability (%)[b]			
				Li^+	Na^+	K^+	NH_4^+
3	92.7	29.5	oil	–	–	–	–
4	68.7	32.0	oil	28.7	58.2	26.9	55.9
5	44.3	31.6	58–60	32.7	77.2	47.0	67.4
6	60.0	41.7	oil	34.2	57.0	32.4	34.1
7	58.2	36.1	oil	30.5	61.2	49.5	45.8
8	70.6	30.1	oil	28.5	58.6	39.6	60.2
9	53.3	38.8	oil	6.5	44.0	15.2	13.7
10	33.7	42.3	126–28	5.9	13.7	6.5	0.9
11	37.0	32.7	48–51	5.6	22.4	8.9	0.1
12	57.7	29.7	60–61	16.2	23.3	20.1	6.1
13	37.8	40.1	56–58	55.6	66.7	59.9	66.8
15	88.0	98.7	oil	–	–	–	–
16	93.1	74.0	oil	–	–	–	–
17	37.7	94.2	oil	17.4	50.0	22.1	24.0
18	40.9	73.6	82–84	65.4	89.7	76.5	80.3

[a] After chromatography.
[b] R.t.; aqueous phase (10 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2 10 mL); [crown ether] = 1×10^{-2} M. Defined as % picrate extracted into the organic phase, determined by UV spectroscopy.

2. Experimental

^1H NMR spectra.: JEOL FX-100 (in $CDCl_3$), TMS as internal standard. UV spectra: Hitachi-Perkin Elmer 124. Mass spectra: JEOL JMS-OL SG-2. Column chromatography: Kieselgel 60 (0.063–0.2 mm, Merck), 23 × 440 mm, 75 g kieselgel, 2–2.5 g crude product, eluent: ethyl acetate–methanol (10 : 1–10 : 3) and toluene–methanol (3 : 1) in the case of compound **7**.

A typical experimental procedure is as follows. *Methyl* 4,6-*O*-*benzylidene*-2,3-*bis*-*O*-[(2-*chloroethoxy*)-*ethyl*]-α-D-*galactopyranoside* (**15**): A solution of **14** (21.8 g) and of tetrabutylammonium hydrogen sulfate (20.0 g) in bis[2-chloro-ethyl] ether (150 mL) was vigorously stirred at room temperature with a 50% aq. NaOH solution (150 mL) for 12 h. Dichloromethane (500 mL) and water (500 mL) were added to the reaction mixture. The organic phase was decanted and the aqueous phase washed with CH_2Cl_2. The organic phases were combined and washed with water, dried with $MgSO_4$, filtered and concentrated under vacuum. The resultant syrup was eluted through a silica gel column with ethyl acetate yielding **15** as a yellow syrup, 33.7 g (Data in Table I).

Methyl 4,6-*O*-*benzylidene*-2,3-*bis*-*O*-[(2-*iodoethoxy*)-*ethyl*]-α-D-*galacto*-*pyranoside* **16**. The mixture of **15** (20 g) and dry NaI (24.2 g) in dry acetone

(400 mL) was heated under reflux for 24 h. After cooling the precipitate was filtered and washed. The combined acetone solution was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (200 mL), washed with water, dried (Na_2SO_4), concentrated and dried in vacuum. Compound **16** was a yellow syrup; yield: 28 g (Data in Table I).

N-benzyl-monoaza-15-*crown*-5 *derivative* **17**. Dry Na_2CO_3 (8.0 g) was suspended in a solution of **16** (6.6 g) and benzylamine (1.12 g) in dry acetonitrile (200 mL). The stirred mixture was heated under reflux for 33 h. After cooling the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solution was evaporated under vacuum. The residue oil was dissolved in $CHCl_3$ (60 mL), washed with water, dried (Na_2SO_4) and concentrated (5.6 g). Chromatography on silica gel with ethyl acetate–methanol (20 : 1–20 : 2) yielded a yellow oil **17**, yield: 1.94 g (Data in Table I).

The structure of all compounds was established by ^{1}H NMR, IR and MS spectroscopy. All products gave satisfactory microanalysis.

^{1}H NMR ($CDCl_3$, TMS, 100 MHz, ppm)

Compound **3**: 7.62–7.20 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.87 (d, 1H, J = 4 Hz, anomeric H); 4.35–3.48 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 3.20 (m, 4H, ICH_2).

Compound **4**: 7.53–7.10 (m, 5H, Ph); 5.44 (s, 1H, PhCH); 4.77 (d, 1H, J = 3.6 Hz anomeric H); 4.19 (d, 2H, J = 5 Hz, CH_2); 4.07–3.48 (m, 16H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.80–2.10 (m, 6H, NCH_2); 1.43–1.10 (m, 4H, CH_2); 0.84 (t, 3H, J = 6.6 Hz, CH_3).

Compound **5**: 7.52–7.20 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.22 (d, 2H, J = 5 Hz, CH_2); 4.0–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.75–2.40 (m, 6H, NCH_2); 1.25 (m, 16H, CH_2); 0.9 (t, J = 6 Hz, 3H, CH_3).

Compound **6**: 7.55–7.17 (m, 5H, Ph); 5.5 (s, 1H, PhCH); 4.75 (d, 1H, J = 3.6 Hz, anomeric H); 4.17 (d, 2H, J = 5 Hz, CH_2); 4.03–3.46 (m, 18H, CH and CH_2 groups); 3.41 (s, 3H, OMe); 2.47–2.83 (m, 6H, NCH_2); 1.95 (s, 1H, OH).

Compound **7**: 7.55–7.20 (m, 5H, Ph); 5.48 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.22 (d, 2H, J = 5 Hz, CH_2); 4.13–3.48 (m, 18H, CH and CH_2 groups); 3.42 (s, 3H, OMe); 3.38 (s, 3H, OMe); 3.03–2.63 (m, 4H, CH_2).

Compound **8**: 7.50–7.10 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.24 (d, 2H, J = 5 Hz, CH_2); 4.0–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.75 (m, 5H, NCH_2 and NCH); 1.72 (m, 4H, CH_2); 1.15 (m, 6H, CH_2).

Compound **9**: 7.50–7.15 (m, 10H, Ph); 5.50 (s, 1H, PhCH); 4.82 (d, 1H, J = 3.6 Hz, anomeric H); 4.25 (d, 2H, J = 5 Hz, CH_2); 4.0–3.46 (m, 18H, CH and CH_2 groups), 3.40 (s, 1H, OMe); 2.75 (m, 4H, NCH_2).

Compound **10**: 7.50–7.10 (m, 5H, Ph); 6.90–6.65 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.87 (d, 1H, J = 3.6 Hz, anomeric H); 4.22 (d, 2H, J = 5 Hz, CH_2); 4.07–3.48 (m, 20H, CH and CH_2 groups); 3.40 (s, 1H, OMe).

Compound **11**: 7.60–7.03 (m, 12H, Ph); 5.47 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.20 (d, 2H, J = 5 Hz, CH_2); 4.0–3.45 (m, 20H, CH and CH_2 groups); 3.40 (s, 3H, OMe).

Compound **12**: 7.55–7.10 (m, 5H, Ph); 6.80–6.50 (m, 4H, Ph); 5.48 (s, 1H, PhCH); 4.80 (d, 1H, J = 3.6 Hz, anomeric H); 4.26 (d, 2H, J = 5 Hz, CH_2); 4.10–3.45 (m, 22H, CH and CH_2 groups); 3.37 (s, 3H, OMe).

Compound **13**: 7.60–7.20 (m, 5H, Ph); 5.50 (s, 1H, PhCH); 4.82 (d, 1H, J = 3.6 Hz, anomeric H); 4.25 (d, 2H, J = 5Hz, CH_2); 4.05–3.50 (m, 16H, CH, CH_2 groups and NH); 3.40 (s, 3H, OMe); 3.06–2.75 (m, 8H, NCH_2).

Compound **15**: 7.55–7.20 (m, 5H, Ph); 5.51 (s, 1H, PhCH); 4.90 (d, 1H, J = 4 Hz, anomeric H); 4.40–3.45 (m, 22H, CH and CH_2 groups); 3.40 (s, 3H, OMe).

Compound **16**: 7.60–7.10 (m, 10H, Ph); 5.50 (s, 1H, PhCH); 4.90 (d, 1H, J = 4 Hz, anomeric H); 4.40–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s 3H, OMe); 3.2 (t, 4H, ICH_2);

Compound **17**: 7.60–7.10 (m, 10H, Ph); 5.50 (s, 1H, PhCH); 4.90 (d, 1H, J = 4 Hz, anomeric H); 4.35–3.45 (m, 20H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.75 (t, 4H, NCH_2).

Compound **18**: 7.60–7.20 (m,5H, Ph); 5.55 (s, 1H, PhCH); 4.95 (d, 1H, J = 4 Hz, anomeric H); 4.50–3.45 (m, 18H, CH and CH_2 groups); 3.40 (s, 3H, OMe); 2.60 (t, 4H, NCH_2); 2.35 (t, 2H, CH_2); 1.25 (m, 16H, CH_2); 0.85 (t, 3H, CH_3).

3. Results and Discussion

The vicinal free hydroxy groups in methyl 4,6-*O*-benzylidine-α-D-glucopyranoside (**1**) and in methyl 4,6-*O*-benzylidine-α-D-galactopyranoside (**14**) were alkylated by the method of Gross *et al.* [18] with bis(2-chloroethyl)ether ($Cl[CH_2]_2O[CH_2]_2Cl$ used as solvent and reagent) under liquid–liquid two-phase reaction conditions using tetrabutylammonium hydrogen sulfate (as a PT catalyst) and 50% aqueous NaOH to give **2** and **15**, respectively. The exchange of chlorine by iodine in **2** and

15 was carried out by NaI in acetone (reflux, 24 h). Reactions of the iodides **3** and **16** with different amines in acetonitrile in the presence of solid dry Na_2CO_3 were much faster than those of **2** and **15**. In dilute solutions (1–3%) the polycondensation type side reactions were suppressed and the intramolecular cyclization became the high yielding main reaction between the bis-iodo compounds and primary amines.The yields of the ring closure steps after chromatography are in Table I.

Treatment of **3** with various aliphatic amines (n-butylamine, n-decylamine, ethanolamine, glycine methyl ester, cyclohexylamine, or benzylamine, (CH_3CN, reflux, 32 h) gave the corresponding 15-membered monoaza-crown ethers **4**, **5**, **6**, **7**, **8** and **9** in good yields, with aromatic amines (aniline, α-naphthylamine). Compounds **10** or **11** were obtained in somewhat lower yields.

The 18-membered diazamacrocycles **12** and **13** were prepared by the reaction of **3** with o-phenylenediamine or ethylenediamine.

The galacto-derivatives **17** and **18** were synthesised from **16** under similar conditions.

The phase transfer abilities of the new azacrown ethers were characterized by extracting picrate salts (Li, Na, K and NH_4 picrate) from water into CH_2Cl_2. The concentrations of the picrates in CH_2Cl_2 we measured by UV spectroscopy [19, 20] (Table I).

It is worth noting that all the azacrowns prefer sodium ions in the complexation. The N-benzyl derivatives **9** and **17** show significant selectivity for the sodium cation among the four cations. The extraction ability depends signficantly on the substituents at the nitrogen atom. The highest values were observed in the case of **5** and **18** both having a decyl side arm at the nitrogen atom, the smallest values in the case of **10** and **11**, compounds having aromatic substituents.

A comparison of the behaviour of 18-membered ring crown ethers suggests that the nonsubstituted compound **13** forms stronger complexes with all cations than that of derivative **12** having an aromatic ring. On the other hand, derivatives in the galacto series **17** and **18** exhibit larger values for extraction than the corresponding compounds **5** and **9** of the glucoseries. This difference in the extraction abilities may be due to the difference in the structure of the two monosaccharide units. The 4-C—O bond in glucosides is in an equatorial position while that in galactosides is in an axial position. The axial orientation of the C—O bond at C(4) of the galactoside ring in both **17** and **18** causes $O(4)$ to be available to participate, together with the ether heteroatoms of the macrocycle, in the complex formation, as a similar phenomenon was observed by Stoddart in the case of other crown ethers [21].

We are investigating the enantioselectivities of the new crown ethers as chiral catalysts in asymmetric reactions.

Acknowledgement

This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T 015677).

References

1. D. A. H. van Maarschalkerwaart, N. P. Willard, and U. K. Pandit: *Tetrahedron* **48**, 8825 (1992).
2. E. V. Dehmlow and V. Knufinke: *Liebigs Ann. Chem.* 282 (1992).
3. M. J. O'Donnell: *Asymmetric Phase Transfer Reactions in Catalytic Asymmetric Synthesis* (Ed.: I. Ojima) VCH Publishers, Inc., New York-Weinheim-Cambridge, pp. 367–387 (1993).
4. T. Wang, J. S. Bradshaw, P. Huszthy, X. Kou, N. K. Dalley, and R. M. Izatt: *J. Heterocyclic Chem.* **31**, 1 (1994).
5. J. F. Stoddart: *Chem. Soc. Rev.* **8**, 85 (1979)
6. J. F. Stoddart: *Synthetic Chiral Receptor Molecules from Natural Products* (Progress in Macrocycles Chemistry, Vol. 2, Ed. R. M. Izatt and J. J. Christensen), p. 173, Wiley (1981).
7. J. F. Stoddart: *Chiral Crown Ethers* (Topics in Stereochemistry, Vol. 17, Ed. E. L. Eliel and S. H. Wielen), p. 207, Wiley (1988).
8. D. A. Laidler and J. F. Stoddart: *J. Chem. Soc., Chem Commun.* 979 (1976).
9. H. F. Beckford, R. M. King, J. F. Stoddart, and R. F. Newton: *Tetrahedron Lett.* 171 (1978).
10. M. Pietraszkiewicz and J. Jurczak. *Tetrahedron* **40**, 2967 (1984).
11. M. Pietraszkiewicz, P. Salanski, and J. Jurczak: *Tetrahedron* **40**, 2971 (1984).
12. G. Tóth, W. Dietrich, P. Bakó, L. Fenichel, and L. Töke: *Carbohydr. Res.* **168**, 141 (1987).
13. P. Bakó, L. Fenichel, L. Töke, and B. E. Davison: *J. Chem. Soc. Perkin Trans. 1* 1235 (1990).
14. P. Bakó, L. Fenichel, and L. Töke: *Liebigs Ann. Chem.* 1161 (1990).
15. G. W. Gokel: *Chem. Soc. Rev.* **21**, 39 (1992) and references therein.
16. M. Zinic, S. Alihodzic, and Skaric: *J. Chem Soc. Perkin Trans. 1* 21 (1993).
17. M. Zinic, L. Frkanec, V. Skarin, Y. Trafton, and G. W. Gokel: *J. Chem. Soc. Chem. Commun.* 1726 (1990).
18. P. Di Cesare and B. Gross: *Synth. Commun.* 4581 (1979).
19. K. Kimura, T. Maeda, and T. Shono: *Talanta* **26**, 945 (1979).
20. T. Maeda, K. Kimura, and T. Shono: *Bull. Chem. Soc. Jpn.* **55**, 3506 (1982).
21. D. A. Laidlerl and J. F. Stoddart: *Carbohydr. Res.* **55**, C1 (1977).