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Polyether-functionalised uridine as an ion receptor

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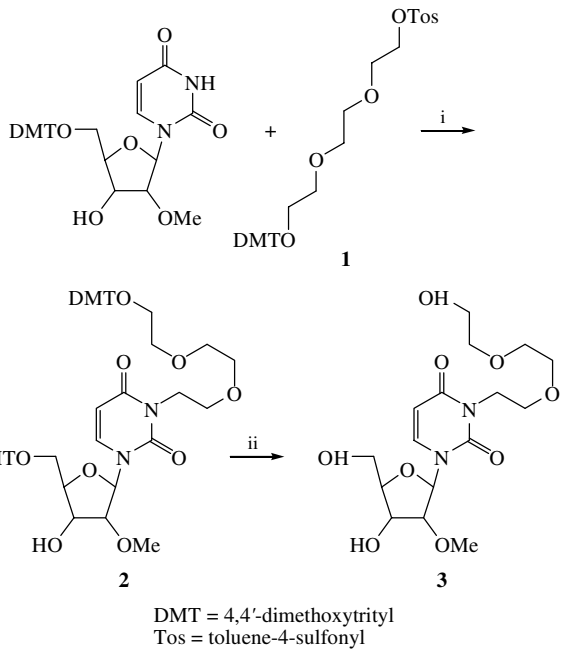
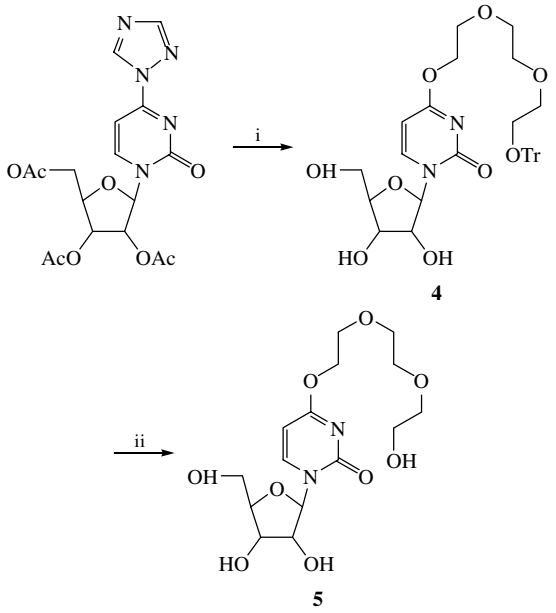
The uridine bearing triethylene glycol chain on N^3 or O^4 was synthesised, and its complexes with alkali ions were studied, revealing two ways of complexation for the N^3 derivative.

Numerous nucleoside conjugates with metal-complexing moieties were developed for various purposes. Their applications include utilization/testing as therapeutic agents,[1,2] analytical tools,[3,4] factors of nanostructure assembly[5] or artificial nucleases.[6,7] Complexing groups were attached to various parts of a nucleoside molecule at sugar (directly,[8] or *via* phosphate ester) and aglycon sites.[9] In these syntheses, the main objective was to introduce a chelator capable of complexing of bivalent or higher valence metal ions.[8,9] Little interest was devoted to the complexation of alkali metal ions. It is unlikely that these ions would exhibit particular catalytic activity, but their abundance in the cytoplasm means that if a nucleoside-bearing complexing group appears in the oligonucleotide chain, the formation of a complex will occur. The presence of such a complex will result in an additional positively charged centre in generally polyanionic oligonucleotide. It can provide an oligonucleotide with greater cellular uptake potential[10] and influence the local charge and acid-base equilibrium or protonation properties. Such local changes are closely related to the overall conformation and function of the chain. Selective ionization can serve as a way to influence the conformation and functional activity of the oligonucleotide.



Scheme 1 Synthesis of N^3-(trioxyethylene) 2′-*O*-methyl uridine **3**. *Reagents and conditions*: i, NaH, DMF, 100 °C, 6 h; ii, 80% acetic acid, room temperature, 30 min.



Scheme 2 Synthesis of O^4-(trioxyethylene) uridine **5**. *Reagents and conditions*: i, triethylene glycol monotrityl ether, DBU, dioxane, 70 °C, 12 h, then conc. ammonia–methanol (1:1), room temperature, 2 h; ii, 80% acetic acid, 100 °C, 10 min.

We synthesised nucleosides bearing complexing substituents like crown ethers and poly(oxaethylene)s. Adenosine derivatised with different crown ether-type macrocycles was reported previously.[11] It showed strong affinity to alkaline ions with selectivity in accordance with the crown size. An open-chain polyether substituent can form more versatile complexing environments for cations depending on neighbouring groups present in the vicinity of the complexing centre.

We undertook the synthesis of uridine with tri(oxaethylene) pendant substituents attached at N^3 and O^4 positions. Since the N^3–H bond easily undergoes alkyl substitution under basic conditions,[12] the first synthesis was straightforward.[13] In order to avoid concurrent alkylation of the 2′-OH position, 2′-*O*-methyluridine was used as a substrate. The primary 5′-OH group was protected as a dimethoxytrityl derivative.

Treatment of 2′-*O*-methyl-5″-*O*-dimethoxytrityl uridine with dimethoxytrityl derivative of triethylene glycol monotosylate **1** in the presence of NaH gave N^3-(3,6-dioxo-8-hydroxy)octyl derivative **2**. The detritylation of intermediate product **2** with 80% acetic acid lead to **3**. The structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy and ESI mass spectrometry.

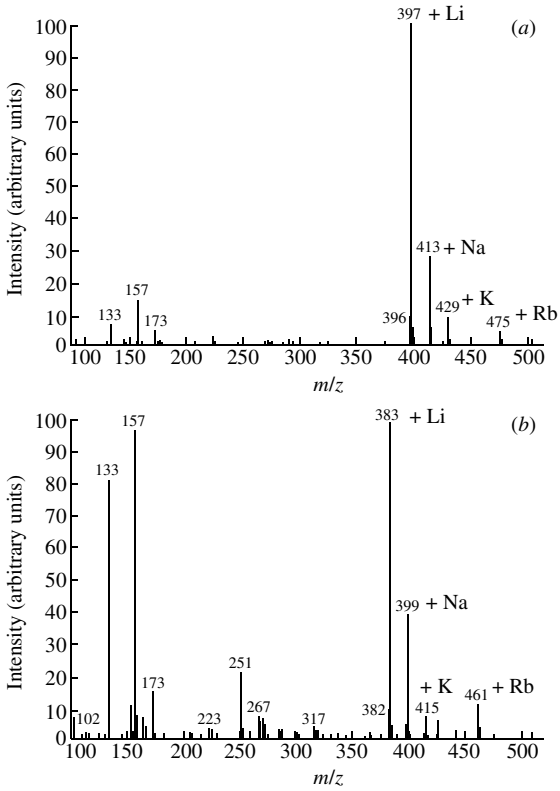


Figure 1 ESI mass spectra of (*a*) **3** and (*b*) **5** in the presence of 5 equiv. of Li^+, Na^+, K^+ and Rb^+.

Alkylation of the O^4 position was achieved according to the known route.[14] When 2′,3′,5′-tri-*O*-acetyl-4-(1,2,4-triazol-1-yl) uridine reacted with monotritylated triethylene glycol[15] in the presence of DBU, the triazolyl group was replaced by a polyether chain. The substitution was accompanied by the partial loss of acetyl protecting groups. On treatment with ammonia, desired compound **4** was obtained in 34% yield after purification by chromatography. Detritylation with acetic acid gave the final product **5**.

Both of uridine derivatives **3** and **5** demonstrated the ability to form complexes with monovalent cations (lithium, sodium, potassium and, to the lesser extent, rubidium and, very slightly, caesium).

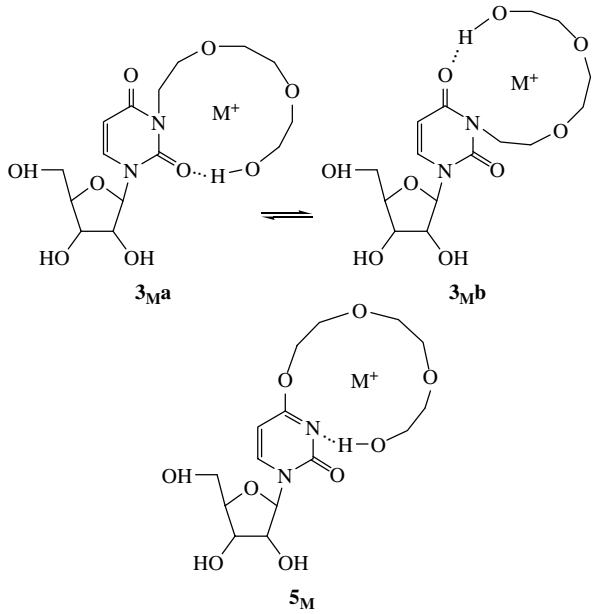


Figure 2 Possible structures of the complexes of M^+ ions with **3** and **5**.

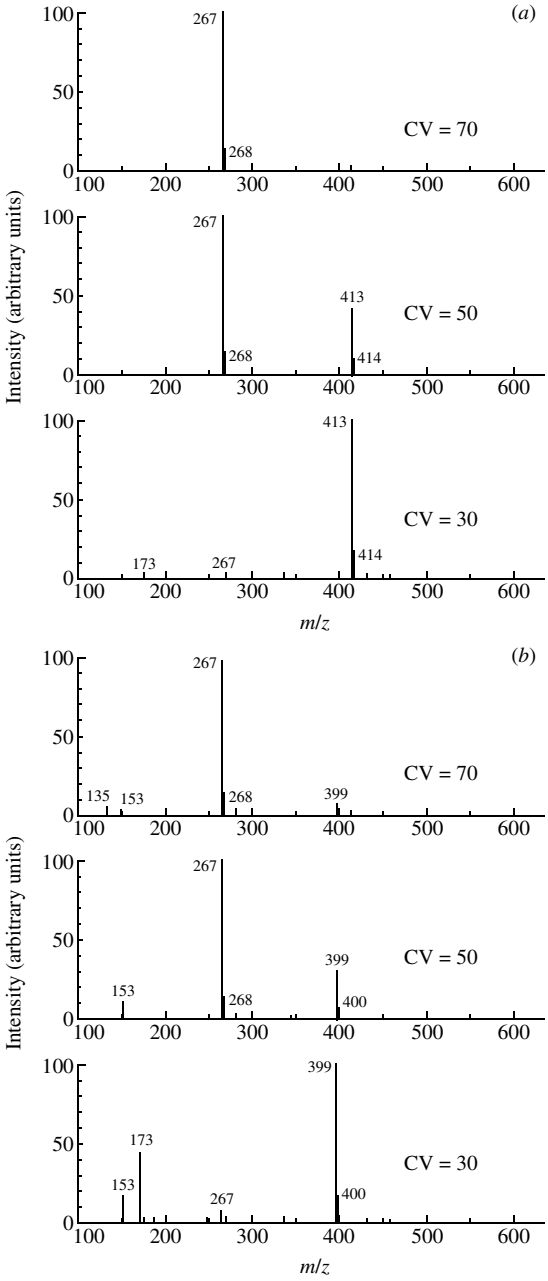


Figure 3 ESI mass spectra of (*a*) **3** and (*b*) **5** complexed with sodium at the cone voltage indicated. Peak at *m/z* 267 corresponds to the uracil with polyether chain at O^4 or N^3 (glycosidic cleavage). Peak at *m/z* 173 corresponds to triethylene glycol (uracil-polyether cleavage).

In the case of **3**, two possible arrangements of oxyethylene chain are possible, engaging either O^4 or O^2 oxygen atom as a part of the metal ion complexing cavity (tentative structures $\mathbf{3_Ma}$ and $\mathbf{3_Mb}$, Figure 2).

The possibility of exchange between two complexation sites may account for greater stability of the complex, as compared to compound **5** where only one complex structure is possible ($\mathbf{5_M}$, see Figure 2). The stability of compounds **3** and **5** depended on the place of attachment of the polyether chain, as illustrated by the ESI mass spectra of the sodium complexes at different cone voltages.[16] In the case of **3**, a greater stability of the complex resulted in fragmentation across the glycosidic bond only (*m/z* 267 corresponding to M^+_{Na} – 146) without any traces of fragmentation in the uracil-polyether part of the molecule. Contrary to this, compound **5** showed appreciable fragmentation of the glycosidic (*m/z* 267) and C^4–O (*m/z* 173 corresponding to the complex of sodium with triethylene glycol) bonds. This effect was visible even at the lowest (30 V) voltage

Table 1 Sodium-23 chemical shifts for sodium perchlorate and its mixtures with **3** or **5** at various uridine concentrations in acetonitrile solution.[a]

[Uridine]/[$NaClO_4$] ratio	^{23}Na chemical shifts/ppm	
	Uridine **3**	Uridine **5**
0:1	–6.35	
0.25:1	–5.12	–5.23
0.50:1	–4.32	–4.05
0.75:1	–4.05	–3.87
1:1	–3.89	–3.76
2:1	–3.88	–3.78

[a]Calculated lg K = 0.72±0.10 (**3**) and 0.83±0.10 (**5**).

applied. Glycosidic bond fragmentation dominated at higher (50 and 70 V) voltages, leaving no unfragmented compound at 70 V or higher.

Acetonitrile solutions of **3** and **5** were titrated with sodium perchlorate and progress of the complexation followed with ^{23}Na NMR spectra. The sodium-23 chemical shift gradually changed with increasing Na^+/ligand ratio, reaching plateau at the 1:1 proportion. The results (Table 1) evidence that the 1:1 complexes between Na^+ and uridines are formed in acetonitrile solution.

An analogous experiment in water could not give the answer due to negligible changes in the chemical shift of sodium complexed with water *vs.* polyether. We are convinced, nevertheless, that the results in a polar solvent (acetonitrile) proved the strong affinity of the uridine derivative to sodium ions.

The above data clearly indicate that uridine–polyether conjugates are efficient ion receptors, which can serve as a way to introduce a local positive charge into the oligonucleotide chain.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2007.01.009.

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