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Preparation and reaction of uracil substituted cyclen and cyclam: formation of tricyclic guanidinium and dihydroimidazolium salts

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ABSTRACT

Di-uracil substituted cyclen derivatives were prepared by the reaction of cyclen with 6-chloro-1-methyluracil or 6-chloro-1,3-dimethyluracil. The reaction of cyclam with 6-chloro-1,3-dimethyluracil gave a similar di-uracil substituted cyclam. The 1,7-di-uracil substituted cyclen was converted to the tricyclic guanidinium salt and acylurea upon heating in DMSO in the presence of weak acid. The 1,8-di-uracil substituted cyclam gave a tricyclic dihydroimidazolium salt under the same conditions. These reactions can be explained by an intramolecular uracil ring-breaking reaction mechanism.

1. Introduction

Azamacrocycles have been studied for a number of reasons ranging from host–guest chemistry to biological and medical use.[1] Cyclen (1,4,7,10-tetraazacyclododecane) is one of the most important macrocycles for use as metal chelators.[2,3] Their derivatives have been widely used for the synthesis of useful materials, such as MRI constant reagents,[4,5] protein active site mimics,[6] supramolecular building units,[7,8] and so on. Azamacrocycles provide a fruitful chemistry because of their selective complexation with metal cations as well as the unique interaction of the metal–azamacrocycle complex with other molecules. Intermolecular interactions between a zinc–cyclen complex and a nucleobase,[9] as well as those within the cyclen–nucleobase conjugates,[10] have already been reported. In these reported systems, the two units, a cyclen and a nucleobase, are present in a different molecule or linked by a phenylene dimethylene group, respectively. In the latter case, cyclen–uracil conjugates form a unique and stable complex with a zinc cation to afford supramolecular structure, which can cleave plasmid DNA. The relationship between the structure and the function of these molecules is not very clear, and a variety of cyclen–uracil conjugates need to be synthesized and tested. Contrary to these flexible systems, there have been no reported cyclen–nucleobase conjugates in which the two components are directly attached to each other.

In our study to develop new supramolecular building units, we focused on the sterically-restricted cyclen–nucleobase conjugates because this steric restriction can cause a change in the binding mode, leading to new properties. In addition to our interest in supramolecular behavior of these molecules, they are expected to give us a clue to explain the structure–function relationship of aforementioned cyclen–uracil conjugates that can cleave plasmid DNA.[10] We also focused on the ring size effect because a subtle change in the ring size sometimes causes considerable effects in their chemical properties, especially in the host–guest chemistry. Cyclam (1,4,8,11-tetraazacyclotetradecane) is a good alternative to cyclen because it has two more carbon atoms.

Unfortunately, it has not been possible to obtain any evidence suggesting a supramolecular interaction as yet. However, newly synthesized uracil substituted cyclen and cyclam gave exotic tricyclic guanidinium and dihydroimidazolium salts by heating in the presence of weak acid. Here we report the preparation and unique reactions of uracil substituted cyclen and cyclam.

2. Results and discussion

The introduction of uracil derivatives on to the nitrogen atoms in cyclen **1A** (n=2) and cyclam **1B** (n=3) were carried out by the reaction of **1** with 6-chloro-1-methyluracil (**2a**) or 6-chloro-1,3-dimethyluracil (**2b**) (Scheme 1).

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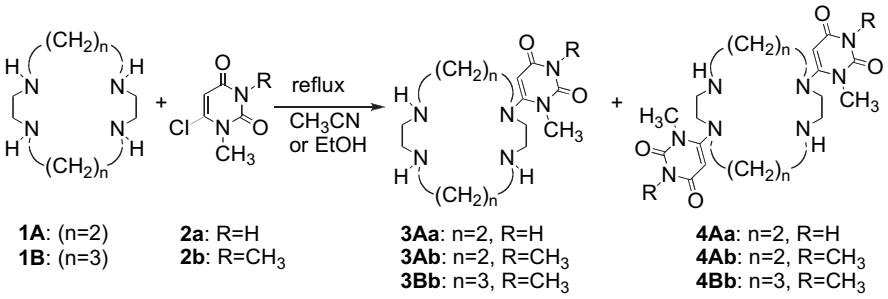


Scheme 1. Synthesis of mono- and di-uracil substituted azamacrocycles.

The reaction of cyclen **1A** with 2 equiv of **2a** afforded a mono-substituted product (**3Aa**) and a di-substituted product (**4Aa**) in 11% and 13% yield, respectively (Table 1). This reaction gave a complex mixture containing both starting material and byproducts together with their target compounds. The isolation of **3Aa** and **4Aa** required a tedious recrystallization-washing process resulting in low yields of the two products. The reaction of cyclen **1A** with 1 equiv of **2b** gave the mono-substituted product (**3Ab**) in 42% yield, whereas the same reaction, this time with 2 equiv of **2b**, afforded a di-substituted product (**4Ab**)[11] in 61% yield. A methyl group on uracil in the 3-position made the isolation of products practicable. However, it was not possible to obtain the tri- or tetra-substituted derivatives probably due to steric congestion on the cyclen ring. The reaction of cyclen **1A** with 6-chlorouracil yielded only a complex mixture. A cyclam–uracil conjugate was also prepared in the same manner, but this time, only the dimethyluracil derivative **2b** was used because the purification of a dimethyluracil substituted cyclam was expected to be easier than the purification of a monomethyl derivative. Another reason why only **2b** was used for the synthesis of the cyclam derivative was that both 1-methyl and 1,3-dimethyluracil derivatized cyclams were expected to have similar reactivity according to the results obtained using cyclen derivatives (vide infra). In this reaction, only the di-uracil substituted cyclam **4Bb** was obtained, the yield of which increased with increasing amount of uracil derivative used. No mono-substituted cyclam **3Bb** was obtained, probably because the cyclam ring has two more carbon atoms compared with cyclen. The larger ring structure is considered to make the second attack on the cyclam ring easier. A UV/Vis spectroscopy study was conducted to estimate the intramolecular uracil–uracil stacking interaction of compound **4A**. The absorption maxima of **3Aa** (λ_{max}: 281.5 nm) and **4Aa** (λ_{max}: 282.5 nm) in water showed only a small difference indicating that the two uracil groups in **4Aa** are not efficiently stacked in aqueous solution.

Table 1

1[a]	2[b]	Molar ratio(**2**/**1**)	Yield (%)	
			3	**4**
A	**a**	2	11	13
A	**b**	1	42	—
A	**b**	2	—	61
B	**b**	1	—	9
B	**b**	2	—	31
B	**b**	5	—	65

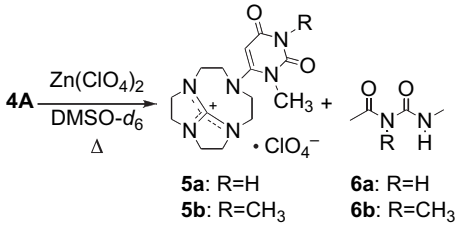
[a] **A**: n=2, **B**:n=3.
[b] **a**:R=H, **b**:R=CH_3.

Complex formation with zinc ions is one of the most attractive events among the metal chelating chemistry of azamacrocycles.[12] To investigate the cyclen–zinc interaction in our system, a ^{1}H NMR analysis in DMSO-d_6 was conducted in the presence and absence of zinc perchlorate.

In the ^{1}H NMR spectra of **3Aa** and **3Ab**, several new peaks appeared, which grew with increasing amount of zinc perchlorate. This change is probably due to the complex formation of zinc with cyclen. An intramolecular interaction between zinc and N1 in pyrimidine is thought to be difficult to achieve because of the steric congestion caused by the methyl group on the N1 position. Another possible explanation for the observed change in the ^{1}H NMR spectra can be derived from the intermolecular interaction that causes dimerization or oligomerization. This possibility is inspired by Kimura and Aoki's work, which shows that the zinc–cyclen complex has a high affinity for uracil by forming a zinc–N interaction at the N3 position in the uracil.[9] In our system, the effect of this intermolecular interaction is not important, because both **3Aa** with a free NH group and **3Ab** with an NCH_3 group at the N3 position on the uracil ring showed similar changes in the ^{1}H NMR spectra.

When zinc perchlorate was added into the NMR samples of **4Aa** and **4Ab** in the range of 0.1–3 equiv, the ^{1}H NMR spectra showed only a small change in chemical shift. This result indicates that compounds **4A** are not a good host molecule for zinc cations, because of the steric congestion caused by the two uracil substituents on the cyclen ring. Weak complexation of **4A** with zinc can also be explained by the fact that only two nitrogen atoms in the cyclen ring are available for coordination to zinc because two nitrogen atoms attached with uracil substituents hardly coordinate to zinc cation.[13] An X-ray crystallographic analysis of a single crystal prepared from a mixed solution of **4Ab** and zinc perchlorate gave an ammonium salt of **4Ab** without a zinc ion accommodated in the azamacrocycle (data not shown), indicating a poor host–guest chemistry.

VT ^{1}H NMR measurements (up to 80 °C) of **4Aa** in the presence of a zinc salt showed only a slight change in chemical shift, and the profile of the spectra was almost the same as that measured at room temperature. During the VT NMR experiments, we noticed that new signals appeared upon prolonged heating at 80 °C. The reaction of both **4Aa** and **4Ab** in DMSO-d_6 in the presence of 1 equiv of zinc perchlorate at 120 °C was monitored by ^{1}H NMR spectroscopy. The ^{1}H NMR spectral change showed that compounds **4Aa** and **4Ab** were almost quantitatively converted to a tricyclic guanidinium salt **5** and acylurea **6** (isolated yields of **5a** and **5b** are 97% and 64%, respectively) as shown in Scheme 2. The structure of **5a** was confirmed by X-ray crystallographic analysis (Fig. 1).



Scheme 2. Reaction of **4Aa** and **4Ab** upon heating in the presence of zinc perchlorate.

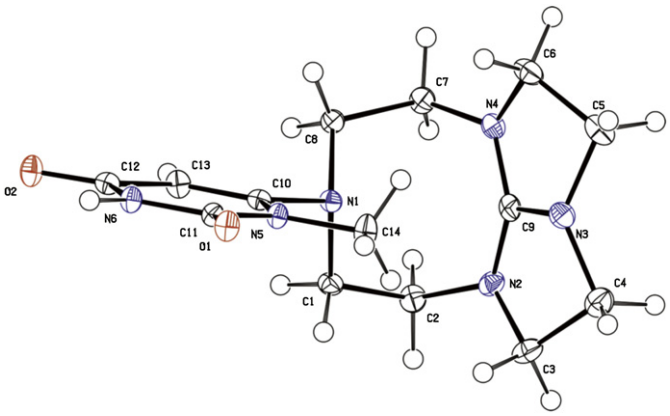


Figure 1. ORTEP drawing of guanidinium salt **5a**. A perchlorate ion was omitted for clarity.

In the present reaction, a guanidinium moiety was formed with a loss of one of the uracil groups on the cyclen ring in **4A**, accompanied by the formation of acylurea. To obtain insights into the requirement for this reaction, a number of control experiments were carried out. Simple heating of **4Aa** in DMSO-d_6 at 120 °C without zinc perchlorate did not show any change in the ^{1}H NMR spectrum, indicating that a zinc ion is necessary for this reaction. Although the addition of zinc perchlorate into a mixed solution of cyclen and 1-methyluracil in DMSO-d_6 caused a change in the ^{1}H NMR spectrum, due to the complex formation of zinc–cyclen with uracil, no reaction was observed after heating of this sample at 120 °C. This result suggests that a uracil unit must be attached directly to the nitrogen atom on cyclen for the present reaction. A 0.5 equiv of zinc perchlorate compared with **4Aa** was enough to complete this reaction, indicating that one zinc ion could convert two **4Aa** compounds to the guanidinium salt (Fig. 2 (a) and (b)). While the use of more than 0.5 equiv of zinc perchlorate caused no harmful effect in this reaction, the use of less than 0.5 M equivalents of zinc perchlorate could not complete the reaction. The whole reaction can be described as follows:

$$2\cdot\mathbf{4Aa} + Zn(ClO_4)_2 + 2H_2O \rightarrow 2\cdot\mathbf{5a} + 2\cdot\mathbf{6a} + Zn(OH)_2$$

The same result was obtained when compound **4Ab** was heated under the same reaction conditions.

The present reaction of **4Aa** in DMSO-d_6 with a few drops of D_2O showed the involvement of water in this reaction (Fig. 2(c)). Deuterium atoms were incorporated into the methyl group in an acetyl position in acylurea **6a** (1.98 ppm). A control experiment showed that no H–D exchange occurred at the acetyl position of **6a** under the same conditions. We also noticed that the integration of the proton signal associated with the C5 position of uracil in product **5a** (5.24 ppm) also decreased. A H–D exchange at the C5 position, as well as the incorporation of D atoms into acylurea **6a**, must provide a clue to understand the reaction process.

We also confirmed that no reaction occurred after heating of **4Aa** with zinc hydroxide. This result means that zinc hydroxide, an expected byproduct of this reaction, is not involved in the formation of **5a**.

Tricyclic guanidinium salts or tricyclic orthoamides were prepared by the reaction of cyclen with dimethylformamide dialkyl acetal[14–17] or ethylorthocarbonate.[18,19] A similar reactive intermediate must exist in the present reaction. We believe that the reaction starts with intramolecular nucleophilic addition of the nitrogen atom in the cyclen ring at the C6 position in uracil. No reaction occurred from the simple heating of **4A** in DMSO-d_6, suggesting that this reaction requires a proton donor to proceed. A zinc ion can provide a proton via Zn^{2+}-bound H_2O. As a result, compound **4A** forms an ammonium salt from which we could obtain a single crystal (vide supra).

Our hypothesis is that compound **4A** itself does not have a good proton source to complete the reaction after the initial nucleophilic

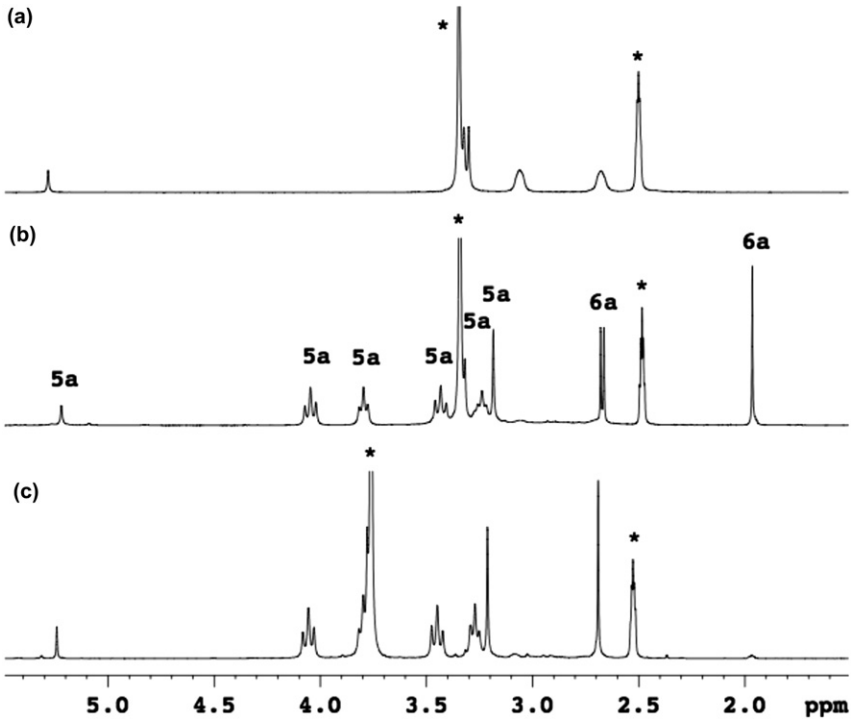
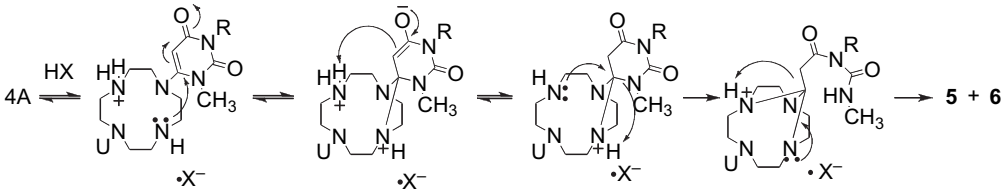
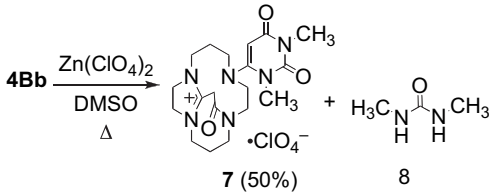


Figure 2. ^{1}H NMR spectra of (a) **4Aa**, (b) **4Aa** after reaction with 0.5equiv of zinc perchlorate, (c) **4Aa** after reaction with 0.5 equiv of zinc perchlorate in the presence of D_2O. Asterisk (*) indicates signals of DMSO and H_2O.



Scheme 3. Proposed reaction mechanism for the reaction of **4A** in the presence of weak acid. **U** denotes uracil substituents.



Scheme 4. Reaction of **4Bb** upon heating in the presence of zinc perchlorate.

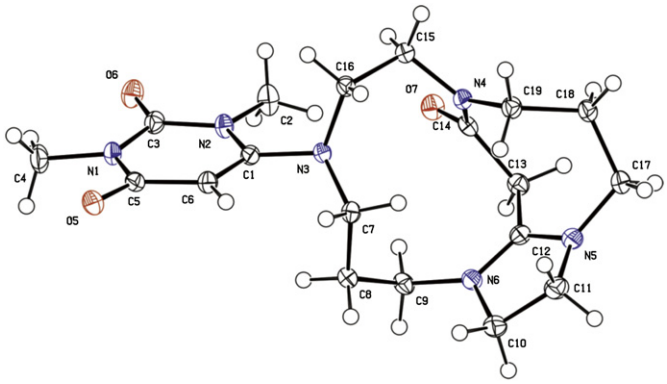


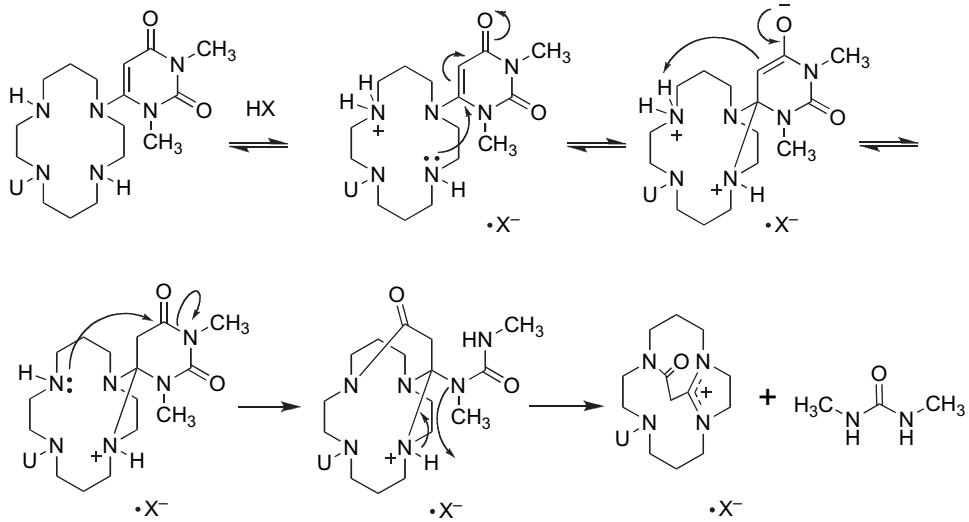
Figure 3. ORTEP drawing of dihydroimidazolium salt **7**. A perchlorate ion was omitted for clarity.

addition, whereas the di-ammonium ion of **4A** lacks a good nucleophile. Only a mono-ammonium ion can possess both a nucleophilic nitrogen atom and a good proton donor (ammonium ion) in close vicinity around the C6 position in uracil. Based on this hypothesis, the present reaction does not always require a zinc ion, but requires a weak proton donor to produce mono-ammonium ions. This prediction was confirmed by a series of reactions in the presence of several acids. The reaction with ammonium chloride, acetic acid, and barbituric acid in DMSO proceeded well, whereas the use of hydrochloric acid gave only a complex mixture. Our proposed reaction mechanism is depicted in Scheme 3.

The reaction remains in equilibrium until one of the uracil rings in **4A** opens. In this mechanism, H–D exchange at the C5 position of the uracil ring occurs during the protonation of an enolate intermediate. This H–D exchange leads to the incorporation of deuterium in both the C5 position of uracil in **5** and the acyl methyl position in **6**, being consistent with the results shown in Figure 2(c).

With regards to the pyrimidine nucleotide metabolism in eukaryotes, the ring-opening reaction is achieved by hydrolysis of the amide bond between the N3 and C4 positions of the dihydropyrimidine ring. This same bond breaks by the reaction of a pyrimidine nucleobase with hydrazine in the Maxam–Gilbert sequencing method. In the present reaction, the C6 position in the uracil ring is attacked twice by the nitrogen of the cyclen resulting in the cleavage of two of the bonds (N1–C6 and C5–C6) in the uracil. The difference in the reaction mode is explained when it is considered that the nucleophilic nitrogen atoms in cyclen are restricted to the proximity of the C6 position of uracil and hardly approach the carbonyl carbon. The C5–C6 bond cleavage in the pyrimidine ring is unique in this compound.

The importance of the steric restriction effect was also confirmed when an azamacrocycle having a slightly bigger ring size was used. Although a similar reaction was observed to take place when the cyclam–uracil conjugate **4Bb** was used instead of cyclen–uracil derivatives **4Aa** and **4Ab** (Scheme 4), the nitrogen on the azamacrocycle attacked the uracil at a different position. The product this time was the dihydroimidazolium salt **7**, the structure of which was determined by X-ray crystallographic analysis (Fig. 3). We also confirmed by ^{1}H NMR that dimethylurea **8** was formed after the reaction.



Scheme 5. Proposed reaction mechanism for the reaction of **4Bb** in the presence of weak acid. **U** denotes uracil substituents.

The plausible reaction mechanism is shown in Scheme 5. To confirm the reaction mechanism, we tried the same experiment for the cyclen–uracil derivative **4A**. The same reaction of **4Bb** shown in Scheme 4 occurred with barbituric acid as the weak acid instead of zinc perchlorate. When D_2O was added to the reaction mixture in the NMR sample tube, the integral of the proton signal due to H5 in the uracil ring as well as the methylene next to the dihydroimidazolium ring were diminished. These results are consistent with the reaction mechanism shown in Scheme 5. The difference in products between the cyclen and cyclam derivatives was considered as follows. Although the first nucleophilic attack occurred at the C6 position in the uracil ring in both cases, the second attack took place at a different carbon atom. The C6 carbon was attacked by the nitrogen atoms in the cyclen, whereas the C4 carbonyl carbon was attacked in the cyclam derivatives. This is because the additional carbon in the cyclam ring compared with the cyclen ring provides enough flexibility for the azamacrocycle to attack the C4 carbon in the uracil ring.

3. Conclusion

In summary, we have synthesized uracil derivatized azamacrocycles. The reaction of di-substituted cyclen and cyclam in the presence of weak acid gave tricyclic guanidinium and dihydroimidazolium salt together with urea, respectively. The difference in the products was due to the ring size of azamacrocycles. Although host–guest chemistry between azamacrocycles and metal cations often depends on the ring size of the macrocycles, this article shows that the reaction of azamacrocycle derivatives also depends on the subtle change in the ring size.

4. Experimental

4.1. General methods

Melting points were determined on a Yanaco micro melting point apparatus. All melting points were uncorrected. Preparative gel permeation chromatography was performed by LC-908 (Japan Analytical Industry) with a JAIGEL GS-310 column with MeOH or JAIGEL 1H+2H columns with $CHCl_3$ as solvent. UV–vis spectra were recorded on a HITACHI U-3010 spectrophotometer. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$, DMSO-d_6, CD_3OD, or D_2O with a JEOL ECP 400 or Bruker Avance 300 spectrometer using tetramethylsilane as an external standard. Elemental analyses were performed by the Instrument Analysis Center of School of Pharmaceutical Sciences, Toho University.

4.2. 1-Methyluracil-6-yl-cyclen (3Aa) and 1,7-bis(1-methyluracil-6-yl)-cyclen (4Aa)

A solution of cyclen (1.7248 g, 10.01 mmol) and 6-chloro-1-methyluracil[20] (3.2110 g, 20.00 mmol) in ethanol (40 ml) were stirred under reflux for 2 h. The suspension was filtered and the precipitate was washed with hot solvent (water/ethanol=1:1). The residual solid was dried under reduced pressure to afford **4Aa** (0.5594 g, 1.331 mmol, 13.3%). From the filtrate derived from reaction mixture, white precipitates were formed. After filtration, the precipitates were washed with hot ethanol, hot acetonitrile and then dried under reduced pressure to afford **3Aa** (0.3323 g, 1.121 mmol, 11.2%). Compound **3Aa**: white crystals. Mp: 198.0–199.0 °C; ^1H NMR (300 MHz, D_2O): δ 2.99 (m, 8H), 3.05 (t, J=6.0 Hz, 4H), 3.25 (t, J=6.0 Hz, 4H), 3.40 (s, 3H), 5.55 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ 32.3 (q), 43.5 (t), 44.2 (t), 45.1 (t), 48.7 (t), 91.2 (d), 153.6 (s), 161.9 (s), 166.1 (s); UV/VIS (H_2O), λ_{max} 281.5 (ε 11,000) nm. Compound **4Aa**: white crystals. Mp: 261.0–262.5 °C; ^1H NMR (300 MHz, D_2O): δ 2.89 (t, J=6.0 Hz, 8H), 3.25 (t, J=6.0 Hz, 8H), 3.35 (s, 6H), 5.50 (s, 2H); ^{13}C NMR (75 MHz, D_2O): δ 33.0 (q), 47.5 (t), 50.4 (t), 92.5 (d), 154.3 (s), 163.8 (s), 166.9 (s); UV/VIS (H_2O), λ_{max} 282.5 (ε 27,200) nm. Anal. Calcd for $C_{18}H_{28}N_8O_4$: C, 51.41; H, 6.71; N, 26.65. Found: C, 51.16; H, 6.66; N, 27.11%.

4.3. 1,3-Dimethyluracil-6-yl-cyclen (3Ab)

A solution of cyclen (0.8631 g, 5.010 mmol), 6-chloro-1,3-dimethyluracil (0.8772 g, 5.025 mmol), and sodium carbonate (0.5231 g, 4.936 mmol) in acetonitrile (25 ml) was stirred under reflux for one day. After the filtration of precipitates, the filtrate was concentrated under reduced pressure. The residue was purified by preparative GPC to afford **3Ab** (0.6440 g, 2.077 mmol, 41.5%). Compound **3Ab**: white crystals. Mp: 104.5–106.0 °C; ^1H NMR (300 MHz, D_2O): δ 2.66 (t, J=5.8 Hz, 4H), 2.77 (m, 8H), 3.13 (t, J=5.8 Hz, 4H), 3.21 (s, 3H) 3.43 (s, 3H), 5.61 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ 27.9 (q), 33.0 (q), 44.1 (t), 44.8 (t), 45.7 (t), 49.0 (t), 90.6 (d), 154.1 (s), 160.8 (s), 165.7 (s). Anal. Calcd for $C_{14}H_{26}N_6O_2\cdot 1.5H_2O$: C, 49.83; H, 8.66; N, 24.91. Found: C, 50.30; H, 8.23; N, 24.71%.

4.4. 1,7-Bis(1,3-dimethyluracil-6-yl)-cyclen (4Ab)

A solution of cyclen (0.6088 g, 3.534 mmol), 6-chloro-1,3-dimethyluracil (1.3094 g, 7.500 mmol), and sodium carbonate (0.7451 g, 7.030 mmol) in acetonitrile (20 ml) was stirred under reflux for one day. After a thermal filtration, white precipitate **4Ab** (0.9648 g, 2.154 mmol, 61.0%) was formed from the filtrate. Compound **4Ab**: white crystals. Mp: 223.0–224.5 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.68 (t, J=6.0 Hz, 8H), 3.07 (t, J=6.0 Hz, 8H), 3.11 (s, 6H), 3.60 (s, 6H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.2 (q), 32.7 (q), 46.2 (t), 49.5 (t), 88.9 (d), 152.7 (s), 159.5 (s), 162.2 (s). Anal. Calcd for $C_{20}H_{32}N_8O_4$: C, 53.55; H, 7.19; N, 24.99. Found: C, 53.43; H, 7.10; N, 25.12%.

4.5. 1,8-Bis(1,3-dimethyluracil-6-yl)-cyclam (4Bb)

A solution of cyclam (0.6007 g, 2.998 mmol), 6-chloro-1,3-dimethyluracil (2.5859 g, 14.81 mmol), and sodium carbonate (1.5925 g, 15.02 mmol) in acetonitrile (40 ml) were stirred under reflux for one day. The reaction mixture was cooled with ice-water bath and the precipitate was filtered. This solid was dissolved in $CHCl_3$ (50 ml) and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure. The resulting solid was dissolved in MeOH (40 ml), white precipitate was formed to afford **4Bb** (0.9212 g, 1.933 mmol, 64.5%). Compound **4Bb**: white crystals. Mp: 245.5–247.5 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (m, 4H), 2.59 (t, J=5.4 Hz, 4H), 2.95 (s, 8H), 3.24 (t, J=5.8 Hz, 4H), 3.34 (s, 6H), 3.50 (s, 6H), 5.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9 (t), 27.8 (q), 32.0 (q), 43.8 (t), 46.1 (t), 48.0 (t), 54.8 (t), 90.8 (d), 153.1 (s), 158.3 (s), 163.1 (s). Anal. Calcd for $C_{22}H_{36}N_8O_4$: C, 55.44; H, 7.61; N, 23.51, Found: C, 55.03; H, 7.49; N, 23.11%.

4.6. 10-(1-Methyluracil-6-yl)-1,4,7,10-tetraazatricyclo[5.5.1.$0^{4,13}$]tridecanium perchlorate (5a)

A mixed solution of **4Aa** (0.0529 g, 0.126 mmol) in DMSO (1 ml) and 0.50 M zinc perchlorate in DMSO (0.25 ml, 0.13 mmol) was heated at 120 °C for 1 h. After cooled to room temperature, chloroform was added to the reaction mixture. Filtration of the precipitates afforded **5a** (0.0497 g, 0.125 mmol, 97%). Compound **5a**: white crystals. Mp: 292.0–293.0 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 3.19 (s, 3H), 3.24 (t, J=5.7 Hz, 4H), 3.44 (t, J=7.5 Hz, 4H), 3.80 (t, J=5.7 Hz, 4H), 4.05 (t, J=7.5 Hz, 4H), 5.23 (s, 1H), 11.13 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.0 (q), 42.1 (t), 45.2 (t), 51.0 (t), 55.5 (t), 91.1 (d), 151.9 (s), 162.4 (s), 162.9 (s), 163.9 (s).

4.7. 10-(1,3-Dimethyluracil-6-yl)-1,4,7,10-tetraazatricyclo[5.5.1.0^{4,13}]tridecanium perchlorate (5b)

A mixed solution of **4Ab** (0.0569 g, 0.127 mmol) in DMSO (1 ml) and 0.50 M zinc perchlorate in DMSO (0.25 ml, 0.13 mmol) was heated at 120 °C for 1 h. After the solvent was evaporated under reduced pressure, water and ether was added to the residue. The aqueous layer was evaporated under reduced pressure and the residue was washed with cold methanol to afford **5b** (0.0339 g, 0.0807 mmol, 63.6 %). Compound **5b**: white crystals. Mp: 232.0–233.0 °C; ^{1}H NMR (300 MHz, D_2O): δ 3.22 (s, 3H), 3.35 (s, 3H), 3.40 (t, J=6.0 Hz, 4H), 3.47 (t, J=7.8 Hz, 4H), 3.81 (t, J=6.0 Hz, 4H), 4.08 (t, J=7.8 Hz, 4H), 5.48 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ 27.9 (q), 33.2 (q), 42.6 (t), 45.2 (t), 51.0 (t), 55.7 (t), 90.5 (d), 154.0 (s), 162.1 (s), 164.1 (s), 165.7 (s). Anal. Calcd for $C_{15}H_{23}N_6O_6Cl\cdot H_2O$: C, 41.24; H, 5.77; N, 19.24. Found: C, 40.86; H, 5.28; N, 18.68%.

4.8. 11-(1,3-Dimethyluracil-6-yl)-1,4,8,11-tetraaza-17-oxo-tricyclo[6.6.3.0^{4,15}]heptadecanium perchlorate (7)

A solution of **4Bb** (0.2388 g, 0.503 mmol) and zinc perchlorate hexahydrate (0.3894 g, 1.046 mmol) in DMSO (2 ml) was heated at 120 °C for 1 h. After the reaction mixture was cooled to room temperature, water and ether was added. The aqueous layer was evaporated under reduced pressure and the residue was recrystallized from methanol to afford **7** (0.1086 g, 0.222 mmol, 44.2 %). Compound **7**: white crystals. Mp: decomp. below 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40–1.61 (m, 1H), 1.93–2.11 (m, 1H), 2.12–2.41 (m, 3H), 2.77 (d, J=12.7 Hz, 1H), 2.96 (d, J=12.7 Hz, 1H), 3.00–3.59 (m, 5H), 3.13 (s, 3H), 3.54 (s, 3H), 3.74 (d, J=14.9 Hz, 1H), 3.65–3.92 (m, 4H), 3.97–4.20(m, 3H), 4.51(d, J=14.9 Hz, 1H), 4.86 (t, J=12.7 Hz, 1H), 5.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.9 (t), 27.3 (t), 27.8 (q), 32.9 (q), 34.2 (t), 43.3 (t), 45.6 (t), 47.0 (t), 49.8 (t), 50.2 (t), 54.5 (t), 88.0 (d), 152.5 (s), 159.3 (s), 162.1 (s), 164.2 (s), 166.7 (s). Anal. Calcd for $C_{19}H_{29}N_6O_7Cl$: C, 46.67; H, 5.98; N, 17.19. Found: C, 46.24; H, 5.87; N, 16.80%.

4.9. X-ray crystallographic analysis

Crystallographic data for **5a** and **7** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 654509 and CCDC 743682, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Crystal data for **5a**: $C_{14}H_{21}N_6O_2\cdot ClO_4$, M_r=404.82, T=100(1) K, monoclinic, space group $C2/c$, Z=8, a=23.995(3) Å, b=8.5986(12) Å, c=19.341(3) Å, β=120.971(3)°, V=3421.5(8) Å ^{3}, D_x=1.572 Mgm^{-3}, R=0.0606, $wR(F^2)$=0.1629.

Crystal data for **7**: $C_{19}H_{29}N_6O_3\cdot ClO_4$, M_r=488.93, T=100(2) K, triclinic, space group P-1, Z=2, a=7.2524(5) Å, b=10.1157(7) Å, c=14.6156(9) Å, α=89.1360(10)°, β=84.8900(10)°, γ=82.0580(10)°, V=1057.74(12) Å ^{3}, D_x=1.535 Mgm^{-3}, R=0.0467, $wR(F^2)$=0.1303.

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References and notes

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