Tetrahedron Letters,Vol.30,No.33,pp 4333-4336,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STRUCTURAL IDENTIFICATION OF A NEW PIPERAZINO-CROWN ETHER DERIVATIVE USING ^{23}NA NUCLEAR MAGNETIC RESONANCE.

Harald D.H. Stöver[1], Christian Detellier[2,*].

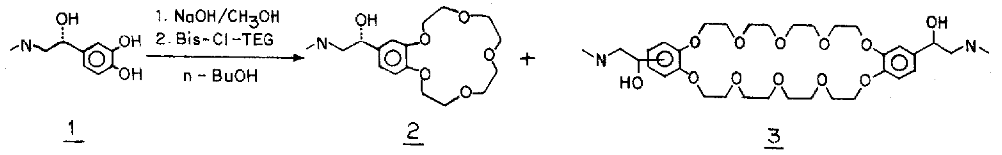
1. Department of Chemistry, Cornell University, Ithaca,
N.Y., 14853-1301 USA

2. Ottawa-Carleton Chemistry Institute, University of
Ottawa Campus, Ottawa (Ont.), K1N 9B4, Canada.

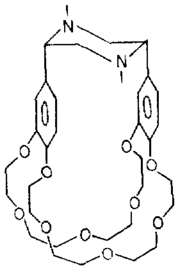
Abstract: ^{23}Na NMR has been used to discriminate between two possible structures for a piperazino-crown ether derived from adrenalin. The determination of the stoichiometry of its complex with the sodium cation in nitromethane allowed its identification as a 30-crown-10 derivative.

Crown ethers built on the catechol function of catecholamines, such as adrenalin or dopamine, combine a selective binding site for metal or ammonium cations with a functionalized side chain [1]. The first report concerning their synthesis described the formation of both monomer 2 and dimer 3 from the reaction of adrenalin 1 with 1, 13-bischloro-4,7,10-trioxatridecane in the presence of base [2]. A more elaborate route giving exclusively the monomer 2 was described a few years later [3]. We report in this letter the synthesis of a new crown ether derivative functionalizing a piperazine ring [4], as well as what we believe is the first application of alkali metal cation NMR in the structural identification of organic compounds.

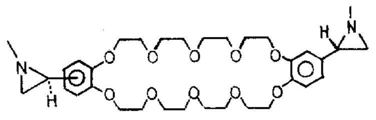
While attempting to repeat the direct route [2] to the monomer 2, we could isolate only a white powdered material characterized by a molecular ion peak in the mass spectrum at m/e = 646. This could correspond to 3, after loss of two molecules of water. However, since the ^{1}H and ^{13}C NMR signals of the isolated material differed from those expected for the adrenalin side chains of 2 and 3 [2,3], the formation of a final product, different from 3, must be considered. Under the experimental conditions of this study, most likely during the work-up involving an alumina column [5], 2 can undergo double condensation to form the final isolated product.



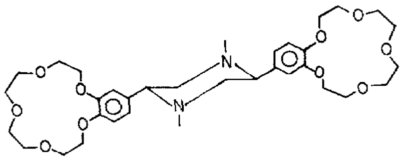
Three possible condensation products were considered. Condensation of 3 could have given either the piperazino-30-crown-10 4, or the bis-aziridino-30-crown-10 5. On the other hand, two molecules of 2 could have condensed to the piperazino-bis-15-crown-5 6. Of these three possible isomeric structures, the bis-aziridino-30-crown-10 5 could be easily eliminated, since the ^{1}H and ^{13}C NMR data point to the presence of a substituted piperazine ring [6]. However, these data did not allow unambiguous discrimination between the two possible piperazine-based structures 4 and 6.



4



5



6

The ^{23}Na NMR chemical shifts and relaxation rates of sodium crown ether complexes are known to reflect the structure and ring size of the crown ether ligand [7]. The distinction between the 30-crown-10 structure 4 and the bis-15-crown-5 structure 6 was made possible by measuring the ^{23}Na chemical shifts and relaxation rates of sodium perchlorate in nitromethane solutions for different concentrations of the unknown crown ether (Figure). In that solvent, the formation of Na^+- crown complexes is characterized by equilibrium constants of formation, K_f, larger than 10^4 [8], which should lead to a linear relationship between the ^{23}Na chemical shift, δ, or the transverse relaxation rate (in the absence of any chemical exchange contribution [9]), T_2^{-1}, and the ratio $\rho = [\text{crown}]/[Na^+]$, with a plateau for $\rho \geq 1.0$ or ≥ 0.5 for the cases of 1:1 and 1:2 crown:sodium complexes respectively [10-12]. The variations of both chemical shifts and relaxation rates between $\rho = 0$ and $\rho = 1.0$ establish the stoichiometry of the complex and thus the presence of only one crown moiety per molecule of unknown compound. The bis-15-crown-5 isomer 6 would have shown singular points for both chemical shifts and relaxation rates at $\rho = 0.5$, as its two well separated 15-crown-5 groups would independently bind one sodium cation each [13]. These results allow us to assign the 30-crown-10 structure 4 to the isolated material.

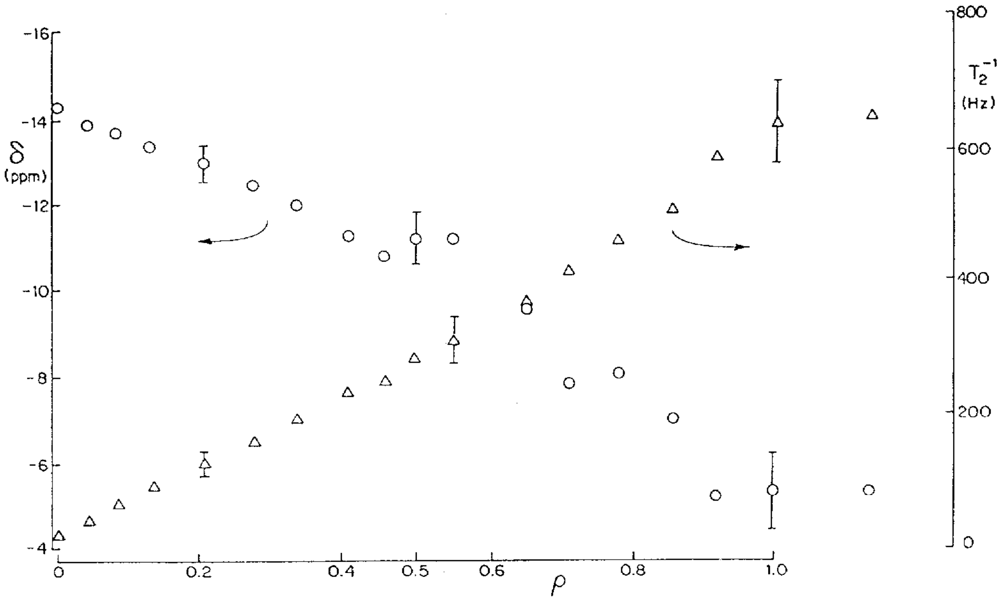


Figure: ^{23}Na chemical shifts, δ (o) and transverse relaxation rates, T_2^{-1} (Δ) as a function of ρ= [4]/[NaClO$_4$] in nitromethane. [NaClO$_4$] = 2.24×10^{-2} M.

Experimental:

NMR: The ^{23}Na NMR spectra were taken at 24°C on a Varian FT-80 NMR spectrometer operating at 21.39 MHz for ^{23}Na. The chemical shifts were referenced to sodium chloride at infinite dilution in D_2O, and corrected for the difference in magnetic susceptibilities between nitromethane and water. The transverse relaxation rates were obtained from the linewidths at halfheight, $T_2^{-1} = \pi \nu_{1/2}$. Nitromethane was dried by distillation from calcium carbide. Sodium perchlorate was dried over phosphorus pentoxide under vacuum at 60°C for several hours. The spectra were obtained by diluting a nitromethane solution, containing crown ether (0.27 M) and sodium perchlorate (0.0224 M), with another nitromethane solution containing only sodium perchlorate (0.0224 M).

Synthesis: Adrenalin (Sigma, 5.0g, 27.3 mmol), sodium methoxide (57 mmol, as 12.5 mL of a commercial 25% solution in methanol) and 1,13-bischloro-3,7,10-trioxatridecane (6.3g, 27 mmol) were refluxed under nitrogen in n-butanol for 20 hours. The residue after evaporation of the solvent was taken up in 100 mL water, and extracted with 3 x 50 mL chloroform. The organic phases were dried with magnesium sulfate, and the solvent evaporated to give a red oil (6.0g). This oil was absorbed onto Celite (30g) from a chloroform solution (100 mL) and packed dry onto an alumina (Woelm, grade IV) column. The product was eluted with ethyl ether, and purified by trituration with ethyl ether, to give 0.45g, 5% of white material. **M.P.:** 184-190°C, m/e: 646, $[\alpha]_D$: -2.0°. **NMR** ^{1}H: NCH_3 2.05ppm, s; NCH_2 3.14ppm, 2.92ppm, d; ^{13}C[$CDCl_3$]: $N\underline{C}H_3$ 43.2ppm; $N\underline{C}H_2$ 64.3ppm; ^{13}C[C_6D_6]: $\underline{C}$H-Ph 77.5ppm. The 1,13-bis-chloro-4,7,10-trioxatridecane was synthesized as described earlier [1].

References and notes.

1. C. Detellier, H.D.H. Stöver, Synthesis (1983), 990.

2. F. Vögtle, B. Jansen, Tetrah. Lett. (1976), 52, 4895.

3. D.E. Fenton, D. Parkin, R.F. Newton, J. Chem. Soc., Perkin Trans. (1981), 449.

4. R. Chênevert, R. Plante, Synthesis (1983), 847.

5. (a) G. H. Posner, Angew. Chem., Int. Ed. Engl. (1978), 17, 487;
(b) C. Hamon, Y. Le Goff, M. Senes, U.S. Patent (1980), 4,209,424.

6. The observed ^{13}C chemical shift values are in good agreement with values calculated for 1,4-dimethyl-2,5-diphenylpiperazine using two ^{13}C increment systems: M. Hesse, H. Meier, B. Zeeh, "Spektroskopische Methoden in der Organischen Chemie", Georg Thieme Verlag, Stuttgart (1979), pp. 230-232.

7. (a) A. I. Popov, J. M. Lehn, in "Coordination Chemistry of Macrocyclic Compounds", G. A. Melson Ed., Plenum Press, New York, 1979; (b) P. Laszlo, Angew. Chem. Int. Ed. Engl., (1978), 17, 254. (c) C. Detellier, in "NMR of Newly Accessible Nuclei", P. Laszlo Ed., Academic Press, N.Y, (1983); Vol. 2, Chapter 5, pp. 105-151; (d) M. Bisnaire, C. Detellier, D. Nadon, Can. J. Chem. (1982), 60, 3071.

8. (a) J.D. Lin, A.I. Popov, J. Am. Chem. Soc. (1981), 103, 3773; (b) A. Delville, H.D.H. Stöver, C. Detellier, J. Am. Chem. Soc. (1987), 109, 7293; (c) K.M. Brière, C. Detellier, J. Phys. Chem. (1987), 91, 6097.

9. H.D.H. Stöver, A. Delville, C. Detellier, J. Am. Chem. Soc. (1985), 107, 4167.

10. It has been shown that 2:1 and 3:2 sodium: dibenzo-30-crown-10 complexes are formed in small amounts in nitromethane solutions [11,12]. Their presence can perturb the linearity of the relationship between δ and ρ. This is in agreement with the slight curvature observed on both relationships of the Figure.

11. M. Shamsipur, A.I. Popov, J. Am. Chem. Soc. (1979), 101, 4051.

12. H.D.H. Stöver, L.J. Maurice, A. Delville, C. Detellier, Polyhedron (1985), 4, 1091.

13. A similarity could be found in the complexation of sodium by spiro-bis-crown ethers [14]. These ligands form dicationic 2:1 complexes, which "are less disfavored than could have been feared on the basis of strong electrostatic repulsions". At 293 K, there is only a factor 40 between K_1 and K_2, the formation constants of the monocationic and dicationic complexes of sodium with the spiro-bis-15-crown-5 [14]. On that basis, one can expect the two binding sites of 6 to be characterized by very similar high formation constants in nitromethane.

14. J. Bouquant, A. Delville, J. Grandjean, P. Laszlo, J. Am. Chem. Soc. (1982), 104, 686.

(Received in USA 29 November 1988; accepted 3 May 1989)