Hydroxyethylation of Macrocyclic Polyamines; Inhibition by Partial Protonation

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The hydroxyethylation of macrocyclic crown-type polyamines with ethylene oxide in water is very sensitive to ring size and chemical structure. When the ring is 12-membered, the reaction is remarkably fast for the free amine, but completely inhibited for the monoprotonated species. Neutralization curves for these polyamines in water also reveal the special properties of the 12-membered ring, being more basic than the others in the first and second step, while further protonation could not be detected.

It is well established that primary and secondary amines of open-chain structure can be readily hydroxyethylated with ethylene oxide under a variety of conditions.[1] Reported examples include molecules with more than one amino function, and these often have a 1,4-relationship. Also macrocyclic amino-ethers have been sucessfully hydroxyethylated under similar conditions. Thus, not only a monoaza crown-ether,[2] but also a few diaza crown-ethers have been hydroxyethylated.[3,4,5] In these latter cases the two NH-functions were well separated from each other in the molecule (1,7- or 1,10-relationship).

It was observed in this laboratory[6] that closely related 12-ring compounds having NH-functions in 1,4-relationship to each other were singularly unreactive. Both 1-oxa-4,7,10-triazacyclododecane *2a* (=triaza-12-crown-4) and 1,4,7,10-tetraazacyclododecane *3a* (=tetraaza-12-crown-4) were recovered unchanged after treatment with ethylene oxide in water or methanol under conditions (pH 8—9) that have been prescribed for other amines.

Since polyamines are often isolated and stored as hydrochlorides or other salts, the amine is usually liberated for the reaction *in situ* by addition of alkali hydroxide. We therefore examined whether the reason for the failure could be that the correct pH for the reaction had not been found. If easy ring opening should require protonation of ethylene oxide, the necessity of having free amine present could result in a narrow pH window for the reaction. However, it was soon found for simple amines (morpholine, diethylamine, diethanolamine, piperazine) that any lowering of the pH by mineral acid decreased the reaction rate. Thus, using morpholine as a model in water at 0 °C, as much as 85 % hydroxyethylation was obtained after 0.5 h, whereas only 47 % had reacted if morpholine was first half-neutralized with HCl. In methanol (no HCl) only 14 % was hydroxyethylated after ½ h. This shows that protonation is not necessary to activate ethylene oxide for ring opening, at least not when water is the solvent.

The experiments further suggested that deactivation of the amine by partial protonation could be the reason for our failure to hydroxyethylate tetraaza-12-crown-4. The tetrahydrochloride was therefore dissolved in concentrated KOH solution and the liberated tetraamine extracted salt-free with $CHCl_3$. Now indeed a remarkably ready reaction with ethylene oxide in water took place, which was finished within less than 2 h at 0 °C. Water turned out to be by far the best solvent for the reaction. The low temperature is an advantage because of the volatility of ethylene oxide, but a too high concentration of ethylene oxide in water gives below 11 °C a crystalline clathrate[7-9] which makes stirring difficult. It proved essential

1   2   3

4   5   6
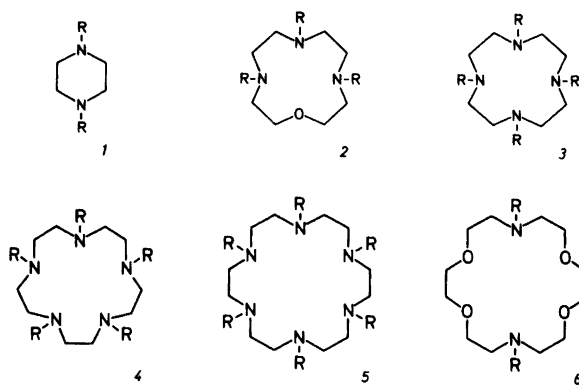
a: R = H   b: R = CH$_2$CH$_2$OH

to use only a reasonable excess (100–200 %) of the stoichiometric quantity of ethylene oxide and to follow the progress of the reaction by ^{13}C NMR spectroscopy. When the optimal reaction time is reached, the excess of ethylene oxide is simply evaporated *in vacuo*. Too long reaction time, large quantities of ethylene oxide, and too high temperature may lead to by-products arising from side-chain elongation. Also ring opening of ethylene oxide, to give ethylene glycol, and polymerization to polyethylene glycols could then be observed.

The fully hydroxyethylated polyamines of other ring sizes were also prepared. They could be isolated and purified as such by crystallization, or through formation of crystalline salt complexes, from which the ligand is liberated by pyrolysis. Otherwise, extraction with CHCl$_3$ is also effective. The fully hydroxyethylated products go preferentially into the CHCl$_3$ phase, whereas incompletely hydroxyethylated and chain-elongated products remain preferentially in the aqueous phase.

In addition to the homologous series of polyamines *1a, 3a, 4a* and *5a*, also the macrocyclic aminoethers *2a* and *6a* were hydroxyethylated under the same conditions. The results are presented in Table 1.

There are some striking features that deserve comments:

(1) When the total yields for full hydroxyethylation are converted to average yields for each reaction step (Table 1), these are not significantly different. Nevertheless, the ^{13}C NMR spectra and mass spectra of the reaction mixture, after a given conversion of the starting material, reveal that only in the case of diaza-18-crown-6 having the NH functions 1,10 to each other, are the byproducts due to elongation of side chains. In all other cases, mainly incompletely hydroxyethylated compounds make up the material that accompanies the desired final product.

(2) The average reaction time needed for each

Table 1. Hydroxyethylation of cyclic poly-amines and -aminoethers.

Starting material	Product	Reaction time Total (h)	Aver./step (h)	Isolated yield (%)	Estimated yield by NMR Total (%)	Aver./step (%)
Piperazine (*1a*)	*1b*	>4	>2	–	>79 [a]	>89
Triaza-12-crown-4 (*2a*)	*2b*	2	0.7	45	88 [a]	96
Tetraaza-12-crown-4 (*3a*)	*3b*	2	0.5	52	74 [a]	93
Pentaaza-15-crown-5 (*4a*)	*4b*	30	6	33	74 [a]	94
Hexaaza-18-crown-6 (*5a*)	*5b*	50	8	16	77 [a]	96
Diaza-18-crown-6 (*6a*)	*6b*	30	15	62	81 [b]	90

[a] Byproducts are mainly incompletely hydroxyethylated compounds. [b] Byproducts are mainly chain-elongated compounds.

step (Table 1) is particularly short for both 12-membered rings as compared with the 15- and 18-membered polyazacrowns. (The very much longer reaction time needed for diaza-18-crown-6 is due to the slowness of the second step, allowing time for side-chain elongation to occur.) This suggests an activation of the NH-function for nucleophilic attack on ethylene oxide by a second amino function ($>$NH or $>$NCH$_2$CH$_2$OH) in 4-position through five-ring hydrogen bonding within a macrocyclic structure. Such interaction could be particularly strong in 12-membered rings, considering the geometry of the well-established square [3 3 3 3] conformation of many saturated 12-ring compounds,[9] among which the tetraether [10] and a substituted tetraamine [11] are of particular relevance.

The tetra-hydroxyethylated tetraaza-12-crown-4 *3b* is an effective complexer for alkali and alkaline earth cations. These properties were already briefly reported [12] and will be dealt with in more detail later. It also forms an extremely stable monohydrate which can be sublimed unchanged *in vacuum*. The crystal structure [12] shows that the water molecule is completely encapsulated.

pH-METRIC TITRATIONS

One would expect the reactivity pattern in hydroxyethylation (Table 1) to be reflected in the relative basicity pattern of the homologous polyamine series *1a, 3a, 4a, 5a*. The pK$_a$ values for these polyamines have already been reported.[14,15,16] However, these were obtained by titrating the polyhydrochlorides with NaOH, and it was important in our case to simulate the conditions under which the hydroxyethylation experiments were actually performed and to ensure that sodium complexation of the ligands would not interfere. Water solutions of the salt-free polyamines (0.05 M) were therefore titrated pH-metrically with HCl (0.1 M).

The titration curves are given in Fig. 1. The inflection points, especially at high pH, do not coincide exactly with the equivalence points, as to be expected when precautions are not taken to exclude CO$_2$. Otherwise, the curves agree well with reported pH-values,[14,16] except that the reported [15] values of pK$_a$=10.85 and 9.65 for the first steps of the pentaamine *4a* appear clearly higher. It is possible that this may be due to the fact that the ionic strength was in this case [15] adjusted by addition of NaClO$_4$.

As seen from Fig. 1, the diamine *1a* (piperazine) shows the expected normal amine basicity in the first neutralization step, and retains moder-
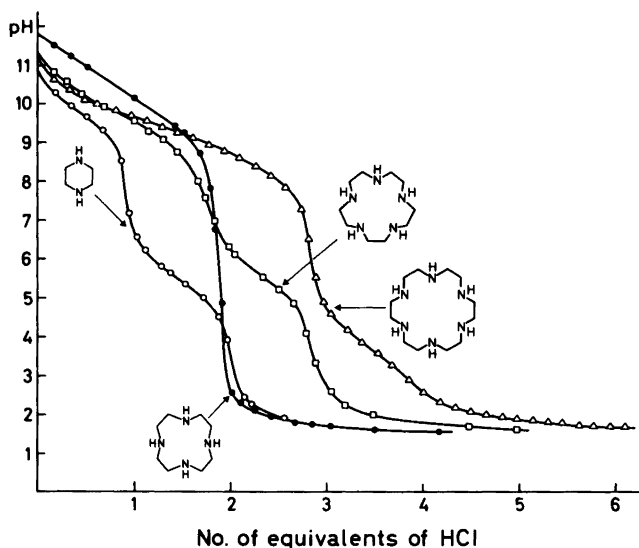

Fig. 1. Neutralization curves for 0.05 M aqueous solutions of the cyclic polyamines *1a* (○), *3a* (●), *4a* (□) and *5a* (△), using 0.1 M HCl.
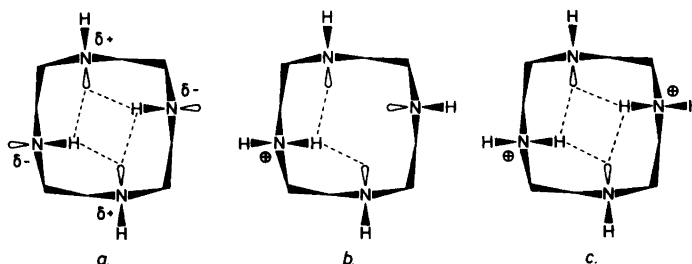
Fig. 2. Proposed conformations and hydrogen-bond interactions for tetraaza-12-crown-4 in (a) the non-protonated, (b) the mono-protonated, and (c) the di-protonated form.

ate basicity in the second step. The tetraamine *3a* clearly represents the extreme case, its first step being more basic than that of any of the other ring sizes, the second being also very basic, whereas the two last steps are hardly observable at all. (Also the tetra-hydroxyethyl derivative *3b* shows this sharp reduction of basicity after diprotonation.[17]) The pentaamine *4a* and the hexaamine *5a* show similar trends, although more weakly, with the two, respectively three, first steps much more basic than the later steps.

We suggest the following interpretation: The free tetraaza-12-crown-4 *3a* has two intramolecularly hydrogen-bonded NH hydrogens (Fig. 2a) reinforcing the basicity (and nucleophilicity) of these nitrogens. The monoprotonated species (Fig. 2b) will have the internal ammonium hydrogen in interaction with the two adjacent NH lone pairs. The lone pair of the NH function in 1,7 relation is of course too distant to accept a genuine hydrogen-bond interaction, but one would at least not expect the NH hydrogen to be directed towards the charge of the ammonium group. Thus, there is no accessible lone pair for nucleophilic reactivity, and it can be understood that hydroxyethylation can not occur at pH 8−9, where the non-protonated species is absent. The diprotonated species (Fig. 2c) will engage both remaining *N*-lone pairs in hydrogen bonding, and further protonation becomes impossible without a complete conformational change.

Similar considerations explain why hexaaza-18-crown-6 *5a* forms so readily the triprotonated species, two adjacent NH groups being needed for each proton. The more lax conformational situation in this larger ring allows, although with greater difficulty, a fourth protonation step.

Pentaaza-15-crown-5 *4a*, finally, can relatively easily accept a third proton after the two first steps, as otherwise the fifth NH-group would be left over.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on Jeol FX60 or FX100 instruments. Mass spectra were recorded on a Micromass 7070 F spectrometer with chemical ionization using isobutane. The pH-metric titrations were monitored with a Metrohm Herisau pH-meter E 396 B, using a glass electrode with a saturated calomel electrode as reference.

Tetrakis-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane. The tetratosyl derivative of the tetraamine *3a* was synthesized according to Richman and Atkins,[18] detosylated in sulfuric acid and isolated as the tetrahydrochloride.[18] The free amine *3a* was obtained by dissolution in 1 M aqueous KOH and extraction with chloroform, m.p. 113−115 °C, after sublimation 119−120 °C (in contrast with reported[19] m.p. 35 °C). ^{13}C NMR in H$_2$O: δ (ref. CH$_3$CN=1.3) 45.2. MS, CI (isobutane): 173 (M+1). Found: C, 55.0; H, 11.1. C$_8$H$_{20}$N$_4$ requires: C, 55.8; H, 11.7. Test for chloride ion was negative.

The tetraamine (0.97 g) was dissolved in water (10 ml) at 0 °C. A solution of ethylene oxide (2.35 g) in water (2 ml) cooled to 0 °C was added, and the cooled mixture stirred for 2 h. The reaction was stopped by evaporation of the excess of ethylene oxide in a Rotavapor. After further concentration at room temperature, the tetrahydroxyethylated product *3b* crystallized as a monohydrate (m.p. 90−92 °C, 1.02 g=52 %). ^{13}C NMR in D$_2$O: δ (ref. CH$_3$CN=1.3) 50.3 (8 ring NCH$_2$), 56.3 (4 side chain NCH$_2$) 58.9 (4

OCH_2). MS, CI (isobutane): 349 (M+1). Found: C, 52.5; H, 10.3. $C_{16}H_{36}N_4O_4 \cdot H_2O$ requires: C, 52.4; H, 10.5.

The actual yield of *3b* is ~74 % as judged from the ^{13}C NMR spectrum of the crude reaction product.

Tris-(2-hydroxyethyl)-1-oxa-4,7,10-triazacyclo-dodecane. The triamine *2a* was prepared according to Rasshofer et al.[20,21] and isolated as the free base in the same way as described for *3a*. Hydroxyethylation was carried out as before with a solution of the triamine (1.23 g) and ethylene oxide (2.90 g) in water (11 ml) for 2 hours. The product was an oil. ^{13}C NMR in D_2O: δ (ref. CH_3CN=1.3) 48.8, 49.8, 53.7, 56.8, 57.5, 59.3 (×2), 69.8. MS, CI (isobutane): 306 (M+1).

A crystalline complex with NaSCN was prepared from ethanol solution (m.p. 154−170 °C, 1.25 g=45 %). ^{13}C NMR in D_2O: δ (ref. CH_3CN=1.3) 49.8 (×2), 51.9, 55.6, 56.1, 58.9 (×2), 66.9. MS, CI (isobutane): 306 (M+1 of ligand). Found: C, 46.7; H, 8.1. $C_{15}H_{31}N_4O_4$ SNa requires: C, 46.6; H, 8.1.

The actual yield of *2b*, as judged from the ^{13}C NMR spectrum of the crude reaction product, is ~88 %.

Pentakis-(2-hydroxyethyl)-1,4,7,10,13-penta-azacyclopentadecane. The pentaamine *4a* was prepared[18] and isolated by ion exchange of the tetrahydrochloride using Dowex 1 (OH⁻), a strong-base anion exchanger. The free amine (0.10 g) was dissolved in water (2.6 ml) at 0 °C, and ethylene oxide (0.23 ml), precooled to −78 °C, added. After stirring for 30 h at 0 °C, the excess of ethylene oxide was evaporated in a Rotavapor. The ^{13}C NMR spectrum showed that the fully substituted compound *4b* was the main product, with the three expected strong ^{13}C lines in D_2O at δ (ref. CH_3CN=1.3) 50.8, 56.4 and 59.2. Distribution between chloroform and water gave a clear enrichment of *4b* in the chloroform layer and of accompanying byproducts in the water layer. An isolated yield of *4b* from the chloroform layer was 33 %, but the actual yield, estimated from the ^{13}C NMR spectrum of the crude reaction product, is ~74 %.

Hexakis-(2-hydroxyethyl)-1,4,7,10,13,16-hexa-azacyclooctadecane. The hexamine *5a* was liberated with $BaCO_3$ from the commercially available tris-dihydrosulfate. The free amine (0.10 g) was hydroxyethylated for 50 h as described for *4a*, using ethylene oxide (0.23 ml) in water (5.6 ml). The ^{13}C NMR spectrum showed that the fully substituted compound *5b* was the main product, with the three expected strong ^{13}C lines in D_2O at δ (ref. CH_3CN=1.3) 51.2, 56.0 and 59.2. Distribution between chloroform and water

gave a clear enrichment of *5b* in the chloroform layer and of accompanying byproducts in the water layer. An isolated yield of *5b* from the chloroform layer was 16 %, but the actual yield is ~77 % as estimated from the ^{13}C NMR spectrum of the crude reaction product.

Bis-(2-hydroxyethyl)-1,4,10,13-tetraoxa-7,16-diazacyclopentadecane. The free diamine *6a* (0.20 g), commercially available as "Cryptofix 2.2", was hydroxyethylated for 30 h as described for *4a*, using ethylene oxide (0.23 ml) and water (1.9 ml). Extraction with chloroform gave the pure bis-hydroxyethyl derivative *6b* (0.17 g=62 %). This compound has been prepared earlier by a different method.[4] ^{13}C NMR in D_2O: δ (ref. CH_3CN=1.3) 53.7, 56.3, 59.1, 68.8, 70.1.

The aqueous phase contained, together with an additional quantity of *6b*, (estimated total yield ~81 %) also byproducts with one and two extra $-CH_2CH_2-O-$ units in the side chains, as evidenced by mass spectrometry (CI, isobutane).

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