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THE SYNTHESIS OF 4H-PYRAN CONTAINING HEMISPHERANDS VIA PYRYLIUM SALTS

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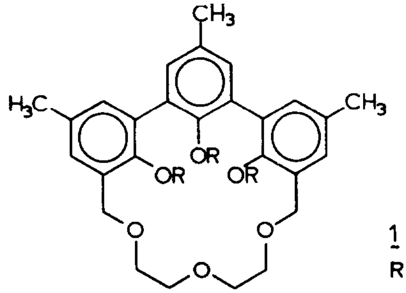
Abstract: Two new hemispherands 2a and 2b containing a central 4H-pyran unit were synthesized via appropiately substituted 2,6-phenyl pyrylium salts; largest ΔG° values of complexation of 2a and 2b with different alkali picrates are found for Na^+ and K^+.

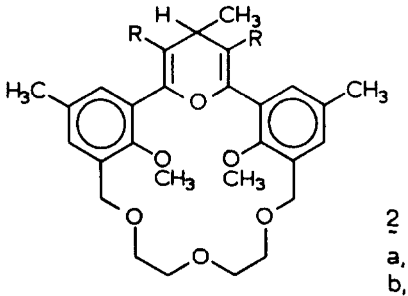
Complexation of alkali cations has received much attention in the past two decades after Pedersen's discovery of the crown ethers[1]. Cram's concept[2] of replacing ethyleneoxy units in crowns by (meta) coupled anisole units in order to have better 'preorganized' ligating sites led to the synthesis of hemispherands[3] and spherands[4]. The hemispherand complexes show an enhanced thermodynamic stability towards the alkali cations whereas the spherands form complexes with even higher thermodynamic stability. The spherands form complexes with the highest thermodynamic stability known thus far ($K_a > 10^{14}$) but only with Li^+ and Na^+.

As we are interested[5] in receptor molecules which form very strong, 'spherand-like' complexes with the larger alkali cations like K^+, Rb^+ and Cs^+ we are heading for (hemi)spherand type compounds which have a somewhat larger cavity. This might be effected by substituting the anisole units in the ligands with units which lack the inward pointing methoxy group but still provide a ligating site like furan, pyran, pyridine and others.

We report here the synthesis of two new hemispherands 2a and 2b with a 4H-pyran moiety, receptor molecules with a modified cavity.



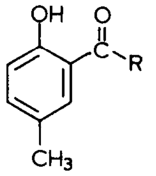
1
R = CH3



2
a, R = H
b, R = CH3

Our synthetic concept is based on the ability of pyrylium salts to be converted into aromatic and heteroaromatic molecules. Once properly functionalized, these salts might act as general precursors for our target receptor molecules.

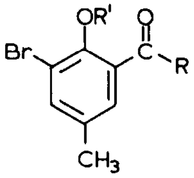
Reaction of 4-methylanisole with acetyl chloride in the presence of aluminum chloride in dichloromethane[6] gave 3a in 92% yield. Introduction of a bromine atom in the 2-position with respect to the hydroxyl group was achieved by reaction with N-bromosuccinimide in dimethyl formamide (DMF) to give 4a (93%, mp 88-89 °C). Methylation of 4a with methyl iodide and K_2CO_3 as a base in dry acetone afforded 5a (94%, bp 100 °C/0.15 mm Hg), the starting material for the pyrylium salt 6a.



3

a, R=CH_3

b, R=CH_2CH_3



4

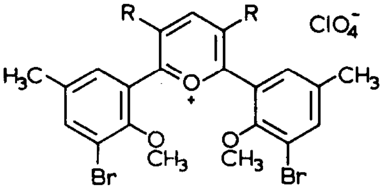
a, R=CH_3 R'=H

b, R=CH_2CH_3 R=H

5

a, R=CH_3 R'=CH_3

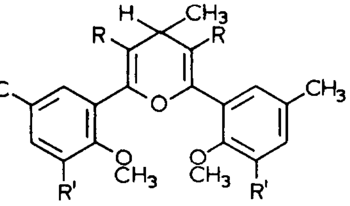
b, R=CH_2CH_3 R'=CH_3



6

a, R=H

b, R=CH_3



7a, R=H R'=Br; b, R=CH_3 R'=Br

8a, R=H R'=CHO; b, R=CH_3 R'=CHO

9a, R=H R'=CH_2OH; b, R=CH_3 R'=CH_2OH

Reaction of 5a with triethyl orthoformate and 70% perchloric acid as described by Dorofeenko et al.[7] gave 6a in 34% yield. The ^1H NMR spectrum (200 MHz, CD_3CN) showed a distinct AB_2 system for the pyrylium hydrogen atoms (δ_A = 8.99 and δ_B = 8.74) and singlets for the methoxy (δ 3.87) and methyl (δ 2.45) hydrogen atoms. The pyrylium salt 6a has bulky substituents in the 2- and 6-positions and is unsubstituted in the 4-position. Therefore this compound is susceptible to nucleophilic addition reactions mainly on the 4-position and 4H-pyrans can be obtained in the reaction with nucleophiles[8]. Reaction of 6a with methylmagnesium iodide in diethyl ether gave the 4H-pyran 7a in 87% yield (as a foam).

Because 7a appeared to be unstable as is often found for 4H-pyrans, it was stored at low temperature and in absence of air and light. Reaction of 7a with tert-butyllithium in diethyl ether at -78 °C gave bromo lithium exchange and the resulting diaryllithium compound was reacted with DMF. Acidic workup and chromatography (SiO_2, $CHCl_3$) afforded 8a in 50% yield as an oil. Reduction of 8a with sodium borohydride in methanol afforded 9a as a white foam in 90% yield. This compound gave 2a by reaction with diethylene glycol ditosylate and sodium hydride as a base in tetrahydrofuran (THF) under high dilution conditions. After purification by chromatography (Al_2O_3, CH_2Cl_2/THF, 9/1) 2a was obtained as a white foam in 44% yield. Methyl groups were introduced in the 3- and 5-position of the 4H-pyran ring by carrying out the preparation of the pyrylium salt with the propiophenone instead of the acetophenone. Reaction of 4-methylanisole with propionyl chloride and aluminum chloride in CH_2Cl_2 afforded 3b[7] (82% yield) which was brominated to 4b as described above in 86% yield (mp 130 °C). Methylation yielding 5b (93%, bp 95-100 °C/0.1 mm Hg) followed by reaction of 5b with triethyl orthoformate and 70% perchloric acid afforded 6b after addition of diethyl ether to the reaction mixture. Recrystallization of the crude salt from acetic acid gave the pure product in 16% yield (mp 225 °C). The ^1H NMR spectrum of 6b (CD_3CN) showed the 4-H atom in the pyrylium ring at δ 8.97 as a singlet.

The chemical shift of the 6-H atom in the phenyl ring was 7.90 for 6a and 7.48 for 6b. This is in accordance with the general observation that the signal of the ortho phenyl H-atoms of phenyl groups of 2,6-disubstituted pyrylium salts with methyl groups in the 3- and 5-position of the pyrylium ring show an upfield shift[9]. This is caused by the hindered rotation around the pyrylium-phenyl bond.

An upfield shift is also observed in the ^{13}C NMR spectra for the signal of the 4-C atom of the phenyl groups which is due to a minor contribution of the resonance structure in which the positive charge is located in this position[10 11], these shifts are 141.9 for 6a and 140.0 for 6b. The pyrylium salt 6b was converted into the 4H-pyran 7b by reaction with methylmagnesium iodide (98%). Conversion of the Br into the CH_2OH substituents was performed as described for 9a. Compound 9b was obtained as a white foam in 63% overall yield. The compounds 7b - 9b appeared to be more stable than 7a - 9a and could be stored for months at 0 °C. Reaction of 9b with diethylene glycol ditosylate and sodium hydride as a base in THF afforded 2b in 31% yield.

Table I. ^1H NMR data of the complexation of alkali picrates with 2a and 2b in $CDCl_3$.

Host	% Extr.[a]	δ Ar-CH_2-O	δ Pyran 4-CH_3	δ Ar-CH_2-O	δ Pyran 4-CH_3
		T = 18 °C		T = -24 °C	
2a	-[b]	4.46 (s)	1.26 (d)[c]	4.51 (s)	
2b	-[b]	4.40 (s)	1.31 (d)[c]	4.9 ; 4.1 (AB)[e]	
2a.NaPic	80	5.16; 3.93 (AB)[d]	1.25; 1.32 (d)[f]		
2b.NaPic	73	5.14; 3.93 (AB)[d]	1.37 (d)[c]		
2a.KPic	72	4.48 (br s)	1.30 (d)[c]	5.1 ; 3.9 (AB)[e]	
2b.KPic	71	4.5 ; 3.9 (AB)[d]	1.34 (d)[c]	5.14; 3.98 (AB)[d]	1.30; 1.38 (d)

a) Experiments with Li-, Na-, K- , Rb- and Cs-picrate were carried out by dissolving the salt in a solution of the hemispherand in $CDCl_3$. b) Free ligand. c) J = 6.7 Hz. d) J = 10.2 ± 0.3 Hz. e) Broad doublet. f) Two conformations.

Both in 2a and 2b the benzylic hydrogen atoms appear as singlets[12] at 18 °C and this points to a fast inversion of the macroring on the ^1H NMR time scale. This is in line with our observations[13] and indicates a much larger conformational flexibility for ligands that lack the central methoxy group compared to the hemispherand 1.[2-4] The two methyl groups in the 4H-pyranmoiety of 2b render the ligand more rigid and at -24 °C the benzylic protons appear as a broad doublet.

The ^1H NMR spectra of 2a and 2b change drastically upon complexation with sodium or potassium picrate in $CDCl_3$ (Table I). The benzylic hydrogen atoms become non-equivalent and give rise to an AB-system. This indicates that complexation of the cation in the cavity renders the inversion of the macroring slow on the ^1H NMR time scale. In the 2a.KPic complex, also thermodynamically the least stable, we observe this non-equivalence only at -24 °C.

A second difference between the spectra of the free ligands 2a and 2b and their complexes is found for the 4-methyl group of the pyran moiety. Whereas in the uncomplexed ligands only one signal is present, the spectrum of 2a.NaPic complex shows two doublets in a ratio 40:60. This can be attributed to slow ringinversion of the pyran moiety which will render the methyl group in the axial and equatorial position non-equivalent.[8] In the spectra of the 2b.NaPic and 2a.KPic complexes we observed only one signal but the 2b.KPic complex also exhibited two doublets (ratio 60:40) for the 4-methyl hydrogen atoms at -24°C.

Table II. Association constants (K_a) and Binding free Energies (-ΔG°) of Complexes of Hosts 1, 2a and 2b with Alkali Picrates in $CDCl_3$ (saturated with D_2O) at 22 °C.[a]

	1		2a		2b	
	K_a	-ΔG°	K_a	-ΔG°	K_a	-ΔG°
Li^+	1.4×10^5	7.0	$1.9 X 10^5$	7.2	2.0×10^5	7.2
Na^+	1.1×10^9	12.3	1.0×10^7	9.6	4.3×10^7	10.4
K^+	1.1×10^9	12.3	6.9×10^6	9.3	2.6×10^7	10.1
Rb^+	4.6×10^7	10.4	9.1×10^5	8.1	5.0×10^6	9.1
Cs^+	3.1×10^6	8.9	7.4×10^9	8.0	2.4×10^6	8.7

a) The association constants were determined by the picrate extraction method as described by Cram et al.[3]. K_a (M^{-1}), ΔG° ($kcal.mol^{-1}$).

The ^1H NMR spectra from the complexation experiments with the smaller Li^+ and the larger Rb^+ and Cs^+ cations only showed broad signals at lower temperatures (+18 to -64 °C) and it was concluded that many interconverting structures exist.

Whereas the terphenyl moiety in **1** is well organized prior to complexation, substitution of the center anisole unit by a 4*H*-pyran unit introduces a higher conformational mobility as can be seen from CPK molecular models.

The lower free energies of complexation of **2a** and **2b** with the alkali cations as compared with those of the complexes of **1** can be fully attributed to this preorganization. The introduction of the methyl groups in the 3- and 5-position of the pyran ring renders the structure more rigid and accordingly the free energy of complexation increases by ~0.8 kcal/mol for all ions except Li^+.

In both **2a** and **2b** the binding pattern is the same as found in **1**, but it shows a diminished discrimination between the larger alkali cations K^+, Rb^+ and Cs^+. The introduction of the 4*H*-pyran unit enables the new hemispherands **2a** and **2b** to adapt other conformations which are favourable for the complexation of the larger cations.

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12. **2a**: mass spectrum, *m/e* 466.235 (M^+, calcd for $C_{28}H_{34}O_6$ 466.229); ^1H NMR ($CDCl_3$, 80 MHz) δ 7.12 (d, 2 H, Ar H), 6.96 (d, 2 H, Ar H), 5.02 (d, 2 H, pyran 3,5-H, J = 3.7 Hz), 4.45 (s, 4 H, Ar CH_2O), 3.69 (s, 6 H, OCH_3), 3.34-3.50 (m, 8 H, OCH_2), 3.25-3.35 (m, 1 H, pyran 4-H), 2.28 (s, 6 H, Ar CH_3), 1.26 (d, 3 H, pyran 4-CH_3).
    2b: mass spectrum, *m/e* 494.268 (M^+, calcd for $C_{30}H_{38}O_6$ 494.267); ^1H NMR ($CDCl_3$, 80 MHz) δ 7.03 (d, 2 H, Ar H), 6.95 (d, 2 H, Ar H), 4.46 (s, 4 H, Ar CH_2O), 3.67 (s, 6 H, OCH_3), 3.36 (s, 8 H, OCH_2), 2.79 (q, 1 H, pyran 4-H), 2.27 (s, 6 H, Ar CH_3), 1.77 (s, 6 H, pyran 3,5-CH_3), 1.31 (d, 3 H, pyran 4-CH_3).
13. P.J. Dijkstra, H.J. den Hertog Jr, D.N. Reinhoudt, to be published.

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