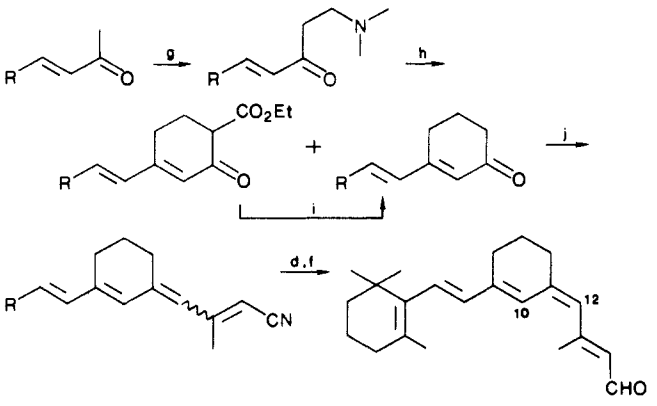
Scheme II

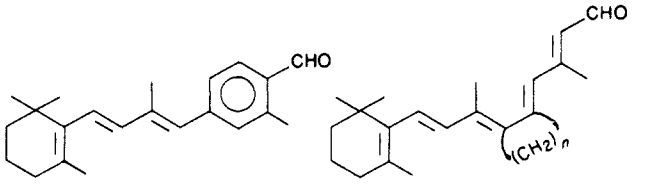


5

[a](g) $(CH_2O)_n$ + Me_2NH-HCl; (h) MeI; $CH_3COCH_2CO_2Et$, NaOMe/MeOH; (i) KOH/MeOH; HOAc; (j) C_5-phosphonate, NaH, DMF/THF; (d) DIBAL; (f) preparative HPLC; R = trimethylcyclohexenyl.

analogue **2**[5] was synthesized according to the reaction sequence of Scheme I. Incubation for 2 h at room temperature of an excess of the analogue with either digitonin or CHAPS solubilized bovine opsin did not yield any detectable amount of new pigments.[6] Since the shape of **2** is similar to that of the proposed chromophore of bathorhodopsin (**1**), this negative observation, obviously not to be considered a proof, is consistent with the suggestion that bathorhodopsin contains the all-trans,10-s-cis chromophore. This result, we might add, cannot readily be accounted for by any arguments based on the length requirement of the binding site.[7] For comparison, analogue **3**,[8] a model for 12-s-cis,all-trans retinal, a structure recently suggested for the chromophore of meta-I-rhodopsin,[9] also failed to interact with bovine opsin.

The instability of bathorhodopsin makes any attempt to prepare a corresponding visual pigment analogue impossible. Thus the merit of any elaborate effort to prepare other less accessible analogues containing the s-cis conformation, such as **4**, becomes questionable.



3 4

A more active approach is to examine effects of structural modification on the photochemical process. Hence, we have synthesized the ring-fused retinal analogue **5**[10] according to the reaction sequence shown. The 11-cis isomer[11] was isolated by preparative HPLC, which upon interaction with bovine opsin yielded a visual pigment analogue with an absorption maximum at 488 nm. The added fused ring negates the possibility of rotation of the C-11 end of the 11,12-double bond in its isomerization (hence shutting off the H.T.-11 process), while rotation of the C-12 end should be relatively unaffected. Its photochemical activity is, therefore, interesting (Scheme II).

Upon irradiation of the visual pigment analogue with visible light at room temperature in the presence of an excess amount of hydroxylamine, the pigment bleached readily. This result clearly cannot be accommodated by the H.T.-11 mechanism. While it is still consistent with the conventional one bond rotational process involving twisting of the C-12 end of the polyene chromophore, the result cannot be considered as a proof for such a mechanism in rhodopsin. In fact, upon reflection there is the added possibility that upon closing of the H.T.-11 channel in this analogue a new chemical pathway for dissipation of the excess electronic excitation energy might have been created. In addition to the one bond twist mechanism, the new pathway could be the H.T.-12 process. The latter, however, should produce a structurally different primary photoproduct (12-s-cis,all-trans instead of 10-s-cis,all-trans) and subsequent bleaching intermediates.[2b,4] Hence, detection and characterization of such intermediates[12] could be of primary importance for possible clarification of the specific mode of isomerization in the primary process of vision (assuming no substantial distortion of protein structure in this analogue). This experiment will be carried out in the laboratory of Professor Yoshizawa.[12]

Acknowledgment. The work was supported by a grant from the U.S. Public Health Services (AM-17806). Dr. V. J. Rao first suggested the use of compound **5** for examining the H.T.-n process.

(5) ^{1}H NMR ($CDCl_3$): δ 1.07 (s, CH_3-1,1), 1.77 (s, CH_3-5), 2.57 (s, CH_3-13), 6.77 (d, H_7), 6.36 (d, H_8), 6.43 (d, H_{14}), 7.46 (d, Ar 2 H), 7.53 (d, Ar 2 H), 10.17 (dd, CHO); $J_{7,8}$ = 16.4, $J_{10,11}$ = 7.3, $J_{14,15}$ = 7.9 Hz. The BR analogue of the same compound has been prepared: Koelling, E.; Gaertner, W.; Oesterhelt, D.; Ernst, L. *Angew. Chem.* **1984**, *96*, 76-78.

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(8) ^{1}H NMR data for **3**: δ 1.05, 1.74, 2.09 and 2.67 (3 H each), 6.31 (d) and 6.21 (d) (1 H each for H_7 and H_8, $J_{7,8}$ = 15.6 Hz), 6.43 (s, H_{10}), 7.19 (s, H_{12}), 7.31 (d) and 7.77 (d) (1 H each, J = 7.5 Hz). The aldehyde was prepared from the corresponding ester. The latter was generously provided by Dr. M. Dawson: Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.-R.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583-592.

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(10) Compound **5** has been synthesized independently by M. Sheves with the fused ring constructed by a totally different route. Private communication of M. Sheeves to R. S. H. Liu.

(11) ^{1}H NMR ($CDCl_3$): δ 6.31 (d, H_7), 6.12 (d, H_8), 6.60 (s, H_{10}), 5.73 (s, H_{12}), 6.04 (d, H_{14}), 10.05 ppm (d, H_{15}); $J_{7,8}$ = 16.2, $J_{14,15}$ = 8.2 Hz.

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A Neutral Water-Soluble Aluminum Complex of Neurological Interest

Martin M. Finnegan, Steven J. Rettig, and Chris Orvig*

Department of Chemistry, University of British Columbia Vancouver, BC, V6T 1Y6 Canada

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The involvement of aluminum in certain neurological dysfunctions has become the subject of considerable debate over the past decade.[1-4] Increased levels of aluminum in the brain have been observed in Alzheimer's disease[2,3] and dialysis encephalopathy,[4] conditions which result in progressive chronic dementia, among other symptoms. This controversy has included suggestions that Al intake should be drastically reduced[5] although it appears that very little Al is absorbed from the diet.[1] While it is generally agreed that elevated levels of Al are involved in the pathogenesis of Alzheimer's disease, there is little agreement on its role and no agreement on how it is delivered to the nuclei of brain cells.

To understand how aluminum arrives at its ultimate intracellular locus in human brain disease, more than a scant knowledge of its chemistry in aqueous solution at neutral pH is required. The extensive complicated hydrolysis chemistry of aluminum[6] has

* To whom correspondence should be addressed.

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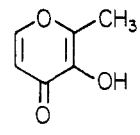
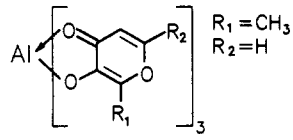
meant that quantitative solution studies of its reactions are usually performed in acid solution[7] and that the preparation of aluminum complexes in aqueous solution is a field ripe for development (necessitating appropriate ligands). The coordination chemistry of Al in aqueous solution can be directly linked to the problem of Al in Alzheimer's disease through the use of ligands which would produce discrete neutral six-coordinate complexes of some stability at physiological pH. The requirements of electroneutrality and a molecular weight of about 400 dalton, or less,[8] are necessary for possible passage of the blood–brain barrier (bbb) while solubility and stability in water are required to deliver the complex to the bbb.

Maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one, **1**) is a natural product which may be obtained by the alkaline hydrolysis of streptomycin[9] and which is used as a flavoring agent, particularly in baked goods. Compounds of **1** with divalent[10] and trivalent[11] metal ions have been characterized and some solution studies of **1** with Al^{3+} have been reported.[12] Herein, we communicate our preliminary results, involving **1**, of a larger project to examine low molecular weight neutral aluminum complexes which are stable and soluble in aqueous solution.



1



2

Combining concentrated aqueous solutions of **1** and $Al(NO_3)_3 \cdot 9H_2O$ (3:1), raising the pH to 8.3, and heating for a few minutes provide a good yield of the compound **2**. Recrystallization from methanol or methanol/diethyl ether gives analytically pure white or off-white plates[13] which are soluble in ethanol, methanol, and water (0.06 M). Spectroscopic properties[14,15] are consistent with bidentate, monoanionic ligation of the metal ion, while analytical[13] and mass spectral[16] results indicate a tris(ligand) complex. Proton chemical shifts for the two ring protons and the exocyclic methyl group in **1** move downfield in **2** by 0.15 to 0.31 ppm and the C=O and C=C stretching frequencies all decrease by ca. 40 cm^{-1}. Assuming that the two possible optical isomers (Λ vs. Δ) are interconverting rapidly in aqueous solution, only the geometrical isomerism remains to be deduced (*fac*ial vs. *mer*idional). The low-temperature ^1H NMR spectrum (−70 °C, CD_3OD) evinces some broadening of the peaks but not enough to indicate the formation of new sets of resonances. The ^{27}Al NMR spectrum has one resonance at 38 ppm[17] (line width 900 Hz) which is consistent with three unsymmetric bidentate uninegative ligands[18] in a pseudooctahedron but ambiguous concerning their arrangement (*fac* vs. *mer*).

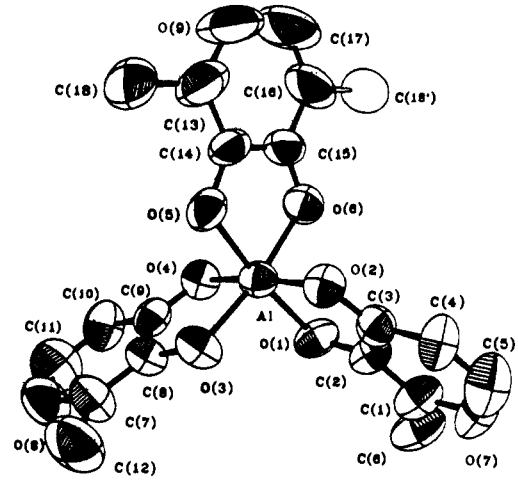


Figure 1. ORTEP view of **2**. Al–O(x) bond lengths: x = 1, 1.874 (2) Å; x = 2, 1.929 (3) Å; x = 3, 1.871 (4) Å; x = 4, 1.926 Å; x = 5, 1.907 (4) Å; x = 6, 1.919 (4) Å. One ligand is disordered with the methyl group refined as 58% occupancy C(18) or 42% occupancy C(18′).

Single crystals were grown from methanol/diethyl ether by a liquid diffusion method[19] and the molecular geometry was found[20] to be *mer* in the solid state (Figure 1). Al–O bond distances are given in the caption. Despite the disorder of one of the hydroxy-γ-pyrone ligands, the two longest Al–O bonds (keto oxygens; Al–O(2), Al–O(4)) are clearly trans, and the two shortest Al–O bonds (hydroxy oxygens, Al–O(1), Al–O(3)) are cis, dictating *mer* geometry. Bond length comparisons with related structures are difficult (as there are few congeners); however, the average Al–O of 1.888 (2) Å in tris(tropolonato)aluminum[21] falls between Al–O(keto) and Al–O(hydroxy), consistent with that structure having delocalized ligands and **2** not having same. The disorder causes Al–O(5) and Al–O(6) to be averaged up and down, respectively, from those distances observable if O(5) was exclusively a hydroxy oxygen and O(6) exclusively a keto oxygen. The observed bond distances are consistent with this averaging, Al–O(5) being slightly shorter than Al–O(6). The bond angles are consistent with a somewhat distorted octahedron with all the *cis*-O–Al–O angles being 90 ± 5.5° and the ligands are quite planar.

Conductivity measurements of **2** in aqueous solution indicate that its solutions are nonconducting; i.e., it maintains its neutral charge in water and does not dissociate. Both the ^1H and ^{27}Al NMR spectra remain unchanged for 3 months at pH 7.5. Variable-pH ^{27}Al NMR has been used to determine that **2** hydrolyses to $[Al(OH)_4]^-$ above pH 9 and that **2** loses its ligands sequentially beginning at pH 4. That an aluminum complex should have such a window of stability to hydrolysis (pH 4–9) is remarkable and suggests that in vivo studies should prove enlightening. Preliminary toxicity studies[22] indicate that **2** is a potent toxin and is unusually neurotoxic (by a factor of about 20) when compared to other aluminum-containing compounds such as the lactate or the tartrate. This suggests that **2** remains intact delivering its Al^{3+} successfully into brain cells rather than simply giving it up to some trivalent metal ion receptor such as transferrin. Further work

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(14) ^1H NMR (D_2O, 25 °C, 80 MHz): δ 2.48 (s, 3 H, CH_3), 6.85 (d, J = 5.3 Hz), 1 H, C*H*C(O)), 8.32 (d, J = 5.3 Hz, 1 H, OC*H*CH).
(15) IR (KBr, all strong): 1617 cm^{-1} (ν_{CO}); 1577, 1522 ($\nu_{C=C}$); 562, 464, 445 (possibly ν_{M-O}).
(16) EIMS (120 °C): m/e 402 (relative intensity 5, $AlL_3^+ = M^+$), 277 (100, AlL_2^+), 153 (12, $AlHL^+$).
(17) Relative to 0.2 M $Al(ClO_4)_3 \cdot 9H_2O$ in 0.1 M $HClO_4$ with added D_2O as a lock signal. For a review, see: Delpuech, J. J. *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 2, pp 153–195.
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(20) Crystals of $Al(C_6H_5O_3)_3$ are orthorhombic, a = 18.402 (1) Å, b = 16.964 (1) Å, c = 11.949 (1) Å, Z = 8, space group *Pbca*. The structure was solved by direct methods and was refined by full-matrix least-squares procedures to R = 0.055 and R_w = 0.054 for 1419 independent absorption-corrected reflections with $I = \geq 2\sigma(I)$ collected at 22 °C with Cu Kα radiation on an Enraf-Nonius CAD4-F diffractometer. One ligand was disordered: O(9) and C(17) were refined as 58/42 O/C and C/O, respectively. Hydrogen atoms were fixed in calculated positions, idealized from observed positions for methyl groups.
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is currently exploiting these interesting properties of this simple ligand system in chemical and in vivo studies with Al and Ga.

Acknowledgment is made to NSERC (Canada) for an operating grant and a University Research Fellowship to C.O. We most gratefully thank Professor J. Trotter for the use of his crystallographic facilities and Professor D. R. McLachlan for preliminary toxicity studies.

Supplementary Material Available: For **2**, preparative procedure and tables of final positional and equivalent isotropic thermal parameters, calculated hydrogen parameters, anisotropic thermal parameters, bond lengths, bond angles, intraannular torsion angles, torsion angles, and measured and calculated structure factor amplitudes (26 pages). Ordering information is given on any current masthead page.

Macrocyclic Receptor Molecules for Urea: The Use of Electrophiles in the (Co)complexation of Neutral Molecules

Veronika M. L. J. Aarts,† Catherina J. van Staveren,† Peter D. J. Grootenhuis,† Johan van Eerden,‡ Laminus Kruise,‡ Sybolt Harkema,‡ and David N. Reinhoudt*†

Laboratories of Organic Chemistry and Chemical Physics, Twente University of Technology 7500 AE Enschede, The Netherlands

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A covalently bound carboxylic group or an electrophilic lithium ion can assist in the complexation of urea by macrocyclic polyethers, provided that the macrocycle is sufficiently large to encapsulate urea.

Although hitherto the work on synthetic macrocyclic polydentate ligands almost exclusively deals with selective complexation of *cations*,[1] there is an increasing interest in the binding of *neutral guest* species.[2] We have recently proven that such complexes exist not only in the solid state but also in solution.[3] Although a crystalline 18-crown-6-urea (1:5) complex has been isolated,[4] complexes of crown ethers with urea in aqueous solutions hardly exist ($\log K_s < 0.1$).[5] More stable complexes are formed between protonated urea (UrH^+X^-) and macrocyclic polyethers,[6] with a coordination as in the corresponding complexes with guanidinium salts.[7] We are currently studying the complexation of urea with

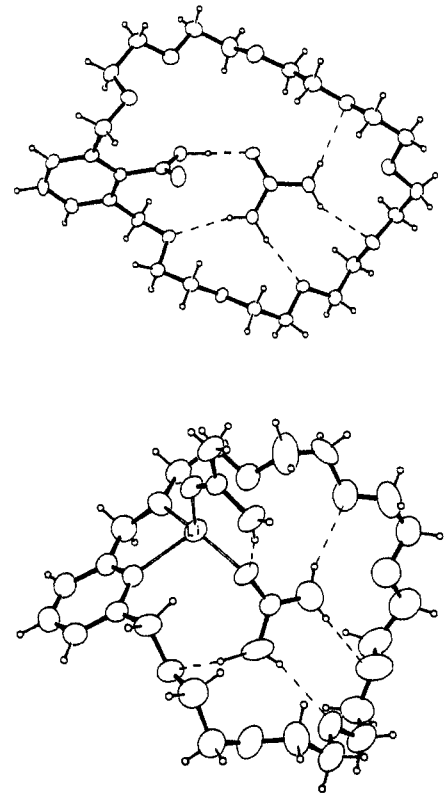
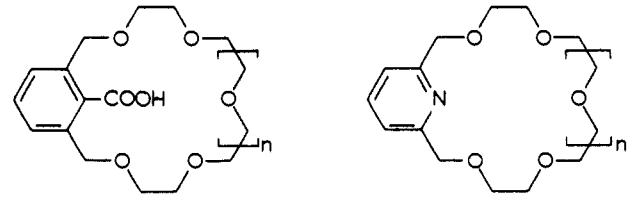


Figure 1. Structures of (a) the 2-carboxyl-1,3-xylyl-30-crown-9-urea complex and (b) the 2,6-pyrido-27-crown-9-bis(urea)-$LiClO_4$ complex (the perchlorate anion is not shown). Hydrogen bonds indicated by dashed lines.

macrocyclic polyethers containing a *covalently linked acidic group*, which can protonate the urea molecule, a very weak base (pK_a = 0.10, H_2O, 25.0 °C).

2-Carboxyl-1,3-xylyl crown ethers **1a-g** were synthesized according to the method described by Cram et al.[8] Accurate



1a, n=0 e, n=4
b, n=1 f, n=5
c, n=2 g, n=6
d, n=3

2a, n=0 e, n=4
b, n=1 f, n=5
c, n=2 g, n=6
d, n=3

determination of the acidities of the carboxylic group in these crown ethers (**1**) (pK_a values ±0.02) showed that the pK_a value depends strongly on the ring size of the crown ether. The extremely high pK_a values of **1a** and **1b** (5.31 and 5.71, respectively) can be attributed to the stabilization of the acid by intraannular hydrogen bonding to a crown ether oxygen atom.[8] The relatively high pK_a values of **1c** (4.38) and **1d** (4.06) must be due to specific coordination of a water molecule in the cavity, stabilizing the

† Laboratory of Organic Chemistry.
‡ Laboratory of Chemical Physics.

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