Pergamon

Tetrahedron Letters, Vol. 36, No. 50, pp. 9193-9196, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01938-3

New Supramolecular Host Systems. 4[1]. Novel Diacetal Podands, Diazacrowns and Cryptands.

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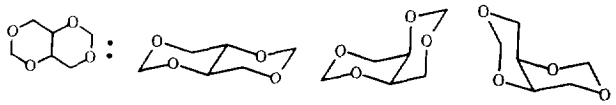
Abstract. *New and important key podands bearing the* **cis***-1,3,5,7-tetraoxadecalin (TOD) core are reported, viz., 2,6-di(hydroxymethyl)-* (**2**) *and 2,6-di(aminomethyl)-* **cis***-1,3,5,7-TOD* (**6**)*, which lead to the first diazacrown-TOD compounds* (**9a**) *and* (**9b**) *and a corresponding cryptand* (**11**) *in the series.* **9a&b** *exhibit very good alkali and earth-alkali ion inclusion ability with selectivity for* K^{+} *and* Ba^{+2}*. Molecular dynamics (Insight/Discover/AMBER) on the crowns and cryptand were performed, including reparametrized MM3-GE calculations. A convincing case for the TOD based hosts was thus established.*

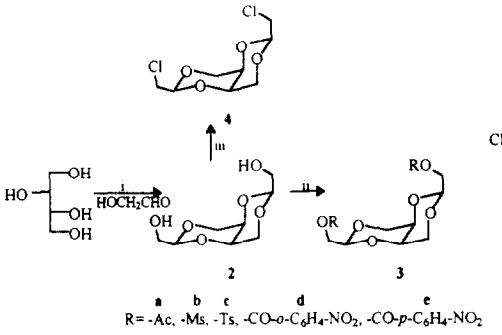
The 1,3,5,7-tetraoxadecalin[†] diacetalic system (**1**) is known mainly from the carbohydrate field[4]. We have recently put forward an approach to a new type of podands and macrocycles built on a molecular "core" consisting of **cis**-1,3,5,7-tetraoxadecalin[†] (1,3,5,7-TOD) in its "O-inside" form (**1ci**)[1-3]. The 1,3,5,7-TOD diastereoisomeric forms have been thoroughly analysed in a structural study[2] and a theoretical - computational one[3], in order to understand the system with its peculiar built-in high lone pair electron concentration in the **cis**-decalin cavity. In that framework, we have reparametrized the MM3 force field (MM3-GE)[3] for TOD and in general O-C-C-O containing molecules (exhibiting the *gauche effect*), to provide a computational tool for reproducing and predicting structure and stability in these systems and diaryl-TOD and corresponding macro-*m*-cyclophanes were made and reported[1].



1 1,3,5,7-TOD | **1t** (9S,10R)-*trans* | **1ci** | **1co** (9R,10R)-*cis*

We present now two important new key podands, *viz.*, judiciously functionalized 2,6-dialkyl-**cis**-1,3,5,7-TOD systems and the highly interesting crown and cryptand macrocyclic systems thereof. Thus, reactions of (*rac*- or) D-threitol with glycolaldehyde (dimer) provided the expected 2,6-di(hydroxymethyl)-**cis**-1,3,5,7-TOD (**2**) product (Scheme 1). This was further derivatized, to give activated ester derivatives (**3a-e**) as well as the chloromethyl derivative (**4**). In spite of their good leaving group character, all these substituents caused surprisingly low reactivity towards standard nucleophilic attack. Some literature parallels could be found, in particular on the retardation of S_N2 rates in β-haloethylbromides[5], but a good explicit explanation is still to come[6].

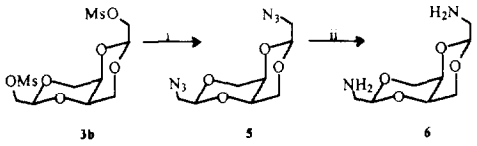
** Part of the Raymond and Beverly Sackler Faculty of Exact Sciences at Tel-Aviv University.



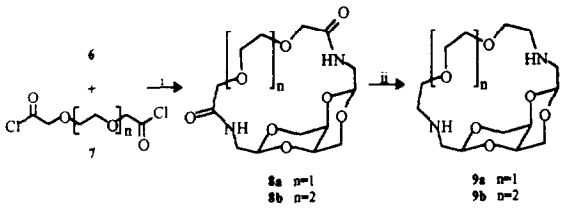
a **b** **c** **d** **e**

R= -Ac, -Ms, -Ts, -CO-*o*-C_6H_4-NO_2, -CO-*p*-C_6H_4-NO_2

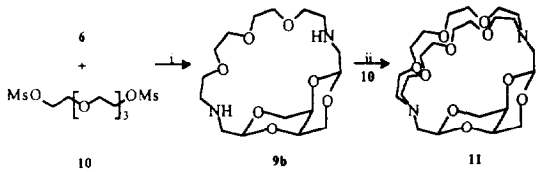
Scheme 1. i: HCl 1M, 15 min, 98%; ii: for **3b**: $MeSO_3Cl$, NEt_3, DMF, 67%. iii: similar to ii but 45 min at 150oC, 24%



Scheme 2. i: DMF, NaN_3, 75%, ii: MeOH, H_2, Pd/C, 97%



Scheme 3. i: DMF, K_2CO_3, 90oC, 7d, n=1: 26%, n=2: 41%; ii: 1. $BH_3.SMe_2$, 2. 10% HCl, n=1: 86%, n=2: 63%



Scheme 4. i: MeCN, K_2CO_3, 80oC, 5d, 17%; ii: MeCN, Na_2CO_3, 80oC, 17%

The dimesylate (**3b**) reacted, though, satisfactorily (albeit slowly) with sodium azide (Scheme 2) and the resulting diazide (**5**) was reduced to give 2,6-di(aminomethyl)-**cis**-1,3,5,7-TOD (**6**). We attribute much importance to **2** and **6**, as precursors of a large variety of future macrocyclic compounds and hosts.

As first achievements in this direction (Scheme 3), the reaction of 2,6-di(aminomethyl)-TOD (**6**) with tri- and tetraglycolic acid dichloride (**7a, 7b**)[7] (as also with the corresponding dimethyl ester[8], albeit in lesser yield) gave the macrocyclic dilactams (**8a, 8b**), which were reduced with $BH_3.SMe_2$[9] to (2,11-diaza-5,8-dioxadodecanyl-1,12-idene)- and 2,6-(2,14-diaza-5,8,11-trioxapentadecanyl-1,15-idene)-1,3,5,7-tetraoxadecalin (**9a, 9b**)[†]. These (**8a&b** and **9a&b**) are the first genuine crown-TOD compounds in this series. In an alternate procedure the diazacrown compounds (**9a&b**) were obtained by reacting the diamine (**6**) with tri- or tetraethyleneglycol dimesylate (**10**)[10] (Scheme 4). In the case of **9a**, addition of one more mole of the dimesylate (**10**) lead to the corresponding cryptand (**11**). These (**8-9**) macrocycles are of the aza-crown, *chiral* type and are of considerable interest, in view of their anticipated complexation behaviour[11].

While the dilactams (**8**) showed only weak ion inclusion ability, the diaza-crown compounds (**9**) exhibited very good alkali and earth-alkali ion inclusion behavior, by any standards[11]. This was probed, using the NMR shift technique[12] in MeOH-d_4/D_2O (2:8) solution and the results for **9b** are given in Figure 1(a), showing that the Ba^{+2} complex has the highest stability constant, so far, followed by Sr^{+2} in the same group and by K^+ among the alkalis (Ba^{+2} and K^+ have similar ionic radii). Complexation studies of other crowns and of the cryptand (**11**) and analogues are in course.

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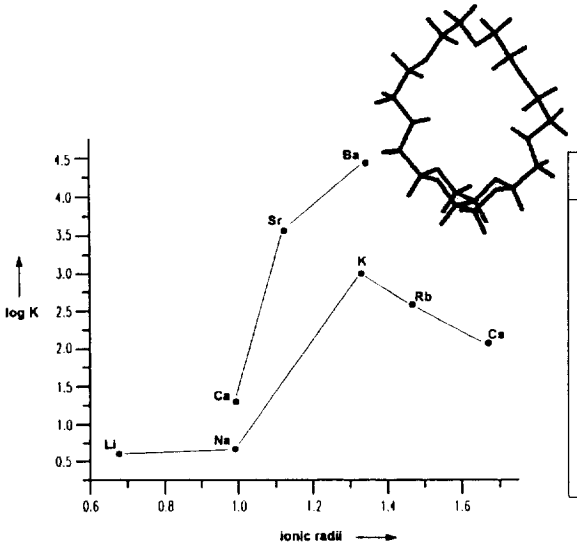
† We use consistently the 1,3,5,7-tetraoxadecalin nomenclature. Other possible names are: (1R)-*cis*-2,4,7,9-tetraoxabicyclo[4.4.0]-decane, 1,3:2,4-di-O-methylene-D-threitol or (4aR)-(4a*r*,8a*c*)-tetrahydro-[1,3]dioxino[5,4-*d*]-1,3-dioxin. Also, due to a minor but basic omission of the CIP rules, one cannot assign configurations to chiral *cis*-decalin (and similar) systems, other than by 9,10-helicity specification. Thus, compound **2** is (2S,6S,9R;9,10-*M*)-2,6-di(hydroxymethyl)-**cis**-1,3,5,7-tetraoxadecalin.

The above crowns and cryptand were reliably characterized by chemical and physical methods but not yet by full X-ray diffraction analysis. We calculated, however, the low energy conformations of the crowns (**9a, 9b**) and the cryptand (**11**), which were obtained in the conformational search carried out using the AMBER force field within the Biosym Insight/Discover software in three consecutive runs of constant temperature molecular dynamics (at 300, 400 and 500 K) for each compound, for 200 ps; sampling and minimization (10 ps) lead to a variety of conformations. The starting structure was taken, using the Insight/Builder module and inferred from available NMR data. Thus, the crown's (**9b**) disymmetric (C_2) minimum (its global minimum is asymmetric) was attained by optimisation with AMBER and, for the sake of force field comparison, was reminimized using the Insight/CFF91 and the MM3-GE force fields, producing C_2 structures with similar dihedral angle sequence pattern, e.g., $(aag)_5$ in the coronand part of the macrocycles, but significantly different bond lengths. The latter turned out to be implausibly long in CFF91 (Figure 1(ii)). MM3-GE is the only force field to account well for both the *anomeric* and the *gauche* effects in the C-O and the C-C bond lengths and appears to provide a reliable computational tool for predictive studies of these and similar systems.



	Force Field	MM3-GE	AMBER	CFF91
TOD:	C_9 - C_{10}	1.519	1.522	1.550
	C_4 - C_{10}	1.518	1.525	1.541
	C_2 - O_3	1.417	1.434	1.434
	C_3 - O_4	1.434	1.432	1.426
CROWN:	C_2 - C_{11}	1.526	1.533	1.530
	C - C	1.514	1.528	1.531
		1.525	1.530	1.536
	C - N	1.466	1.455	1.463
		1.463	1.456	1.465
	C - O	1.421	1.430	1.423
		1.422	1.431	1.424

(i) (ii)

Figure 1. Molecular model of the symmetric (C_2) form of the diazacrown-TOD **9b**, on top of (i) a plot of its complex stability constants with alkali and alkaline earth ions (in methanol-d_4/water-d_2) vs. ionic radii and (ii) its tabulated bond lengths, from various force field calculations.

Selected Experimental Data.

2: ^{1}H-NMR (360 MHz, $CDCl_3$) δ (ppm): 3.70, 3.73 (bs and d, ^3J = 4.7 Hz, 6H, CH and CH_2OH), 3.93 (dd, ^2J = 12.6, ^3J = 1.4 Hz, 2H, CH_2 (ax)), 4.23 (bd, ^2J = 12.6 Hz, 2H, CH_2 (eq)), 4.76 (t, ^3J = 4.7 Hz, 2H, OCH); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ (ppm): 63.7, 69.3, 69.6, 100.1; EI-MS (7 ev), m/z (%): 189 (7), 175 (100), 145 (27), 133 (71), 103 ($M/2^+$, 25). $[\alpha]_D^{25}$ = -18.9 (c=1, MeOH); analysed correctly for $C_8H_{14}O_6$.
6: ^{1}H-NMR (200 MHz, D_2O) δ (ppm): 2.57 (m, 4H, CH_2NH_2), 3.71 (s, 2H, CH), 3.83 (d, ^2J = 13.1 Hz, 2H, CH_2 (ax)), 3.92 (d, ^2J = 13.1 Hz, 2H, CH_2 (eq)), 4.57 (t, ^3J = 4.9 Hz, 2H, OCH). $[\alpha]_D^{25}$ = -31.8 (c=1, methanol); analysed correctly for $C_8H_{16}O_4N_2$.

9a: ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 2.06 (bs, 2H, NH), 2.8-3.0 (m, 8H, CH_2NHCH_2), 3.58-3.65 (m, 8H, CH_2OCH_2), 3.66(bd, ^2J = 11.9 Hz, 2H, CH_2 (ax)), 3.68 (s, 2H, CH_{ang}), 4.10 (bd, ^2J = 11.9 Hz, 2H, CH_2 (eq)), 4.79 (t, ^3J = 2.3 Hz, 2H, OCH); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ (ppm): 29.9, 49.56, 52.26, 62.6, 68.8, 69.02, 69.45, 96.61; EIMS: m/z (%) = 318 (M^+, 87); analysed correctly for $C_{14}H_{26}O_6N_2$.

9b: ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 1.66 (m, 2H, NH), 2.88 (m, 8H, CH_2NHCH_2), 3.57-3.67 (m, 14H, CH, CH_2OCH_2), 3.83 (dd, ^3J = 1.3, ^2J = 12.6 Hz, 2H, CH_2 (ax)), 4.13 (d, ^2J = 12.6 Hz, 2H, CH_2 (eq)), 4.72 (t, ^3J = 3.6 Hz, 2H, OCH); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ (ppm): 48.75, 51.60, 69.13, 69.24, 69.70, 70.21, 70.64, 99.81; EIMS: m/z (%) = 362 (M^+, 58); $[\alpha]_D^{25}$ = -6.8 (c=1, chloroform); analysed correctly for $C_{16}H_{30}O_7N_2$.

11: ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 2.81-3.10 (m, 12H, CH_2N), 3.48-3.71 (m, 28H, CH_2OCH_2, CH_2 (ax), CH), 4.07 (d, ^2J = 12.0 Hz, 2H, CH_2 (eq)), 4.81 (m, 2H, OCH); EIMS: m/z (%) = 520 (M^+, 10). $[\alpha]_D^{25}$ = -6.8 (c=1, chloroform); analysed correctly for $C_{24}H_{44}O_{10}N_2$.

Acknowledgments. This work was supported in part by research grants from the Israel Science Foundation administered by the National Academy of Sciences and from the Ministry of Science and the Arts. A postdoctoral fellowship (to K. F.) from the Kurt Lion Foundation and the Konstanz-Tel-Aviv Förderkreis and a grant-in-aid from the Ministry of Absorption (to L. G.) are gratefully acknowledged. Skillful technical assistance was provided by Mrs. Sarah Weinman.

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(*Received in UK* 10 *August* 1995; *revised* 9 *October* 1995; *accepted* 13 *October* 1995)