ORGANIC LETTERS

2003
Vol. 5, No. 22
4141−4144

Pyrazine Analogues of Dipyrrolylquinoxalines

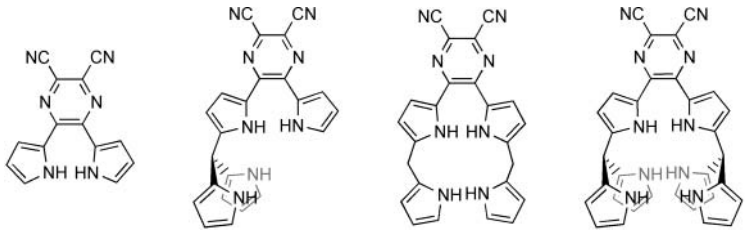
Jonathan L. Sessler,* G. Dan Pantos, Evgeny Katayev, and Vincent M. Lynch

Department of Chemistry and Biochemistry and Institute for Cellular and Molecular Biology, 1 University Station A5300, University of Texas at Austin, Austin, Texas 78712-0165

sessler@mail.utexas.edu

Received August 20, 2003

ABSTRACT



The synthesis of novel pyrazine derivatives bearing pyrrolic substituents is reported; the ability of these systems to bind certain biologically relevant anions in dichloromethane is also detailed.

Stimulated in part by a growing awareness of the environmental and clinical importance of anions,[1] considerable effort has been devoted recently to the design and synthesis of new anion-binding agents. Nonetheless, despite impressive advances, there remains a need for anion receptors displaying higher binding affinities and improved binding selectivities. This need reflects not only the relative newness of the field but also the fact that, in contrast to cations, anions are characterized by a variety of geometries, including many that are nonspherical, and a full range of charge-to-size ratios.[2]

Over the last 10 years or so, our group has developed a variety of pyrrole-based anion receptors, including ones based on calixpyrroles,[3] sapphyrins,[4] and dipyrrolylquinoxalines.[5,6] The latter systems offer the advantage of being easy to prepare and allowing for the direct, so-called naked eye detection of fluoride and, in certain cases, phosphate-type anions. Generalization of the dipyrrolylquinoxaline (DPQ) strategy could lead to receptors with different intrinsic binding properties. In this paper, we report the synthesis of a new set of DPQ analogues, the pyrazine-oligopyrroles **2**−**7**, and show that certain members of this class (e.g., **7**) bind biologically relevant anions such as chloride, dihydrogenphosphate, and mono- and dicarboxylates in dichloromethane with selectivities that differ from those of the corresponding DPQ derivative (i.e., **8**).[6]

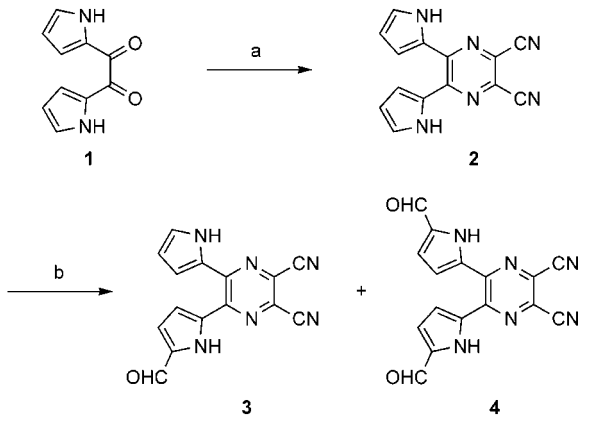
The synthesis of the pyrazine oligopyrrole receptor **7** begins with 1,2-bis-(1*H*-pyrrol-2-yl)ethane-1,2-dione **1**,[5] which upon reaction with diaminomaleonitrile (DAMN) yields 5,6-bis(1*H*-pyrrol-2-yl)pyrazine-2,3-dicarbonitrile **2** in 55% yield. Vilsmeier formylation of this simple DPQ analogue using 1.2 equiv of the formylating agent produces the monoformylated species **3** in 62% yield. The diformylated derivative **4** is obtained, again via a Vilsmeyer procedure, in 71% yield when 3 equiv of the formylating agent is used (Scheme 1).

In analogy to what proved true in the DPQ series,[6] once in hand, the formylated intermediates **3** and **4** could be

(1) Sorochinskii, V. V.; Kurganov, B. I. *Appl. Biochem. Microbiol.* **1997**, *33*, 579. Schreerder, J.; Engbersen, J. F. J.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 307.
(2) Beer P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486.
(3) Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L.*Coord. Chem. Rev.* **2001**, *222*, 57.
(4) Sessler, J. L.; Davis, J. M. *Acc. Chem. Res.* **2001**, *34*, 989.
(5) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438. Mizuno, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 1134. Kirkovits, G. J.; Zimmerman, R. S.; Huggins, M. T.; Lynch, V. M.; Sessler, J. L. *Eur. J. Org. Chem.* **2002**, 3768.
(6) Sessler, J. L.; Maeda, H.; Mizuno, T.; Lynch, V. M.; Furuta, H. *Chem. Commun.* **2002**, 862.

10.1021/ol0355635 CCC: $25.00
Published on Web 10/01/2003

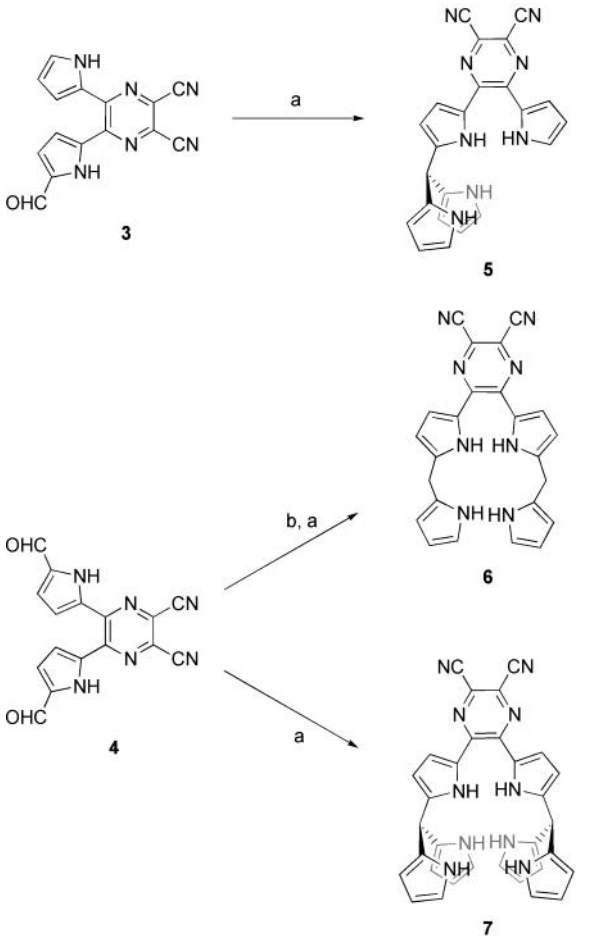
Scheme 1[a]



[a] Key: (a) DAMN, BF_3Et_2O, CH_2Cl_2, rt, 12 h; (b) (i) $POCl_3$, DMF, 1,2-dichloroethane, reflux, 2 h; (ii) NaOAc, reflux, 1 h.

reacted with pyrrole in the presence of a catalytic amount of TFA to give the tetra- and hexapyrrolic species **5** and **7** in yields of 50% and 84%, respectively (Scheme 2). The symmetrical tetrapyrrolylpyrazine **6** is obtained by reducing

Scheme 2[a]



[a] Key: (a) pyrrole, TFA, rt, 2 h; (b) LiH_3Bpyrr, THF, rt, 6 h.[11]

the dialdehyde **4** to the corresponding dialcohol[7] and then reacting immediately with pyrrole in the presence of a catalytic quantity of TFA; this yields the desired tetrapyrrolylpyrazine **6** in 28% yield (cf. Scheme 2).

The solid-state structure of the basic dipyrrolypyrazine (DPP) core was determined by subjecting single crystals of **2** to X-ray diffraction analysis (Figure 1). The two pyrrole

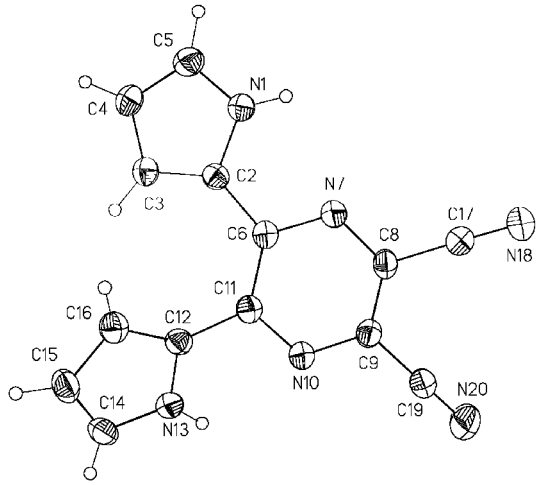


Figure 1. X-ray structure of **2** with all heavy atoms labeled. The thermal ellipsoids were scaled to the 50% probability level.[8]

NHs are pointing away from each other, as observed in the original dipyrrolylquinoxaline systems.

There are two crystallographically independent molecules of **2** per asymmetric unit. These molecules alternate along the **a** axis and are found in the form of an extended two-dimensional array. This array and likely the conformations of the individual DPP molecules are stabilized by complementary hydrogen bonds between the pyrrole NH (N1) and cyano N (N18) moieties of a first molecule of **2** and the corresponding pair (N20′, N13′, respectively) of a second molecule. The geometry of these interactions are: N1−H1···N18 (related by $1 - x$, $1 - y$, $1 - z$); N···N 2.958-(2) Å, H···N 2.12(2) Å, N−H···N 161(2)°; N1′-H1′···N18′ (related by 2-x, 1-y, 1-z); N···N 3.136(3) Å, H···N 2.30(2) Å, N−H···N 165(2)°; N13′-H13′···N20′ (related by $1 - x$, $2 - y$, $1 - z$); N···N 3.063(2) Å, H···N 2.31(2) Å, N−H···N 152(2)°. (Dashed lines are indicative of a H-bonding interaction.)

To probe the possible solution-state conformational properties of the DPPs, NOESY experiments were performed using the unsymmetric derivative **5.** No coupling was observed between the four β-pyrrole hydrogens, indicating that the conformation where the two internal pyrrole moieties point away from each other, likely exists only in the solid state. This lack of coupling can be ascribed to the ability of the pyrroles in these "claw"-like systems to rotate freely in

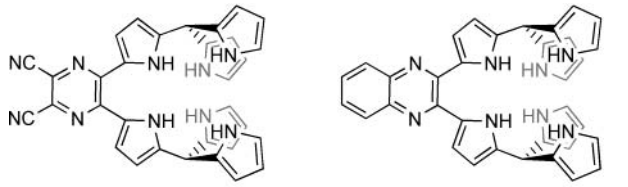
(7) Collins, C. J.; Fischer, G. B.; Reem, A.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 529.

solution at room temperature. An important consequence of the resulting, inferred, low barrier to rotation is that it should allow each pyrrole subunit present in receptors such as **7** to adjust their spatial orientation individually so as to adopt collectively a conformation that is conducive to anion binding.

The interaction of **7** and **8**, its DPQ analogue, with several biologically relevant anions, including mono- and dicarboxylates, was studied in dichloromethane solution using UV−vis spectroscopy. The relative host/guest stoichiometries were determined via Job plots. In both cases, standard protocols, as used previously by our group[5,9] (and others), were employed. In analogy to previous studies, the anions were used in the form of their corresponding tetrabutylammonium salts. Because they were not available commercially, the ditetrabutylammonium salts of oxalic, malonic, and succinic acids were prepared in accord with literature procedures.[10]

As revealed by inspection of Table 1, receptor **7** displays a higher affinity for acetate anion (K_a: 176 000 ± 11 000 M^{-1}) compared to the other anions subject to study (i.e., chloride, dihydrogenphosphate, oxalate, malonate, and succinate). While acetate anion is neither the smallest of the anions analyzed nor the one with the highest charge density, it does have a size and shape that differs from the others. In particular, it is characterized by a charged carboxylate "head" that could fit between the "pyrrolic claws", as well as by a methyl "tail" that could function as a cap for the host−guest ensemble by isolating the complex and its anionic "head" from solvent or reducing interactions with the tetrabutylammonium countercation.

Table 1. Affinity Constants (M^{-1}) for Anion Binding Receptors **7** and **8** As Determined from UV−vis Spectroscopic Titrations in CH_2Cl_2. The Anions Were Studied in the Form of Their Tetrabutylammonium Salts



7 **8**

anion	K_a (**7**/guest)[a]	K_a(**8**/guest)[a]
Cl^-	48 000 ± 2700	5800[c]
$H_2PO_4^-$	30 000 ± 1500	300 000[c]
acetate	175 000 ± 11 000	46 000 ± 4600
oxalate	24 000 ± 1300	30 000 ± 2100
malonate	2100 ± 200	21 000 ± 2800
succinate	2000 ± 150[b]	53 000 ± 8000

[a] The R^2 values for the curve fits used to determine the affinity constants range between 0.969 and 0.998. [b] In the case of succinate + **7**, a 2:1 binding stoichiometry is observed. The tabulated value is for the first binding interaction, K_{a1}; the calculated equilibrium constant for the second binding event is 1.4 ± 0.5 M^{-1}. [c] From ref 6.

Although admittedly speculative, the above rationalizations cannot be effectively evoked in the case of the other anions considered in this study. Thus, a closer correspondence between charge density and affinity is expected. In fact, with the exception of acetate, the relative affinity of **7** decreases with increasing anion size as follows: chloride/dihydrogenphosphate/oxalate/malonate/succinate = 914:562:453:40:1.

Here, it is important to note that the binding constant for the succinate anion used to determine this set of ratios was taken as the square root of the product of $K_{a1} \times K_{a2}$ since Job-plot analysis for the interaction of **7** with succinate anion revealed a 2:1 binding mode. By contrast, the other anions were all found to be bound in a 1:1 stoichiometry, as judged from such analysis (Table 1). Needless to say, the malonate/succinate selectivity is much lower if the K_a for malonate is compared to effective equilibrium constant (K_{a1}) associated with the binding of the first anionic equivalent of succinate to receptor **7**. Using these values, a malonate/succinate selectivity of 1.1:1 is obtained.

To provide a basis for comparison between this new series of receptors and the DPQs reported earlier, the anion recognition behavior of receptor **8** was analyzed using the same series of anions. Whereas the interactions between **8** and both Cl^- and $H_2PO_4^-$ have been reported, its ability to bind mono- and dicarboxylate anions was not previously considered. As revealed by the findings summarized in Table 1, this functionalized DPQ derivative binds carboxylate-type anions well. However, in contrast to **7**, the affinities for this class of anions are found to be nearly invariant to structure and a 1:1 anion-to-receptor stoichiometry was observed. Also, in further contrast to what is true for **7**, it is phosphate, not chloride, that is bound with highest affinity within the series of studied anions.

Comparing the two receptors, **7** and **8**, supports the emerging notion that small changes in the overall molecular architecture can have a significant influence on the binding capabilities of a given type of anion binding motif. In the present instance, the more rigid nature of the bridging aromatic unit (quinoxaline vs pyrazine) present in **8** could render differences in anion size less important (due to existing preorganization imposed by the spacer).[12] Likewise, the larger nature of the overall host−guest ensemble could mitigate the beneficial effects of the protective methyl "tail" present in the acetate complex. In any case, it is important to appreciate that "fine-tuning" of anion affinities and selectivities is possible in the context of dipyrrolylquinoxaline-type receptors.

In summary, a new set of polypyrrole-based anion receptors has been synthesized. While X-ray diffraction analysis

(8) Crystallographic data for **2**: $C_{29}H_{18}Cl_2N_{12}$, M_w = 605.45, triclinic, *P*-1, a = 7.3374(1) Å, α = 79.514(1)°, b = 12.8235(2) Å, β = 80.208(1)°, c = 15.6794(3) Å, γ = 84.107(1)°, V = 1425.60(4) Å^3, D_c = 1.410 g cm^{-3}, Z = 2, R = 0.0464, GOF = 1.023 ($I > 2\sigma(I)$), R_w = 0.1186 (all data), CCDC 217630. See the Supporting Information for CIF files.

(9) Bucher, C.; Zimmerman, R. S.; Lynch, V.; Kral, V.; Sessler, J. L *J. Am. Chem. Soc.* **2001**, *123*, 2099. Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17.

(10) Cotton, F. A.; Lin, C.; Murillo, C. A. *Inorg. Chem.* **2001**, *40*, 478.

(11) LiH_3Bpyrr = lithium pyrrolidinoborohydride was synthesized according to the literature; see: Thomas, L. S.; Collins, C. J.; Cuzens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.

reveals that the two pyrroles in the basic dipyrrolypyrazine core are oriented in opposite directions, NOESY experiments provide support for the notion that pyrrolic subunits are free to rotate in solution and hence interact effectively with anionic species. In accord with such a conclusion, solution-phase anion-binding studies (dichloromethane) reveal that the hexapyrrole pyrazine derivative **7** is an effective anion receptor. It binds oxalate with high selectivity relative to malonate and succinate (K_a ratio of 450:40:1 in CH_2Cl_2). However, it binds the simple monocarboxylate anion, acetate, even more effectively. By contrast, the corresponding hexapyrrolic quinoxaline derivative, **8**, binds acetate no more strongly than oxalate, malonate, or succinate (again in dichloromethane solution). This disparate set of findings supports the conclusion that small changes in structure can lead to oligopyrrolic receptors with different anion binding properties and sets the stage for further design and synthesis efforts in the pyrrole-based anion recognition area.

(12) We performed molecular modeling calculations, using HyperChem, v7.1 in order to calculate the rotational barrier for the C2−C6 and C11−C12 bonds (numbering of the atoms is according with the X-ray structure). We used the di-*tert*-butyl analogues of both **7** and **8** so as to keep the calculations tractable. The PM3 semiempirical method in conjunction with the Conformation Search module was used to determine the structure with the minimum energy. The criteria for convergence was a difference in energy between two sequential structures below 0.01 kcal/(A mol). The results of these calculation show that the rotational barrier is 37% higher in the case of **8** vs **7**. This is consistent with preorganization and conformation affects being significant aryl bridged dipyrrole anion receptors, and more so in the case of the larger dipyrrolylquinoxalines than in the smaller dipyrrolylpyrazines.

Acknowledgment. This work has been supported by the National Institutes of Health (Grant No. GM 58907 to J.L.S.). Mr. Won-Seob Cho and Mr. Hiromitsu Maeda are warmly thanked for many helpful discussions.

Supporting Information Available: Detailed descriptions of experimental procedures; detailed anion binding data and X-ray experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0355635