analyses revealed two sets of doublets in the ratio of 64:36, which were assigned to the (dichlorofluoromethyl)phosphonium salt and the (bromochlorofluoromethyl)phosphonium salt, respectively.

Reaction of $[Ph_3P^+-CFClX]Y^-$ with Ph_3P. Triphenylphosphine was added to an NMR sample tube which contained methylene chloride and a small amount of the solid which was isolated in the previous procedure. ^{19}F and ^{31}P NMR analyses, after 1 h, revealed the re-formation of the fluorinated phosphoranium salt.

Acknowledgment. We gratefully acknowledge the Air Force Office of Scientific Research and the National Science Foundation for their generous support of this research.

Registry No. 3 (X = Cl), 84195-43-7; 3 (X = BF_4), 111635-51-9; 8, 81962-38-1; 10, 111635-56-4; **12a** (X = Br), 111635-53-1; **12b** (X = Br), 111635-54-2; **12c** (X = Br), 111635-55-3; **15a** (X = Br), 88410-13-3; **15b** (X = BF_4), 111635-52-0; **15b** (X = Br), 88410-12-2; **17a** (X = Cl), 111635-58-6; **23** (X = BF_4), 111635-61-1; **24** (X = BF_4), 111689-14-6; **25a**, 111635-57-5; **25b**, 111635-59-7; $[Et_3P^+C^-FP^+Et_3]Cl^-$, 111635-49-5; $[Ph_3{}^+PC^-FHBr]Br^-$, 111635-62-2; $CFCl_3$, 75-69-4; $CFBr_3$, 353-54-8; Bu_3P, 998-40-3; Ph_3P, 603-35-0; $(o\text{-}MeOC_6H_4)_3P$, 4731-65-1; $(o\text{-}MeC_6H_4)Ph_2P$, 5931-53-3; $[(o\text{-}MeOC_6H_4)_3P^+CFBr_2]Br^-$, 111902-72-8; $[(o\text{-}MeOC_6H_4)_3P^+CHFBr]Br^-$, 111902-73-9; $[(Ph_3P^+CFH_2]Br^-$, 111902-74-0; $[(Bu_3P^+CHFP^+Bu_3]Cl^-OH^-$, 111902-75-1; $[(Ph_3P^+CHFP^+Ph_3]Br^-Cl^-$, 111902-76-2; $[Ph_3P^+CHFP^+Et_3]Br^-Cl^-$, 111902-77-3; $[Ph_3P^+CHFP^+Bu_3]Br^-Cl^-$, 111902-78-4; $[Ph_3P^+CHFP^+Oc_3]Br^-Cl^-$, 111902-79-5; $[Ph_3P^+CHFP^+Ph_3]Br^-OH^-$, 111902-80-8.

Supplementary Material Available: Spectroscopic data for the compounds described in the Experimental Section (5 pages). Ordering information is given on any current masthead page.

4*H*-Pyran and Pyrylium Hemispherands: Partly Preorganized Ionophores with Reactive Molecular Cavities

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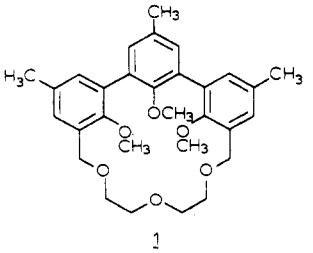
The synthesis and reactivity of a 2,6-diaryl-substituted pyrylium cation incorporated in an 18-membered macrocycle (**3a,b**) has been studied. Hemispherands with a central pyridine (**4a,b**) and with alkyl- or phenyl-substituted pyridinium ions (**5a,b**) were obtained by reaction with ammonium acetate or primary amines. The reactivity of the pyrylium 4-methyl group was demonstrated by converting **3b** into the corresponding 4-methylenepyran derivative **6** or novel pyrylium hemispherands **3c,d**. The pyrylium hemispherands **3a,b** were prepared through the 4*H*-pyran hemispherands **2a,b** in a linear synthesis starting from **7a,b**. The stable bis(hydroxymethyl) derivative **12b** gave the hemispherand **3b** in 65% yield. The X-ray crystal structures of the sodium picrate complexes of **1**, **2b**, and **4c** have been determined and compared with the crystal structures of the free ligands (**1**, **4c**). These structures reveal that the conformational changes upon complexation are reflected in the binding free energies ($-\Delta G°$) of the hemispherands with alkali picrates, measured via two-phase partition ($H_2O/CDCl_3$).

Introduction

Host–guest chemistry can be based on two major principles, viz. complementarity between host and guest and preorganization of the host. Good examples of the complementarity principle are the complexes of uronium (urea)[1] and guanidinium[2] cations with 27–30-membered crown ethers. The preorganization approach has been demonstrated by the complexation of alkali and ammonium cations by the fully preorganized spherands.[3] Molecular cavities of synthetic hosts can also be *partially* organized prior to complexation, e.g., by incorporating meta-coupled anisyl units[4] or anisyl units in combination with cyclic urea units.[5] Molecular models of these hemispherands, the prototype of which is **1**, show that the



1

electron pairs of the anisyl oxygen atoms must converge onto the cavity, and this will cause a substantial O–O repulsion. Besides, the cavity is partly deshielded from solvent molecules by the diverging oxygen methyl groups. Contrarily, the bridging poly(ethylene glycol) is conformationally rather mobile. These hemispherands appeared to be attractive molecules for a systematic study of the effect of preorganization on the structure-binding relationship with alkali and ammonium cations[5] and with neutral molecules, e.g., malononitrile.[6] Studies with hemispherands in which the central anisyl unit of **1** has been substituted for methoxycyclohexane,[7] pyridine, or a

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‡ Laboratories of Chemical Physics.

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nitroaryl moiety[8] revealed that these variations have large effects on the complexation of alkali cations.

Our interests in macrocyclic host molecules with preorganized cavities are related to their application in ion-selective sensors[9] and in organ imaging using radioactive alkali cations.[10] An important aspect of our work on (hemi)spherands is to provide synthetic methods that allow modification of the outer sphere[11] in order to have the possibility to link the host covalently to polymers and biologically active compounds.

The anisyl hemispherands, e.g., **1** have been synthesized from a preformed rigid building block.[4,5] Macrocyclization with a poly(ethylene glycol) generally proceeds in low to moderate yield. Previously we have reported a similar synthesis of hemispherands in which the central anisyl moiety has been substituted by a 2,6-pyridyl or a 1-nitro-2,6-aryl moiety in variable yields. Therefore it seems that the yields obtained in these macrocyclization reaction reflect the rigidity of the building blocks. Thus, preorganizing ligating sites in the ligand has to be paid for in the macrocyclization step.

Recently we have reported an alternative synthesis method, to avoid this lower yields of macrocyclization, by rigidification of a flexible macrocycle.[12] Reaction of a 1,3-dianisylpropanone moiety incorporated in a flexible 18-membered macrocycle with nitromalondialdehyde gave in high yield the corresponding hemispherand, the driving force of the reaction being the formation of an aromatic 4-nitrophenol ring.

In this paper we report a novel strategy for the synthesis of hemispherands that contain a building block which allows further *variation in the structure of the molecular cavity*. This strategy provides a general method for the modification of the central anisyl unit as present in **1**. Such a synthetic building block must be readily available from simple starting compounds, stable under the reaction conditions in macrocyclization, and easy to modify when incorporated in the molecular cavity. A 2,6-dianisyl-substituted 4*H*-pyran building block seemed to meet these requirements. In principle a 4*H*-pyran moiety can be converted into a pyrylium cation that has different reactive sites. The 2,6-carbon atoms of the pyrylium ring are reactive toward nucleophiles,[13] and conversions into new aromatic rings have been investigated. As a reactive site in the 4-position of the pyrylium ring a 4-methyl group can be introduced. This methyl group provides the possibility of functionalization at the outer sphere because it acts as a nucleophile with high reactivity to many electrophiles.[14] Some preliminary results of this approach have been published.[15]

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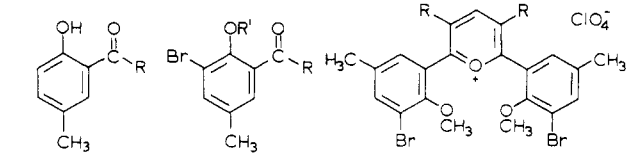
Results and Discussion

In a previous paper the synthesis of 2,4,6- and 2,6-aryl-substituted pyrylium salts, bearing different groups in the 2,6-aryl rings, has been described.[9] We anticipated that the 2,6-diaryl-substituted pyrylium salts would also be suitable precursors for the synthesis of 4*H*-pyrans. The 4*H*-pyrans may be obtained by nucleophilic attack at the unsubstituted 4-position of the pyrylium ring.[16] The reaction of 1-aryl ketones with triethyl orthoformate to give 4-unsubstituted pyrylium salts[13a] was chosen because the starting acetophenones are generally obtained in good yield.

The acetophenone **8a**[9] was reacted with triethyl orthoformate and 70% perchloric acid to give **9a** in 34% yield. Reaction of **9a** with methylmagnesium iodide in diethyl ether afforded **10a**, which appeared to be unstable at room temperature. Since the stability of 4*H*-pyrans may be increased either by the introduction of extended π-conjugation with substituents (e.g., CN) or by increased substitution,[16] we have introduced methyl groups at the 3- and 5-positions of the 4*H*-pyran for which the readily available propiophenone **7**[17] could be used as the starting material. Bromination of **7** with *N*-bromosuccinimide in dimethyl formamide (DMF) gave **8b** in 86% yield. Methylation of the hydroxyl group in **8b** with methyl iodide gave **8c** in 93% yield, which upon reaction with triethyl orthoformate and perchloric acid gave the pyrylium salt **9b** in 16% yield. The 4*H*-pyran derivative **10b**, obtained by reacting **9b** with methylmagnesium iodide in 93% yield, appeared to be much more stable than **9a** and can easily be handled at room temperature.

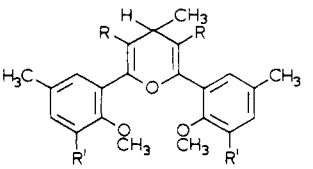
The reaction of aryllithium compounds with DMF to give benzaldehydes[18] was used to introduce two formyl groups ortho to the methoxy substituents in **10a** and **10b**.



7 R = CH_2CH_3

8 a, R = CH_3, R' = CH_3; b, R = CH_2CH_3, R' = H; c, R = CH_2CH_3, R' = CH_3

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



10 a, R = H, R' = Br; b, R = CH_3, R' = Br
11 a, R = H, R' = CHO; b, R = CH_3, R' = CHO
12 a, R = H, R' = CH_2OH; b, R = CH_3, R' = CH_2OH

Bromo to lithium exchange either in **10a** or **10b** with *tert*-butyllithium in diethyl ether and subsequent reaction of the corresponding dilithio compounds with DMF afforded **11a** and **11b** in yields of 50% and 66%, respectively. Sodium borohydride reduction of **11a** and **11b** gave the bis(hydroxymethyl) derivatives **12a** and **12b** in 90% and 95% yield, respectively. Macrocyclization of **12a** and **12b**

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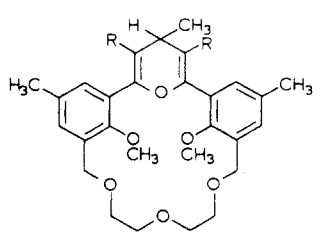
with diethylene glycol ditosylate and sodium hydride as a base in tetrahydrofuran gave the 4*H*-pyran hemispherands **2a** and **2b** in 30% and 65%, respectively. The lower yield of **2a** is due to decomposition of **12a** during the reaction.

The ^{1}H NMR spectra ($CDCl_3$) of the new macrocycles revealed the different conformational mobility of the two macrorings. The benzylic hydrogen atoms appear as singlets at δ 4.45, which means that ring inversion in **2a** and **2b** is fast on the ^{1}H NMR time scale at room temperature. However, **2b** gave a broad AB system at a temperature below −24 °C, indicating that the ring inversion has become slow. The good yield obtained in the macrocyclization reaction of **12a**, compared to the analogous reaction in the synthesis of **1** (28% yield),[4] confirms a general observation: increased organization renders the macrocyclization reaction less efficient.

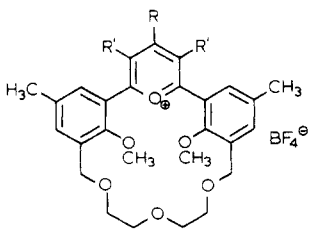
We anticipated that the 4*H*-pyran moiety might be oxidatively dehydrogenated to a macrocyclic pyrylium salt, which subsequently might be converted into a new (hetero)aromatic ring. In fact, the 4*H*-pyran moiety may be regarded as a synthetic equivalent of a pyrylium ion. Together with the good yield obtained in the macrocyclization of **12b**, this methodology might be generally used to modify both the molecular cavity and the outer sphere of hemispherand type of molecules.

4*H*-Pyran hemispherands **2a** and **2b** were oxidatively dehydrogenated to the pyrylium hemispherands **3a** (45%) and **3b** (98%), respectively, upon reaction with tri-



2

a, R = H
b, R = CH_3



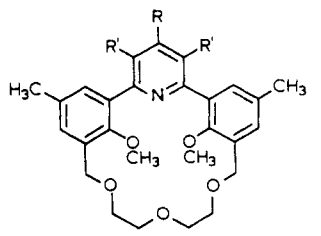
3

a, R = CH_3, R' = H
b, R = CH_3, R' = CH_3
c, R = CH=CHPh, R' = CH_3

phenylcarbenium tetrafluoroborate in dimethoxyethane.[19] Both **3a** and **3b** showed singlets for the benzyclic hydrogen atoms at δ 4.46, indicative of a fast ring inversion on the ^{1}H NMR time scale.

Pyrylium salts generally react with nucleophiles at one of the 2,6-positions due to the high charge delocalization at these carbon atoms. The intermediate formed may cyclize to a new carbocyclic or hetereoaromatic ring, the driving force being the aromatization energy from the isomerization. These reactions provide hemispherands with a modified *inner* sphere.

Reaction of **3a** or **3b** with ammonium acetate in acetic acid afforded the hemispherands **4a** and **4b**, respectively. Whereas **4b** was obtained in 89% yield, **4a** was prepared in low yield and therefore only characterized spectroscopically. Since **2a** was also difficult to prepare, further reactions of **3a** have not been investigated. The hemispherand **4b** showed the characteristics of increased rigidity due to the two methyl groups in the 3- and 5-position of the pyridine ring.[8] The benzylic hydrogen atoms appear in the ^{1}H NMR spectrum ($CDCl_3$) as a broad AB system, indicating that ring inversion is slow on the ^{1}H NMR time



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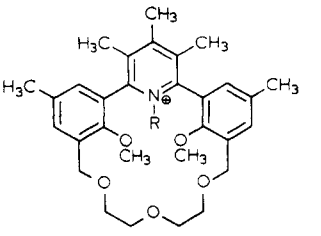


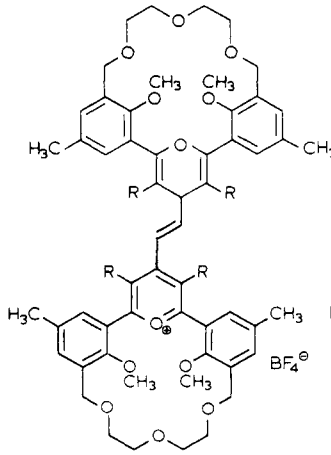
5

a, R = CH_3, R' = H
b, R = CH_3, R' = CH_3
c, R = Ph, R' = H
d, R = CH=CHPh, R' = CH_3

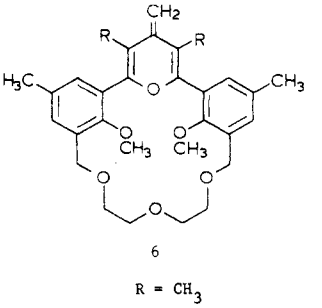
a, R = CH_3
b, R = Ph

scale. The introduction of further steric barriers was investigated by reacting **3b** with primary amines to give the corresponding pyridinium hemispherands. Reaction of **3b** with methylamine in aqueous ethanol gave **5a** in 63% yield. The ^{1}H NMR showed the pyridinium N-methyl hydrogen atoms at δ 3.55 and the benzylic hydrogen atoms at δ 5.21 and δ 3.94 (J_{AB} = 7.80 Hz). The N-methyl group introduces a steric barrier large enough to give slow ring inversion on the ^{1}H NMR time scale and is at least comparable to the steric barrier introduced by the central methoxy substituent in **1**. Reaction of **3b** with aniline gave the *N*-phenylpyridinium salt **5b** in 77% yield. Distinct multiplets at δ 7.75 (1 H), 6.90 (3 H), and 6.52 (1 H) in the ^{1}H NMR spectrum (CD_3CN) were observed for the *N*-phenyl hydrogen atoms. The ^{13}C NMR spectrum (CD_3CN) even showed five distinct doublets at δ 136–128 for the N-phenyl carbon atoms. These data indicate that the rotation of the *N*-phenyl substituent around the N–C axis is slow on the NMR time scale. CPK molecular models reveal that ring inversion is indeed completely inhibited by the introduction of the N-phenyl group. This means that the aromatization energy is sufficient to introduce a large steric barrier in the hemispherands.

Although alkylidenepyrans (anhydro bases of pyrylium salts) are generally unstable compounds, the anhydro base **6** obtained from **3b** upon reaction with aqueous sodium bicarbonate appeared to be stable. The increased stability



3d
R = CH_3



6
R = CH_3

obviously is due to the high degree of substitution of the pyran ring. The electron density at the exocyclic carbon atom in anhydro bases is high and consequently this position is reactive toward electrophiles. Reactions of pyrylium salts that have 2- or 4-methyl groups proceeding through their anhydro bases are well established and give

(19) Kieselack, P.; Helland, C.; Dimroth, K. *Chem. Ber.* **1975**, *108*, 3656.

new pyrylium salts.[14] These reactions are of interest for our work because this method allows the introduction of different functional groups at the *outer* sphere of the molecule. We have investigated the reaction of benzaldehyde or triethyl orthoformate with **3b**. Condensation of **3b** with benzaldehyde yielded **3c** in 87% yield as a yellow crystalline compound. This new pyrylium salt was characterized by conversion into the corresponding pyridine **4d** upon reaction with ammonium acetate in acetic acid. Reaction of **3b** with triethyl orthoformate[20] gave the trimethine cyanine derivative **3d** as a blue foam in 61% yield after repeated trituration. The deep blue **3d** was characterized spectroscopically. The charge delocalization is shown by the ^1H NMR and ^{13}C NMR (CD_3CN) spectra of the molecule. The =CH protons in the ^1H NMR spectrum were found at δ 8.84 (J = 13 Hz) and 6.79 (doublet, 2 H, J = 13 Hz). Methoxy and methyl hydrogen atoms were found as singlets, whereas the benzylic hydrogen atoms gave a very broad signal at δ 4.50. The ^{13}C NMR spectrum also showed one set of signals for all carbon atoms, indicating charge delocalization over the entire molecule.

Crystal Structure of Complexes 1·NaPic, 2b·NaPic, and 4c·NaPic. In a previous paper we have described the X-ray crystal structure of the hemispherand **4c**.[8] The structure revealed that the methoxy groups are situated at opposite faces of the macroring and one of the methoxy methyl groups converges onto the cavity. Complexation of **4c** with malononitrile[6] has shown that conformational changes take place. In the complex the methoxy groups are situated at the same face of the macroring and the structure of **4c**. $CH_2(CN)_2$ resembles strongly the X-ray crystal structure of $1{\cdot}CH_2(CN)_2$.[6] CPK molecular models of **2a** and **2b** reveal that the macrocycles have a similar conformational mobility as **4c**. This is confirmed by the spectral data in solution (vide supra).

To investigate the effects of these structural variations viz. situating the oxygen atom of the central methoxy group of the hemispherand **1** in a 4*H*-pyran ring or by a substitution for a pyridine nitrogen atom, which is a much better ligand, we have determined the X-ray crystal structure of the sodium picrate complexes of **1**, **2b**, and **4c**.

In Figure 1 views of these structures are presented, showing the Na^+ coordination and the hemispherand conformations. Data on the Na^+ coordination are summarized in Table I. In all three structures there is an almost square-planar coordination of Na^+ by the two flanking methoxy oxygens and the two adjacent ether oxygens. These four oxygens are within 0.04 Å of their mean plane, out of which Na^+ is displaced by 0.21–0.45 Å. The central oxygen of the polyether bridge and the central methoxy oxygen of **1** also coordinate Na^+, whereas the 4*H*-pyran oxygen (Na^+···O distance 4.18 Å) and the pyridyl nitrogen (Na^+···N distance 3.84 Å) are situated in the macrocyclic cavity in such a way that they cannot participate in the Na^+ coordination. The picrate anion completes the Na^+ coordination by means of the phenoxide oxygen and a nitro oxygen (for 1·NaPic and **2b**·NaPic).

The data on Na^+ coordination in Table I compare well with literature values. In a survey of cation complexes with macrocyclic hosts, Dalley[21] reports a Na^+···O distance range of 2.3–2.9 Å and Na^+ coordination numbers of 6–8. For ether and methoxy oxygens the Na^+···O distances found by Cram et al.[4] in two Na^+ complexes of cryptahemispherands were 2.34–2.46 and 2.53–2.78 Å, respectively. A short distance between Na^+ and the phenoxide oxygen (2.24–2.36 Å), from ionic interaction, has also been reported for the structures of complexes of benzo[22] and cyclohexano[23] crown ethers with sodium picrate. Additional coordination by an ortho nitro oxygen as found in 1·NaPic and **2b**·NaPic (2.62, 2.63 Å) was also reported[22] with somewhat shorter distances (2.40–2.51 Å).

Table I. Na^+ Coordination in the Crystal Structures of the NaPic Complexes of 1, 2b, and 4c

	1·NaPic	2b·NaPic	4c·NaPic
distances,[a] Å			
Na^+···O_{ether}	2.46–2.85	2.44–2.56	2.40–2.66
Na^+···$O_{methoxy}$	2.51–2.57	2.45–2.59	2.42–2.48
Na^+···$O_{phenoxide}$	2.36	2.28	2.24
Na^+···O_{nitro}	2.62	2.63	
displacmt (Å) of Na^+ out of "receptor" plane[b]	0.21	0.45	0.35
Na^+ coordn no.[a]	8	7	6

[a] Maximum coordination distance 2.9 Å. [b] Plane defined by two flanking methoxy and adjacent ether oxygens.

Table II. Hemispherand Dimensions in the Crystal Structures of the NaPic Complexes of the Ligands 1, 2b, and 4c

	1^{24}	1·NaPic	2b·NaPic	4c·NaPic	4c[8]
	Distances (Å) between Heteroatoms				
$OArCH_2O$[a]	2.71/3.59[e]	2.93	2.92	2.86	2.97
	3.55	2.95	2.99	2.95	3.15
OArArO[b]	2.84	2.77	2.95	2.82	2.88
	2.85	2.78	3.06	3.00	2.97
OArArArO[c]	3.56	3.61	3.09	3.25	4.98
Displacements (Å) of Methoxy Oxygens Out of Plane of Attached Aryl					
	0.02	0.11	0.05	0.00	0.14
	0.04	0.14			
	0.06	0.17	0.08	0.17	0.19
Aryl–Aryl Dihedral[d] (Degrees)					
	56	50	56	50	47
	60	53	64	65	54

[a–c] Displayed are the distances (*a*) between flanking methoxy and adjacent ether oxygens ($OArCH_2O$), (*b*) between flanking methoxy oxygens and central heteroatoms (OArArO for **1**, OArPyrO for **2b**, OArPyrN for **4c**), and (*c*) between the two flanking methoxy oxygens (OArArArO, OArPyrArO, resp.). [d] Aryl–aryl (pyran, pyridyl, resp.) dihedrals. [e] Two values due to positional disorder of the ether oxygen.

From a comparison of the structures of the uncomplexed ligands 1^{24} and **4c** and the NaPic complexes of **1** and **4c**, as presented in Table II, information about the reorganization of the ligands upon complexation can be obtained. In **1** the conformation of the teranisyl unit does not change significantly upon Na^+ complexation; the up–down–up arrangement of the methoxy oxygens and the divergence from the cavity of the methoxy methyl groups are retained. The polyether bridge of **1** does reorganize, as indicated by the change in the $OArCH_2$ distances, in order to create a cavity for Na^+. In the uncomplexed ligand the cavity is filled by inward-turning methylene groups in order to reduce oxygen–oxygen repulsion and to obtain more favourable van der Waals interactions.

In the uncomplexed ligand **4c** the two methoxy groups are on either side of the mean macrocyclic plane and one of the methoxy groups converges onto the cavity which is

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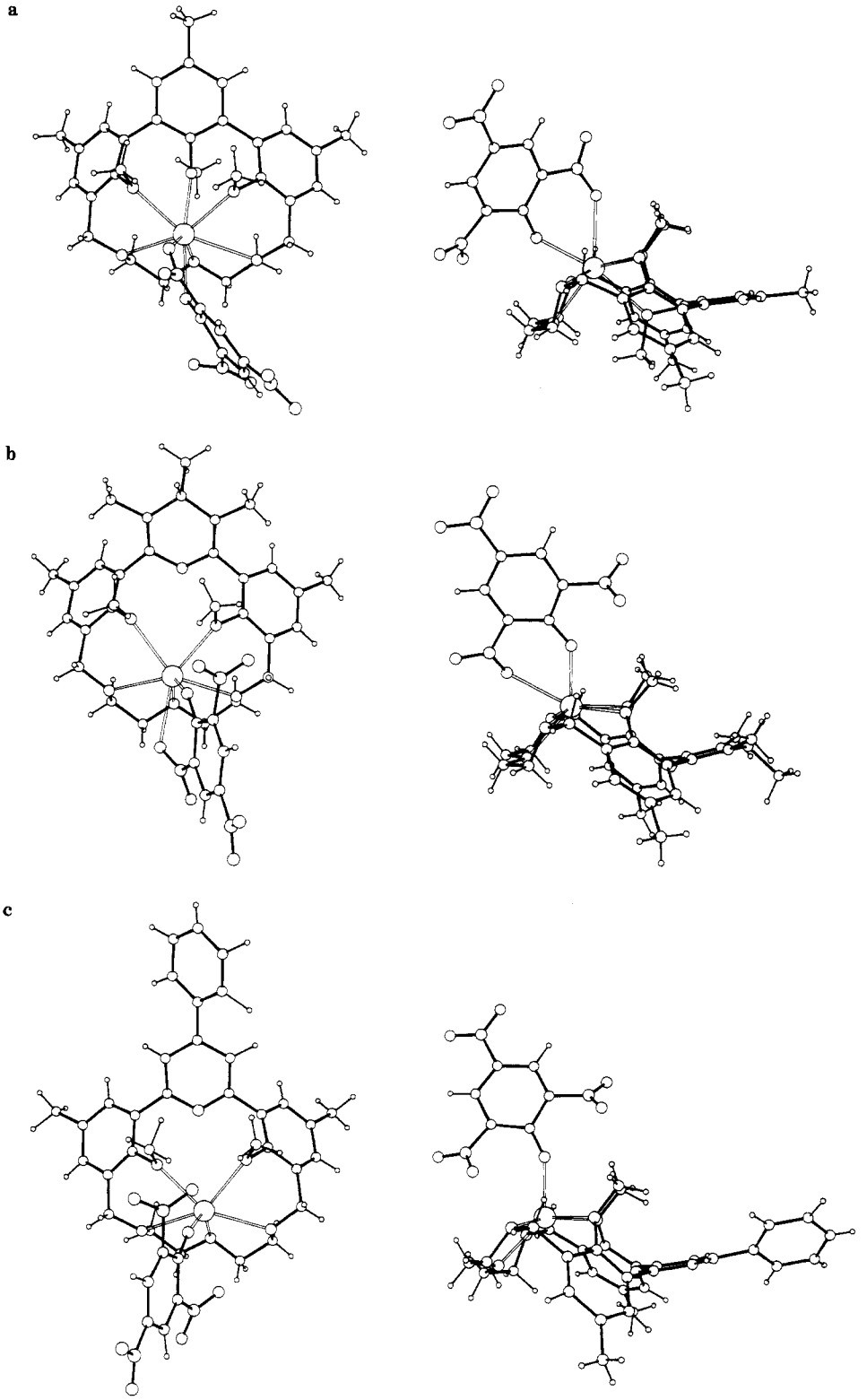

Figure 1. Top (left) and side (right) views of the crystal structures of the sodium picrate complexes of **1** (a), **2b** (b), and **4c** (c).

thereby partly filled by the methyl group. This conformation results in a large OArPyrArO distance and severe anisyl deformation (displacement of methoxy oxygen out of the mean plane of the attached aryl group), by as much as 0.19 Å. In **4c** more extensive reorganization upon Na^+ complexation is observed. In the complex **4c**·NaPic the methoxy oxygens are on the same face of the macrocyclic plane and the methoxymethyl groups diverge from the cavity. The polyether bridge also reorganizes in order to create an optimal Na^+ receptor site. For the complexation of malononitrile by **1** and **4c** the same kind of reorganization has been observed.[6] Complexation of **1** with *tert*-butylammonium perchlorate also results in the same conformation of the hemispherand.[4] The same features, methoxy oxygens on the same face of the macrocyclic plane and diverging methoxy methyl groups, are observed in the NaPic complex of **2b**.

More subtle effects of Na^+ complexation can also be deduced from the hemispherand dimensions in Table II. In ligand **1** the anisyl deformation, as measured by the displacement of the methoxy oxygens out of the plane of their attached aryls, increases upon Na^+ complexation.

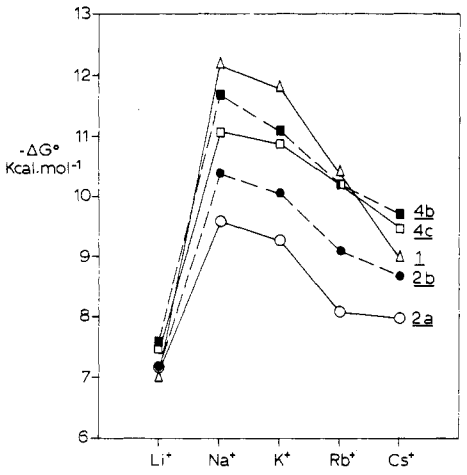

Figure 2. Binding free energies ($-\Delta G°$) of alkali picrate complexes ($CDCl_3$ saturated with H_2O, 22 °C).[26]

This increase of internal strain has also been observed for the complexes of **1** with malononitrile and *tert*-butylammonium perchlorate. Thus it can be concluded that the uncomplexed ligand **1**, which is preorganized for binding guests of a very different nature, has relatively low internal strain; this was also found in molecular mechanics calculations on several conformations of **1**.[25] For ligand **4c** the reverse situation is observed. The uncomplexed ligand has a large anisyl deformation, caused by the converging methoxy group, which is somewhat relieved by the reorganization upon the complexation of Na^+ or malononitrile. Due to the absence of the central methoxy group, the ligands **2b** and **4c** have a smaller anisyl deformation than **1** in their NaPic complexes. Likewise, the distance between the two flanking methoxy oxygens is shorter in **2b** and **4c**, 3.09 and 3.26 Å vs. 3.61 Å in **1**, which means that the absence of the central methoxy group results in a smaller cavity. From Tables I and II it can be seen that with increasing cavity size, as measured by the OArArArO distance, the displacement of Na^+ out of the "receptor" plane decreases, i.e., the fit of Na^+ in the cavity improves.

Complexation. The binding free energies ($-\Delta G°$) of **2a**, **2b**, and **4b** were determined with the picrate extraction method.[26] The $-\Delta G°$ values obtained were compared with those obtained for **1**[4] and **4c**[8] and are given in Figure 2. The binding patterns found resemble each other, showing highest values for sodium picrate complexation. There are several characteristic differences between the three types of hosts. Firstly, the decrease in binding free energies of **2a,b** and **4b,c** shows the effect of situating the central ligating site at a larger distance from the cavity. This renders the 4*H*-pyran oxygen or pyridine nitrogen hardly capable to cooperate in the binding of the cation. This is confirmed by the X-ray structure of **2b**·NaPic and **4c**·NaPic. (vide supra). Secondly, introducing a small steric barrier to arylpyran or arylpyridine rotation *by methyl substituents in the central ring* gives increased $-\Delta G°$ values. Thirdly, the increased flexibility of the hosts **2a,b** and **4c** compared to **1** is reflected in a diminished discrimination in complexing the larger alkali cations K^+, Rb^+, and Cs^+.

The ^1H NMR spectra ($CDCl_3$) confirm the data obtained from the X-ray structure analysis and of the binding free energies.[15] The free ligands **2a,b** and **4c** are conformationally mobile at room temperature whereas **4b** shows slow ring inversion, and for **1** no ring inversion is observed on the ^1H NMR time scale. On lowering the temperature **2b** and **4b,c** show that a conformation is frozen out, which is likely to be a conformation resembling the conformation as found for **1**. Upon complexation with complementary guests (Na^+, K^+) a single conformation is found resembling the X-ray structure of the sodium picrate complexes.

Conclusion. The synthesis of the pyrylium hemispherand **3b** via the 4*H*-pyran building block **12b** provides a method for the synthesis of novel hemispherand type of molecules. The reactivity of the pyrylium ring allows the introduction of heteroaromatic rings in a partially rigid molecular cavity, the driving force being the aromatization energy of the new ring that is introduced. Outer sphere functionalization is possible through the reactive pyrylium 4-methyl group. Both types of reaction provide a methodology for future work on more complex receptor molecules with specific intraannular ligating sites.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Bruker WP-80 spectrometer and ^{13}C NMR spectra were recorded with a Nicolet MT 200 spectrometer in $CDCl_3$ unless otherwise indicated (Me_4Si as an internal standard). Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer Model 257 spectrophotometer. Absorbance readings in the UV for association constants were taken on a Zeiss M4QIII spectrophotometer. Elemental analyses were carried out by A. M. Christenhusz of the Laboratory of Chemical Analysis of the University of Twente.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl, whereas *N,N*-dimethylformamide (DMF) and diethyl ether were dried on 4-Å molecular sieves. All reactions in which dry solvents were used were carried out in a nitrogen atmosphere. Chromatographic separations menti ed were performed on silica gel 60 (SiO_2) (E. Merck, p icle size 0.040–0.063 mm, 230–240 mesh) or aluminum oxide $_2O_3$) (E. Merck, neutral grade, particle size 0.063–0.300 mm, 70–230 mesh ASTM). All mass spectra were calculated for ^{79}Br.

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-propanone (8b). *N*-Bromosuccinimide (139 g, 0.84 mol) in 200 mL of DMF was dropwise added to a solution of **7** (149 g, 0.84 mol) in 440 mL of DMF at 0 °C. The reaction mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure, and to the residue 2 L of water was added. The mixture was stirred to give a crystalline product, which was filtered off and recrystallized from ethanol to give **8b** as pale yellow crystals: yield 86%; mp 130 °C; mass spectrum, *m/e* 241.997 (M^+, calcd 241.994); ^1H NMR δ 12.75 (s, 1 H, OH), 7.50 (s, 2 H, Ar H), 3.02 (q, 2 H, CH_2), 2.29 (s, 3 H, Ar CH_3), 1.22 (t, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.40; H, 4.56. Found: C, 49.78; H, 4.64.

1-(3-Bromo-2-methoxy-5-methylphenyl)-1-propanone (8c). A mixture of **8b** (76 g, 0.32 mol), K_2CO_3 (51 g, 0.73 mol), and methyl iodide (114 g, 0.84 mol) in 500 mL of dry acetone (K_2CO_3) was stirred for 16 h at room temperature. The solvent and excess methyl iodide were removed under reduced pressure, whereupon 250 mL of 1 M HCl and 300 mL of diethyl ether were added. The aqueous phase was extracted with another 300 mL of diethyl ether, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was distilled to give a pale yellow oil: yield 93%; bp 95–100 °C (9.5 mmHg); mass spectrum, *m/e* 256.010 (M^+, calcd for $C_{11}H_{13}BrO_2$ 256.010); ^1H NMR δ 7.48 (d, 1 H, Ar H), 7.25 (d, 1 H, Ar H), 3.82 (s, 3 H, OCH_3), 2.95 (q, 2 H, CH_2), 2.31 (s, 3 H, Ar CH_3), 1.17 (t, 3 H, CH_3); ^{13}C NMR δ 206.6 (s, C=O), 153.1 (s, Ar C-2), 136.7 (d, Ar C-H), 135.4 and 135.0 (s, Ar C-5 and C-1), 128.9 (d, Ar C-H), 117.7 (s, Ar C-3), 62.4 (q, OCH_3), 36.0 (t, CH_2), 20.3 (q, Ar CH_3), 8.3 (q, CH_3); IR (NaCl) 1710 (C=O) cm^{-1}.

2,6-Bis(3-bromo-2-methoxy-5-methylphenyl)pyrylium Perchlorate (9a). To a mixture of **8c** (33.4 g, 0.14 mol) and triethyl orthoformate (49.6 g, 0.33 mol) heated at 70 °C was added 70% perchloric acid (6.5 mL, 75 mmol) at a rate that maintained

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reflux. The reaction mixture was heated at 70 °C with an oil bath for 2 h. After cooling to room temperature, the pyrylium salt was filtered off and washed with diethyl ether: yield 34%; mp 246–248 °C; mass spectrum, m/e 477.969 (M^+ + H, calcd for $C_{21}H_{20}Br_2O_3$ 477.978); ^1H NMR (CD_3CN) δ 8.99 (m, 1 H, pyrylium 4-H, J_{AB} = 7.9 Hz), 8.74 (d, 2 H, pyrylium 3,5-H, J_{AB} = 7.9 Hz), 7.90 (s, 4 H, Ar H), 3.87 (s, 6 H, OCH_3), 2.45 (s, 6 H, Ar CH_3); ^{13}C NMR (CD_3CN) δ 171.6 (s, pyrylium 2,6-C), 158.8 (s, pyrylium 4-C), 125.0 (d, pyrylium 3,5-C).

2,6-Bis(3-bromo-2-methoxy-5-methylphenyl)-3,5-dimethylpyrylium perchlorate (9b) was prepared from **8b** as described for **9a**. The product precipitated from the reaction mixture by the addition of diethyl ether and was recrystallized from acetic acid to give yellow crystals: yield 16%; mp 225 °C; ^1H NMR (CD_3CN) δ 8.97 (s, 1 H, pyrylium H), 7.81 (s, 2 H, Ar H), 7.48 (s, 2 H, Ar H), 3.62 (s, 6 H, OCH_3), 2.51 (s, 6 H, pyrylium CH_3), 2.39 (s, 6 H, Ar CH_3); ^{13}C NMR (CD_3CN) δ 170.9 (s, pyrylium 2,6-C), 160.1 (s, pyrylium 4-C).

2,6-Bis(3-bromo-2-methoxy-5-methylphenyl)-4-methyl-4*H*-pyran (10a). To a suspension of **9a** (7.0 g, 12.1 mmol) in dry diethyl ether (40 mL) was rapidly added a freshly prepared solution of methylmagnesium iodide (16.0 mmol) in 15 mL of diethyl ether. The reaction mixture was stirred for 15 min at room temperature, hydrolyzed with 50 mL of water, and acidified with 4 M HCl. After separation of the organic phase, the water layer was extracted with another two portions of diethyl ether. The combined organic layers were washed with 2 M HCl and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a pale yellow foam. The product was purified by chromatography (SiO_2, $CHCl_3$) to give a white foam, which was kept in an argon atmosphere at −20 °C: yield 87%; mass spectrum, m/e 476.967 ($M^+ - CH_3$, calcd for $C_{21}H_{19}Br_2O_3$ 476.970); ^1H NMR δ 7.30 (s, 4 H, Ar H), 5.47 (d, 2 H, pyran 3,5-H), 3.79 (s, 6 H, OCH_3), 3.22 (m, 1 H, pyran 4-H), 2.28 (s, 6 H, Ar CH_3), 1.26 (d, 3 H, pyran CH_3); ^{13}C NMR δ 145.2 (s, pyran 2,6-C), 107.1 (d, pyran 3,5-C), 27.0 (d, pyran 4-C).

2,6-Bis(3-bromo-2-methoxy-5-methylphenyl)-3,4,5-trimethyl-4*H*-pyran (10b) was prepared from **9b** similar to **10a** as a white foam: yield 98%; mass spectrum, m/e 520.025 (M^+, calcd for $C_{24}H_{26}Br_2O_3$ 520.025); ^1H NMR δ 7.33 (d, 2 H, Ar H), 7.03 (d, 2 H, Ar H), 3.77 (s, 6 H, OCH_3), 2.74 (q, 1 H, pyran H), 2.27 (s, 6 H, Ar CH_3), 1.58 (s, 6 H, pyran 3,5-CH_3), 1.30 (d, 3 H, pyran 4-CH_3); ^{13}C NMR δ 141.1 (s, pyran 2,6-C), 111.0 (s, pyran 3,5-C), 37.6 (d, pyran 4-C).

3,3′-(4-Methyl-4*H*-pyran-2,6-diyl)bis(2-methoxy-5-methylbenzaldehyde) (11a). To a solution of **10a** (5.0 g, 10.1 mmol) in 100 mL of dry diethyl ether was slowly added *tert*-butyllithium (14.5 mL, 20.3 mmol) at −78 °C. The reaction mixture was stirred for 10 min and *N,N*-dimethylformamide (2.5 g, 34.2 mmol) was added. After being stirred for 20 min, the reaction mixture was warmed to room temperature and hydrolyzed by the addition of 100 mL of 2 M HCl. The layers were separated and the aqueous phase was twice extracted with 50 mL of diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvent evaporated under reduced pressure. After chromatographic purification (SiO_2, toluene) **11a** was obtained as a white foam: yield 50%; mass spectrum, m/e 392.160 (M^+, calcd for $C_{24}H_{24}O_5$ 392.162); ^1H NMR δ 10.42 (s, 2 H, CHO), 7.61 (s, 4 H, Ar H), 5.50 (d, 2 H, pyran 3,5-H), 3.92 (s, 6 H, OCH_3), 3.30 (q, 1 H, pyran 4-H), 2.36 (s, 6 H, Ar CH_3), 1.32 (d, 3 H, pyran CH_3); ^{13}C NMR δ 190.0 (s, C=O), 145.1 (s, pyran 2,6-C), 107.3 (d, pyran 3,5-C), 27.0 (d, pyran 4-C).

3,3′-(3,4,5-Trimethyl-4*H*-pyran-2,6-diyl)bis(2-methoxy-5-methylbenzaldehyde) (11b) was prepared from **10b** similar to **11a**. The product was obtained as a white foam: yield 66%; mass spectrum m/e 405.169 ($M^+ - CH_3$, calcd for $C_{25}H_{25}O_5$ 405.170); ^1H NMR δ 10.39 (s, 2 H, CHO), 7.63 (d, 2 H, Ar H), 7.36 (d, 2 H, Ar H), 3.90 (s, 6 H, OCH_3), 2.80 (q, 1 H, pyran H) 2.34 (s, 6 H, Ar CH_3), 1.63 (s, 6 H, pyran 3,5-CH_3), 1.35 (d, 3 H, pyran 4-CH_3); ^{13}C NMR δ 190.0 (d, C=O), 140.6 (s, pyran 2,6-C), 111.5 (s, pyran 3,5-C), 37.6 (d, pyran 4-C).

3,3′-(4-Methyl-4*H*-pyran-2,6-diyl)bis(2-methoxy-5-methylbenzenemethanol) (12a). To a suspension of **11a** (2.0 g, 5.1 mmol) in 50 mL of methanol was added sodium borohydride (0.5 g, 13.0 mmol) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and 30 min at room temperature. To the reaction mixture was added 100 mL of water, and the products were extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with water and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a white foam. The compound could be used directly for the following reaction: yield 90%; mass spectrum, m/e 396.195 (M^+, calcd for $C_{24}H_{28}O_5$ 396.194); ^1H NMR δ 7.27 (s, 2 H, Ar H), 7.12 (s, 2 H, Ar H), 5.39 (d, 2 H, pyran 3,5-H), 3.80 (s, 6 H, OCH_3), 3.20 (m, 1 H, pyran 4-H), 2.30 (s, 8 H, Ar CH_3 and OH), 1.26 (d, 3 H, pyran 4-CH_3); ^{13}C NMR δ 145.9 (s, pyran 2,6-C), 106.4 (d, pyran 3,5-C), 27.1 (d, pyran 4-C).

3,3′-(3,4,5-Trimethyl-4*H*-pyran-2,6-diyl)bis(2-methoxy-5-methylbenzenemethanol) (12b) was prepared from **11b** similarly to **12a**. The product was obtained as a white foam: yield 95%; mass spectrum, m/e 424.226 (M^+, calcd for $C_{26}H_{32}O_5$ 424.225); ^1H NMR δ 7.06 (bs, 4 H, Ar H), 4.64 (s, 4 H, CH_2), 3.80 (s, 6 H, OCH_3), 2.75 (q, 1 H, pyran H), 2.27 (s, 8 H, Ar CH_3 and OH), 1.60 (s, 6 H, pyran 3,5-CH_3), 1.31 (d, 3 H, pyran 4-CH_3); ^{13}C NMR δ 141.6 (s, pyran 2,6-C), 110.5 (s, pyran 3,5-C), 37.6 (d, pyran 4-C).

25,26-Dimethoxy-4,9,23-trimethyl-13,16,19,27-tetraoxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,5,7,9,11(26),21,23-octaene (2a). A solution of **12a** (0.23 g, 0.58 mmol) and diethylene glycol ditosylate (0.36 g, 0.87 mmol) in 50 mL of dry THF was added over a 10-h period to a boiling suspension of sodium hydride (0.07 g, 2.92 mmol) in 75 mL of dry THF. After addition, the reaction mixture was refluxed for another 8 h, cooled to room temperature, and 5 mL of 2 M HCl added. The solvent was removed under reduced pressure and the residue was partitioned between 25 mL of water and 25 mL of chloroform. The water layer was extracted with another two portions of chloroform. The combined organic layers were washed with water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Column chromatography (Al_2O_3, dichloromethane/THF, 9/1) afforded **2a**. The white foam was stored in an argon atmosphere at −20 °C in the absence of light: yield 44%; mass spectrum, m/e 466.235 (M^+, calcd for $C_{28}H_{34}O_6$ 466.229); ^1H NMR 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), 3.50–3.34 (m, 8 H, OCH_2CH_2O), 3.30 (m, 1 H, pyran 4-H), 2.28 (s, 6 H, Ar CH_3), 1.26 (d, 3 H, pyran 4-CH_3); ^{13}C NMR δ 156.5 (s, *C*-OCH_3), 149.8 (s, pyran 2,6-C), 103.1 (d, pyran 3,5-C), 27.1 (d, pyran 4-C).

25,26-Dimethoxy-3,4,5,9,23-pentamethyl-13,16,19,27-tetraoxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,5,7,9,11-(26),21,23-octaene (2b) was prepared from **12b** similar to **2a**. After workup **2b** was obtained as a white foam: yield 65%; mass spectrum, m/e 494.268 (M^+, calcd for $C_{30}H_{38}O_6$ 494.267); ^1H NMR 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_2CH_2O), 2.79 (q, 1 H, pyran 4-H), 2.27 (s, 6 H, pyran 3,5-CH_3), 1.31 (d, 3 H, pyran 4-CH_3).

Anal. Calcd for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 72.59; H, 7.79.

2b·sodium picrate was prepared by stirring solid sodium picrate with **2b** in $CHCl_3$. After filtration the solvent was removed under reduced pressure. The solid obtained was dissolved in acetone and crystallized by slow evaporation: mp 273–276 °C; ^1H NMR δ 8.91 (s, 2 H, Ar H picrate), 7.00 (s, 4 H, Ar H), 5.40 (d, 2 H, J = 10.0 Hz, Ar CH_2O), 3.91 (d, 2 H, J = 10.0 Hz, Ar CH_2O), 3.90 (s, 6 H, OCH_3), 3.84–3.35 (m, 8 H, OCH_2CH_2O), 2.75 (q, 1 H, J = 6.5 Hz, pyran 4-H) 2.28 (s, 6 H, Ar CH_3), 1.71 (s, 6 H, pyran 3,5-CH_3), 1.36 (d, 3 H, J = 6.5 Hz, pyran 4-CH_3).

Anal. Calcd for $C_{36}H_{40}N_3O_{13}Na$: C, 57.98; H, 5.41; N, 5.63. Found: C, 58.07; H, 5.48; N, 5.58.

25,26-Dimethoxy-4,9,23-trimethyl-13,16,19-trioxa-27-oxoniatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11-(26),21,23-nonaene Tetrafluoroborate (3a). A suspension of **2a** (0.10 g, 0.21 mmol) and triphenylcarbenium tetrafluoroborate (0.10 g, 0.30 mmol) in 2 mL of ethylene glycol dimethyl ether was stirred for 16 h at room temperature. The product was filtered off and washed with diethyl ether to give **3a** as yellow crystals: yield 45%; mp >210 °C dec; mass spectrum, m/e 464.219 (M^+, calcd for $C_{28}H_{32}O_6$, 464.220); ^1H NMR (CD_3CN) δ 8.20 (s, 2 H, pyrylium H), 7.56 (s, 2 H, Ar H), 7.49 (s, 2 H, Ar H), 4.45 (s, 4 H, Ar CH_2), 3.55 (s, 6 H, OCH_3), 3.51 (s, 8 H, OCH_2CH_2O), 2.87 (s, 3 H, pyrylium CH_3), 2.41 (s, 6 H, Ar CH_3); ^{13}C NMR (CD_3CN) δ 172.4 (s, pyrylium 2,6-C), 123.6 (d, pyrylium 3,5-C), 176.7 (s, pyrylium 4-C).

25,26-Dimethoxy-3,4,5,9,23-pentamethyl-13,16,19-trioxa-27-oxoniatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6-(27),7,9,11(26),21,23-nonaene tetrafluoroborate (3b) was prepared from **2b** as described for **3a** to give **3b** as pale yellow crystals: yield 98%; mp 208–210 °C; mass spectrum, *m/e* 492.246 (M^+, calcd for $C_{30}H_{36}O_6$ 492.251); ^1H NMR (CD_3CN) δ 7.42 (s, 2 H, Ar H), 7.35 (s, 2 H, Ar H), 4.46 (s, 4 H, Ar CH_2), 3.46 (s, 6 H, OCH_3), 3.42 (s, 8 H, OCH_2CH_2O), 2.76 (s, 3 H, pyrylium 4-CH_3), 2.57 (s, 6 H, pyrylium 3,5-CH_3), 2.38 (s, 6 H, Ar CH_3); ^{13}C NMR (CD_3CN) δ 168.9 (s, pyrylium 2,6-C), 133.5 (s, pyrylium 3,5-C), 177.4 (s, pyrylium 4-C).

25,26-Dimethoxy-4,9,23-trimethyl-13,16,19-trioxa-27-azatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11-(26),21,23-nonaene (4a). A solution of **3a** (0.10 g, 0.18 mmol) and ammonium acetate (0.14 g, 1.8 mmol) in 2 mL of glacial acetic acid was heated under reflux for 3 h. After being cooled to room temperature, the reaction mixture was poured into 10 mL of water. The mixture was extracted with chloroform (3 × 10 mL) and the combined organic phases were washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Crystallization from ethanol gave **4a** as white crystals: yield <10%; mp 142–152 °C; mass spectrum, *m/e* 463.235 (M^+, calcd 463.236); ^1H NMR δ 7.28 (s, 2 H, pyridine H), 7.11 (s, 2 H, Ar H), 7.03 (s, 2 H, Ar H), 4.56 (s, 4 H, Ar CH_2), 3.55–3.51 (m, 8 H, OCH_2CH_2O), 3.48 (s, 6 H, OCH_3), 2.50 (s, 3 H, pyridine CH_3), 2.30 (s, 6 H, Ar CH_3).

25,26-Dimethoxy-3,4,5,9,23-pentamethyl-13,16,19-trioxa-27-azatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6-(27),7,9,11(26),21,23-nonaene (4b) was prepared from **3b** as described for **4a** to give pure **4b** as white crystals by recrystallization from ethanol: yield 89%; mp 273–275 °C; mass spectrum, *m/e* 491.277 (M^+, calcd 491.267); ^1H NMR δ 6.99 (s, 2 H, Ar H), 6.94 (s, 2 H, Ar H), 4.77 and 4.38 (AB br, 4 H, Ar CH_2), 3.66–3.30 (bs, 8 H, OCH_2CH_2O), 3.48 (s, 6 H, OCH_3), 2.35 (s, 9 H, Ar CH_3 and pyridine 4-CH_3), 2.26 (s, 6 H, pyridine 3,5-CH_3).

Anal. Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85. Found: C, 73.01; H, 7.56; N, 2.68.

25,26-Dimethoxy-3,5,9,23-tetramethyl-4-methylene-13,16,19,27-tetraoxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1-(25),2,5,7,9,11(26),21,23-octaene (6). A solution of **3b** (0.5 g, 0.86 mmol) in 5 mL of chloroform was shaken with 10 mL of a 10% $NaHCO_3$ solution. The organic phase was separated and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The product was crystallized from ethanol to give pure **6**: yield 99%; mp 185–187 °C; mass spectrum, *m/e* 492.254 (M^+, calcd 492.251); ^1H NMR δ 7.05 (s, 2 H, Ar H), 7.01 (s, 2 H, Ar H), 4.46 (s, 6 H, Ar CH_2 and $=CH_2$), 3.66 (s, 6 H, OCH_3), 3.38 (s, 8 H, OCH_2CH_2O), 2.28 (s, 6 H, Ar CH_3), 1.92 (s, 6 H, pyran CH_3).

Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.14; H, 7.37. Found: C, 73.16; H, 7.67.

4-[[3-[25,26-Dimethoxy-3,5,9,23-tetramethyl-13,16,19,27-tetraoxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,5,7,9,11-(26),21,23-octaen-4-ylidene]-1-propenyl]]-25,26-dimethoxy-3,5,9,23-tetramethyl-13,16,19-trioxa-27-oxoniatetracyclo-[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene Tetrafluoroborate (3d). A mixture of **3b** (0.05 g, 0.09 mmol), triethyl orthoformate (0.036 g, 0.24 mmol), and pyridine (0.03 mL) in 0.5 mL of glacial acetic acid was heated under reflux for 0.5 h. To the mixture was added 5 mL of chloroform and 5 mL of water. The organic phase was washed with another 5 mL of water, 10% $NaHCO_3$, and water. The organic phase was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a blue foam, which was stirred with isopropyl ether/ethanol 3:1. The solid was filtrated and washed with diethyl ether to give **3d** as a blue foam: yield 61%; mp 187–189 °C; ^1H NMR δ 8.82 (t, *J* = 13.2 Hz, 1 H, C=CHC), 7.21 (s, 4 H, Ar H), 7.16 (s, 4 H, Ar H), 6.80 (d, 2 H, HC=CCH), 4.50 (bs, 8 H, Ar CH_2), 3.58 (s, 12 H, OCH_3), 3.42 (bs, 16 H, OCH_2CH_2O), 2.54 (s, 12 H, CH_3), 2.36 (s, 12 H, Ar CH_3); ^{13}C NMR (CD_3CN) δ 160.4 (s, pyrylium 4-C), 157.8 (pyrylium 2,6-C).

25,26-Dimethoxy-3,5,9,23-tetramethyl-4-(2-phenylethenyl)-13,16,19-trioxa-27-oxoniatetracyclo[19.3.1.1^{2,6}.1^{7,11}]-heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene Tetrafluoroborate (3c). A solution of **3b** (0.09 g, 0.16 mmol) and benzaldehyde (0.04 g, 0.38 mmol) in 3 mL of ethanol was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure to give a yellow solid. Diethyl ether (25 mL) was added and the mixture was stirred for 16 h. The yellow crystals were filtered off and washed with diethyl ether: yield 87%; mp 140–142 °C; mass spectrum, *m/e* 580.282 (M^+ – H, calcd for $C_{37}H_{40}O_6$ 580.281); ^1H NMR δ 7.91–7.26 (m, 11 H, Ar H and CH=CH), 4.46 (s, 4 H, Ar CH_2), 3.50 (s, 6 H, OCH_3), 3.44 (s, 8 H, OCH_2CH_2O), 2.67 (s, 6 H, pyrylium 3,5-CH_3), 2.40 (s, 6 H, Ar CH_3); ^{13}C NMR δ 147.7 (d, =CH), 138.5, 133.3, 132.7, 130.3, 129.6 (d, Ar CH), 123.1 (d, =CH), 71.1, 69.9, 69.1 (t, OCH_2), 64.4 (q, OCH_3), 20.6 (q, Ar CH_3), (q, pyrylium CH_3).

25,26-Dimethoxy-3,5,9,23-tetramethyl-4-(2-phenylethenyl)-13,16,19-trioxa-27-azatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene (4d) was prepared from **3c** as described for **4a** to give **4d** as a pale yellow foam: yield 65%; mass spectrum, *m/e* 579.298 (M^+, calcd for $C_3H_{41}NO_5$ 579.299); ^1H NMR δ 7.50–6.78 (m, 11 H, Ar H and =CH), 4.80–4.00 (bs, 4 H, Ar CH_2), 3.44 (s, 6 H, OCH_3), 3.38 (s, 8 H, OCH_2CH_2O), 2.34 (s, 6 H, Ar CH_3), 2.23 (s, 6 H, pyridine CH_3).

25,26-Dimethoxy-3,4,5,9,23,27-hexamethyl-13,16,19-trioxa-27-azoniatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6-(27),7,9,11(26),21,23-nonaene (5a). A mixture of **3b** (0.15 g, 0.26 mmol) and methylamine (0.225 mL, 40 wt % solution in water) in 1.5 mL of ethanol was heated under reflux for 1.5 h. To the mixture were added 10 mL of water and 10 mL of chloroform. The organic phase was washed with another 10 mL of water and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a white solid. The solid was dissolved in ethanol and diethyl ether was added until crystals appeared. The crystals were filtered off and washed with diethyl ether: yield 62%; mp 145–148 °C; mass spectrum, *m/e* 506.286 (M^+, calcd for $C_{31}H_{40}NO_5$ 506.291); ^1H NMR δ 7.19 (s, 2 H, Ar H), 7.08 (s, 2 H, Ar H), 5.21 (AB, *J* = 11.8 Hz, 2 H, Ar CH_2), 3.94 (AB, *J* = 11.8 Hz, Ar CH_2), 3.36 (s, 6 H, OCH_3), 3.5–2.9 (m, 8 H, OCH_2CH_2O), 2.72 (s, 3 H, CH_3), 2.64 (s, 6 H, CH_3), 2.38 (s, 6 H, Ar CH_3).

25,26-Dimethoxy-3,4,5,9,23-pentamethyl-13,16,19-trioxa-27-phenyl-27-azoniatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1-(25),2,4,6(27),7,9,11(26),21,23-nonaene tetrafluoroborate (5b) was prepared from **3b** and aniline similarly as described for **5a**: yield 77%; mp 288–291 °C; mass spectrum, *m/e* 568.303 (M^+, calcd 568.306); ^1H NMR (CD_3CN) δ 7.76 (m, 1 H, Ar H), 6.94–6.82 (m, 7 H, Ar H), 6.53 (m, 1 H, Ar H), 4.67 (AB, *J* = 11.2 Hz, 2 H, Ar CH_2), 4.08 (AB, *J* = 11.2 Hz, 2 H, Ar CH_2), 3.62–3.44 (m, 8 H, OCH_2CH_2O), 3.52 (s, 6 H, OCH_3), 2.71 (s, 3 H, pyridinium CH_3),

Table III. Crystal Data and Data Collection Parameters

parameter	1·NaPic	2b·NaPic	4c·NaPic
formula	$C_{36}H_{38}N_3O_{13}Na$	$C_{36}H_{40}N_3O_{13}Na$	$C_{39}H_{37}N_4O_{12}Na$
mol form	743.71	745.72	776.74
lattice type	orthorhombic	triclinic	triclinic
space group	*Pbca*	$P\bar{1}$	$P\bar{1}$
T, K	293	147	168
cell dimensions			
a,Å	14.965 (5)	15.291 (2)	10.932 (2)
b,Å	21.060 (4)	11.771 (3)	12.330 (3)
c,Å	22.902 (5)	11.947 (1)	14.927 (7)
α,deg		99.59 (2)	70.06 (3)
β,deg		115.88 (1)	85.91 (3)
γ,deg		68.48 (1)	82.48 (1)
V,Å^3	7218 (5)	1800 (1)	1874 (1)
Z	8	2	2
D_c, g cm^{-3}	1.37	1.38	1.38
F(000)	3120	784	812
μ, mm^{-1}	0.11	0.11	0.11
θ range, deg	3–25	3–25	3–25
no. unique reflns			
measured	6282	6323	6602
observed	2093	4610	3701
no. variables	479	649	653
R,%	3.8	3.4	6.5
R_w,%	4.9	4.3	9.5
weighting factor p	0.05	0.04	0.04
extinctn *g*(10^{-7})	0.8(2)	4.4(7)	0.0(5)

2.47 (s, 6 H, Ar CH_3), 2.07 (s, 6 H, pyridinium CH_3).

Anal. Calcd for $C_{36}H_{42}NO_5 \cdot BF_4$: C, 65.96; H, 6.46; N, 2.14. Found: C, 65.67; H, 6.44; N, 1.93.

X-ray Crystallography. X-ray diffraction measurements were performed on a Philips PW1100 or an Enraf-Nonius CAD4 diffractometer, both using graphite-monochromated Mo Kα radiation. Crystal data and data collection parameters are in Table III. Lattice parameters were determined by a least-squares method from 19–25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of 3 control reflections, measured every hour, and for Lorentz polarization, but not for absorption.

The structures were solved by direct methods[27] and refined with full-matrix least-squares. Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered observed and included in the refinement (on F); weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, $\sigma(I)$ based on counting statistics and p an instability factor obtained from plots of F_o vs weighted error. Due to disorder of methyl groups not all hydrogens were located on difference Fourier maps. Depending on data/parameter ratio and data quality the hydrogens were included in the refinement (**2b**·NaPic and **4c**·NaPic) or put in calculated positions (C–H distance 0.96 Å) and treated as riding on their parent C atoms ($B_{iso}(H) = 1.2B_{eqv}(C)$).

Parameters refined were the overall scale factor, isotropic extinction parameter g (correction of F_c with $(1 + gI_c)^{-1}$), positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms (if included), and occupancy factors for a positionally disordered nitro oxygen (**2b**·NaPic). Refinement converged with a shift/error ratio less than unity, except for the disordered atom in **2b**·NaPic. Final difference Fourier maps showed no significant features. All calculations were done using SDP.[28]

Acknowledgment. We thank the Dutch Kidney Fund and the Netherlands Foundation for Technical Research (STW), Future Technical Science Branch/Division of the Netherlands Organization for the Advancement of Pure Research (ZWO), for support of these investigations.

Registry No. 1·NaPic, 112021-14-4; **2a**, 106942-89-6; **2b**, 106942-96-5; **2b**·NaPic, 111999-83-8; **3a**, 111999-71-4; **3b**, 111999-73-6; **3c**, 111999-77-0; **3d**, 112021-13-3; **4a**, 112021-11-1; **4b**, 111999-74-7; **4c**·NaPic, 111999-84-9; **4d**, 111999-78-1; **5a**, 111999-80-5; **5b**, 111999-82-7; **6**, 111999-75-8; **7**, 938-45-4; **8b**, 2892-30-0; **8c**, 106942-90-9; **9a**, 106942-86-3; **9b**, 106942-92-1; **10a**, 106942-87-4; **10b**, 106942-93-2; **11a**, 106960-71-8; **11b**, 106942-94-3; **12a**, 106942-88-5; **12b**, 106942-95-4; diethylene glycol ditosylate, 7460-82-4.

Supplementary Material Available: Positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms, and bond distances and angles and selected torsion angles for the X-ray crystal structures of the NaPic complexes of **1**, **2b**, and **4c** (24 pages). Ordering information is given on any current masthead page.

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Rearrangements in Heterocyclic Synthesis: A Novel Translocation of an (*N*-Amino-*N*-methylamino)methylene Group from a Heterocyclic *N*-Amino-*N*-methylformamidine Side Chain to the Vinylogous Nitrile Function[1]

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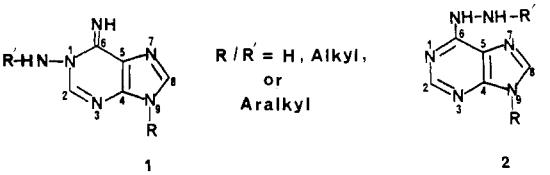
Reaction of the imidate 1-benzyl-4-cyano-5-[(methoxymethylene)amino]imidazole (**5**) with an equivalent of hydrazine provided 1-amino-9-benzyl-6-iminopurine (**6**), which, upon treatment with excess hydrazine, rearranged to 9-benzyl-6-hydrazinopurine (**7**). Reaction of **5** with methylhydrazine gave *N*-amino-*N*-methyl-*N'*-(1-benzyl-4-cyanoimidazol-5-yl)formamidine (**8b**). Thermolysis of **8b** in refluxing toluene–methanol, catalyzed by trifluoroacetic acid, provided an equimolar mixture of 5-amino-1-benzyl-4-cyanoimidazole (**9**) and 3-(5-amino-1-benzylimidazol-4-yl)-1-methyl-1,2,4-triazole (**10**). Compound **9** was recycled to **8b** via **5**. The structure of **10** was established by spectral data coupled with an unequivocal synthesis. The conversion **8b** to **10** represents a novel "translocative" rearrangement involving the transfer of an $NH_2N(Me)CH=$ group from the imidazole 5-position to the nitrile function at position 4. Successful application of the rearrangement to the analogous pyrazole system is demonstrated. The rearrangement carries useful practical implications in the synthesis of the otherwise not easily accessible heterocycles of potential biological and medicinal significance.

1-Amino-6-iminopurines (**1**) and 6-hydrazinopurines (**2**) are potential chemotherapeutic agents[2] which have been little explored. As part of a program to study structure–activity relationships of such compounds, we set out to synthesize various derivatives of **1** and **2**. To this end, the Taylor–Loeffler transformation[3] (**3** → **4**; Scheme I) offered



1 **2**

a convenient route to the synthesis of both **1** and **2**. The course of this endeavor has, however, led us to discover a new "translocative" rearrangement[4] which carries useful

(1) This paper is dedicated to Professor Nelson J. Leonard of the University of Illinois, Urbana, on the occasion of his 70th birthday.

(2) See the introductory paragraphs and the references contained therein of: (a) Wiemer, D. F.; Leonard, N. J. *J. Org. Chem.* **1974**, *39*, 3438. (b) Maeda, M.; Kawazoe, Y. *Chem. Pharm. Bull.* **1975**, *23*, 844.

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