

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

This full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/16274>

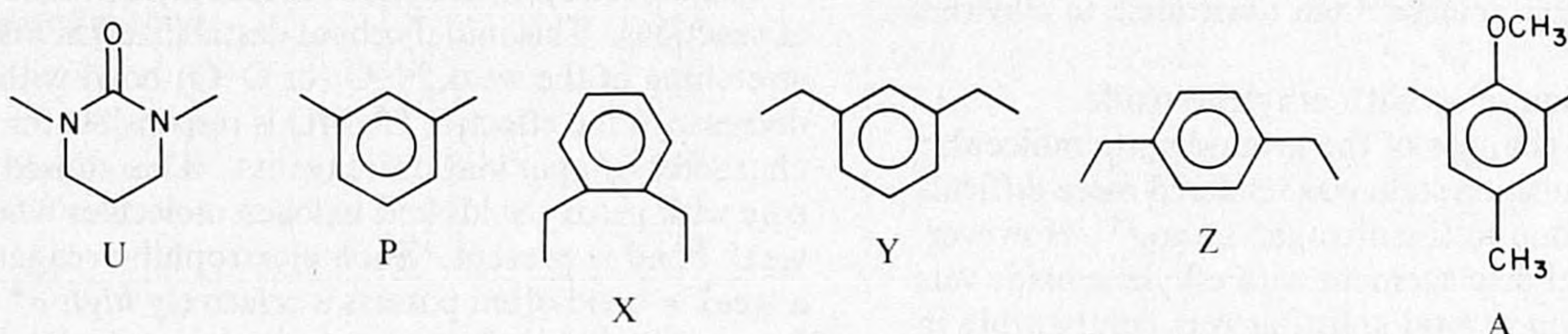
Please be advised that this information was generated on 2014-11-13 and may be subject to change.

Host-Guest Complexation. 27. Hosts Containing Only Cyclic Urea Binding Sites¹

Roeland J. M. Nolte and Donald J. Cram*

Contribution from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024. Received August 4, 1983

Abstract: Four new hosts have been designed, synthesized, and examined for their complexing abilities toward alkali metal, ammonium, and alkylammonium ion guests. Three of these hosts are unique in the sense that they contain inward-turned carbonyl groups of three cyclic urea units as their only ligating sites. The macrocycles are composed by bonding three cyclic urea units (U) through their nitrogens to one another in a triangular arrangement through spacer units, two of which are 1,3-phenylenes (P). The third spacer unit was used to vary the ring size: 1,2-xylyl (X), 19-membered ring; 1,3-xylyl (Y), 20-membered ring; 1,4-xylyl (Z), 21-membered ring; or 2-methoxy-5-methyl-1,3-xylyl (CH₂ACH₂), 20-membered ring. The



starting materials for the critical ring-closing reactions were prepared by conventional means. They possessed the structures H-UPUPU-H, XBr₂, YBr₂, ZBr₂, and BrCH₂ACH₂Br. The ring closures were carried out in (CH₂)₄O-NaH at high dilution. The reactions of H-UPUPU-H with XBr₂ gave U(PU)₂X in 47% yield; with YBr₂, U(PU)₂Y in 73% yield; with ZBr₂, U(PU)₂Z in 27% yield; and with BrCH₂ACH₂Br, U(PUCH₂)₂A in 55% yield. All new compounds were characterized. Spectroscopic experiments (¹H NMR) demonstrated that the four hosts formed 1:1 complexes with NH₄⁺, CH₃NH₃⁺, and *t*-BuNH₃⁺ ions in CDCl₃ and 2:1 complexes with Na⁺, K⁺, Rb⁺, and Cs⁺ ions. By the CDCl₃-D₂O picrate extraction method, the binding free energies were obtained for the 1:1 complexes of the four hosts with NH₄⁺, CH₃NH₃⁺, and *t*-BuNH₃⁺ and for the 2:1 host-guest complexes of the other ions. The -ΔG° values (kcal mol⁻¹) in CDCl₃ at 25 °C binding the ammonium and alkylammonium ions provided the following ranges: for U(PU)₂X, 7.0-7.3; for U(PU)₂Y, 7.0-8.6; for U(PU)₂Z, 8.0-9.1; for U(PUCH₂)₂A, 8.4-9.5. In all cases, *t*-BuNH₃⁺ > CH₃NH₃⁺ > NH₄⁺ in magnitudes of -ΔG° values. The ranges for the -ΔG° values (kcal mol⁻¹) for the Na⁺, K⁺, Rb⁺, and Cs⁺ forming 2:1 host-guest complexes are as follows: U(PU)₂X, 10.2-9.1; U(PU)₂Y, 10.1-9.4; U(PU)₂Z, 10.6-8.2; U(PUCH₂)₂A, 13.7-11.0. Lithium appears to form both kinds of complexes. These hosts are both poorer complexing agents and less discriminating than their counterparts, in which A units are substituted for P units.

Hundreds of papers have been published on host-guest complexes based on chrand and cryptand hosts in which the binding sites are composed mainly of CH₂OCH₂ units.² Although biological receptors are rich in the carbonyl group of amide and ester units, very few hosts have been designed and synthesized whose *only binding sites* are carbonyl groups. The cyclic urea unit has been used respectively as an appendage³ and as a ring component in a macrocyclic chrand⁴ and in a hemispherand.⁵ It has also been used as the dominant ring component in spherands.^{6,7} Hosts U(AU)₂X (1) and U(AUCH₂)₂A (2), which contain both cyclic urea (U) and 2,6-disubstituted-4-methylanisyl units (A), were found to bind ammonium, alkylammonium, and alkali metal picrates in CDCl₃ with -ΔG° values that ranged between ~18.3 and 11.4 kcal mol⁻¹ at 25 °C.⁶

The present work reports the synthesis and binding properties of hosts 3-6, which are composed of three cyclic urea units whose carbon-oxygen double bonds are held in convergent positions by bonding their attached nitrogens to three rigid spacer units. Two

1,3-phenylenes (P units) are common to all four cycles. The third unit is used to vary the size of the macrocycle. In U(PU)₂X (3), a 1,2-xylyl unit (X) provides a 19-membered ring. In U(PU)₂Y (4) a 1,3-xylyl unit (Y) and in U(PUCH₂)₂A (6) a 2-methoxy-5-methyl-1,3-xylyl unit (CH₂ACH₂) complete 20-membered rings. In U(PU)₂Z (5) a 1,4-xylyl unit (Z) as a spacer gives a 21-membered ring. Thus 3-5 are hosts that contain only cyclic urea units as binding sites. Examinations of molecular models (CPK) of U(PUCH₂)₂A indicate its single methoxyl group can only reach the larger alkali metal ions as guests. Crystal structure determination of U(AUCH₂)₂A·(CH₃)₃CNH₃⁺ and of the analogues A'(A'UCH₂)₂A·Na⁺ and A'(A'UCH₂)₂A·Cs⁺ confirmed this conclusion (A' is a 2,6-disubstituted anisyl unit).⁶ The current investigation was conducted to determine how important the presence of the ArOCH₃ groups was to the binding power of these hosts. We also wished to construct organized ligand systems whose only binding sites were cyclic urea units.

Results

Syntheses. Treatment of 3-nitroaniline with trichloromethyl chloroformate⁸ and pyridine gave *N,N'*-bis(*m*-nitrophenyl)urea (7, 97%), which was cyclized with 1,3-dibromopropane and sodium hydroxide under phase-transfer conditions to give cyclic urea 8 (40%). This substance was reduced to diamine 9 (70%) with iron and hydrochloric acid. Diamine 9 with 3-chloropropyl isocyanate⁹ was converted to compound 10 (81%), which when mixed with potassium *tert*-butoxide-*tert*-butyl alcohol underwent a double ring closure to provide the key intermediate, tris-urea 11 (96%).

(1) This work was supported by the U.S. Public Health Service Grant GM-12640 from the Department of Health, Education and Welfare and by a grant from the National Science Foundation, CHE 72-04616 A04.

(2) For recent monographs, see the following: Izatt, R. M.; Christensen, J. J., Eds. "Synthetic Multidentate Macrocyclic Compounds"; Academic Press: New York, 1978; pp 1-324, "Progress in Macrocyclic Chemistry"; Wiley-Interscience: New York, 1979; Vol. 1, pp 1-276; *Ibid.*, 1981; Vol. 2, pp 1-347.

(3) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928-4941.

(4) Kaplan, L. J.; Weisman, G. R.; Cram, D. J. *J. Org. Chem.* **1979**, *44*, 2226-2233.

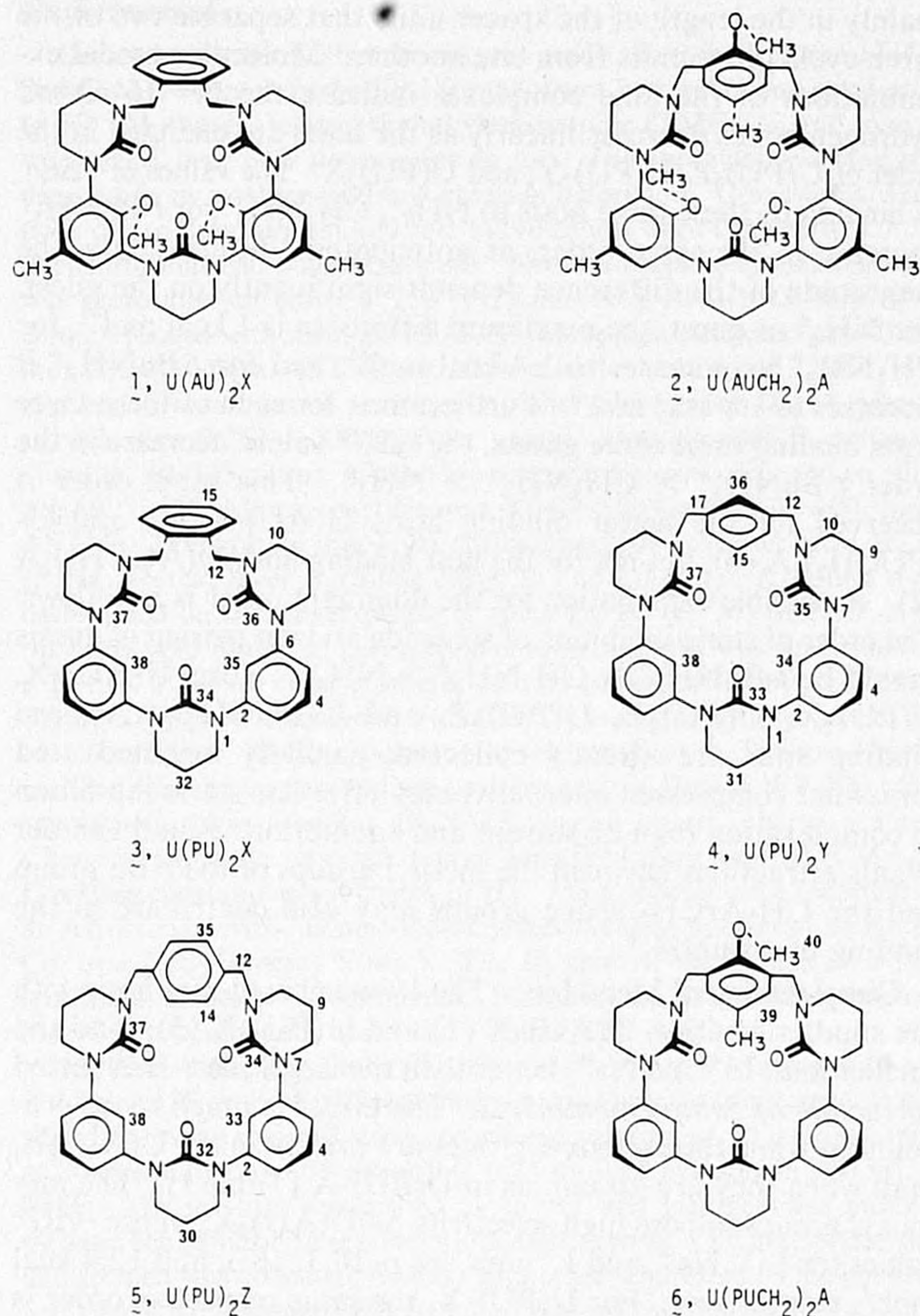
(5) Cram, D. J.; Dicker, I. B.; Lein, G. M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6827-6828.

(6) Cram, D. J.; Dicker, I. B.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6828-6830.

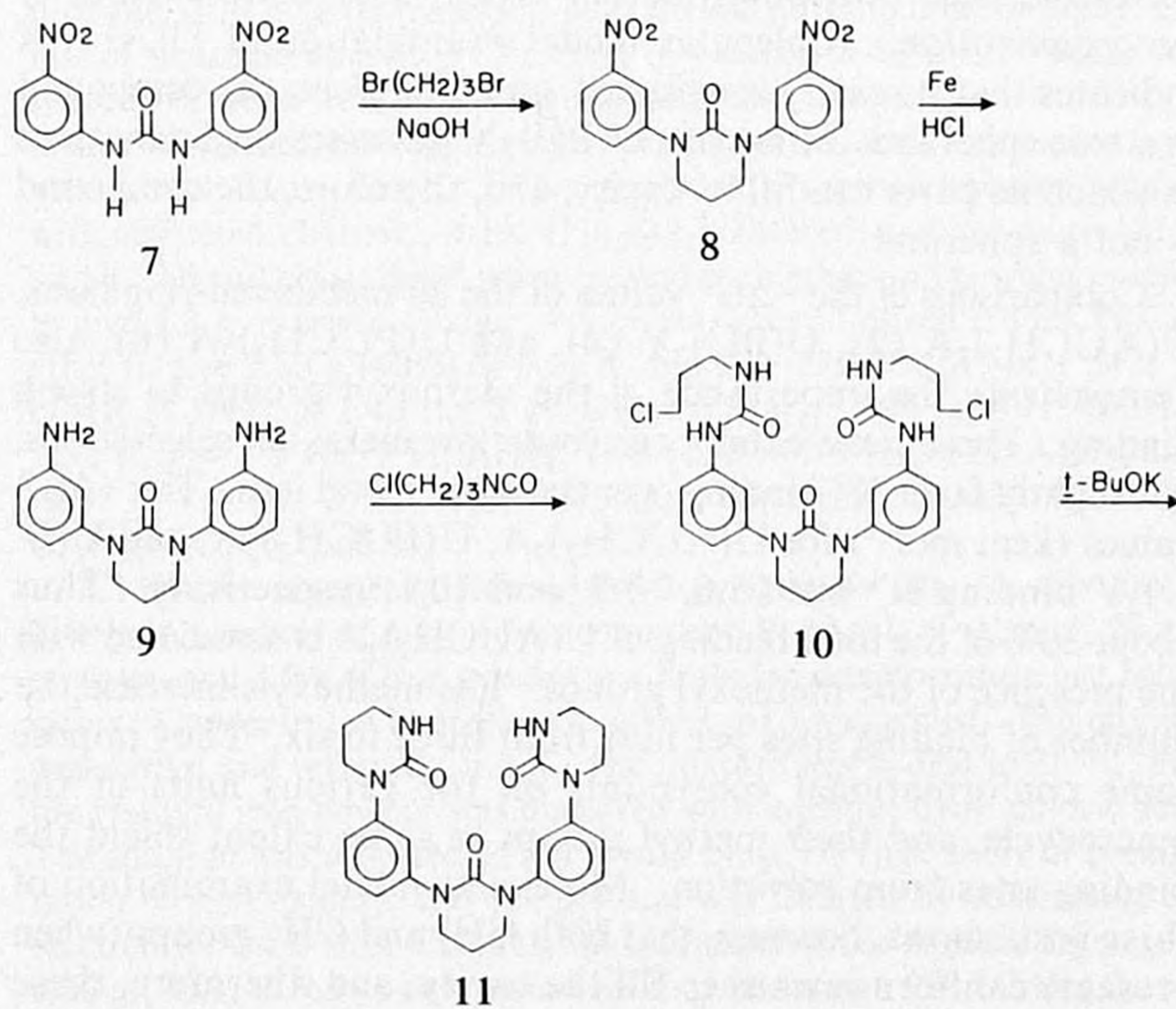
(7) Cram, D. J.; Dicker, I. B. *J. Chem. Soc., Chem. Commun.* **1982**, 1219-1221.

(8) Skorna, G.; Ugi, I. *Angew. Chem.* **1977**, *89*, 267-268.

(9) (a) Nystrom, R. F.; Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 3245-3246. (b) Brändström, A.; Lamm, B.; Palmertz, I. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 699-701.



Closures of the macrocyclic systems were carried out under high-dilution conditions in (CH₂)₄O by treating the disodium salt of **11** (prepared with sodium hydride) with various dibromides. With *o*-xylyl dibromide, **11** gave U(PU)₂X (**3**, 47%); with *m*-xylyl dibromide, U(PU)₂Y (**4**, 73%); with *p*-xylyl dibromide, U(PU)₂Z (**5**, 27%); and with 2,6-bis(bromomethyl)anisole,¹⁰ U(PUCH₂)₂A (**6**, 55%).



Complexation. The stoichiometry of complexation of U(PU)₂Y (**4**) with Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺, and (CH₃)₃CNH₃⁺ picrates and of **3**, **5**, and **6** with (CH₃)₃CNH₃⁺ picrates was examined through ¹H NMR spectral measurements in CDCl₃ at ambient temperature.¹¹ The changes in chemical shifts of the benzyl protons

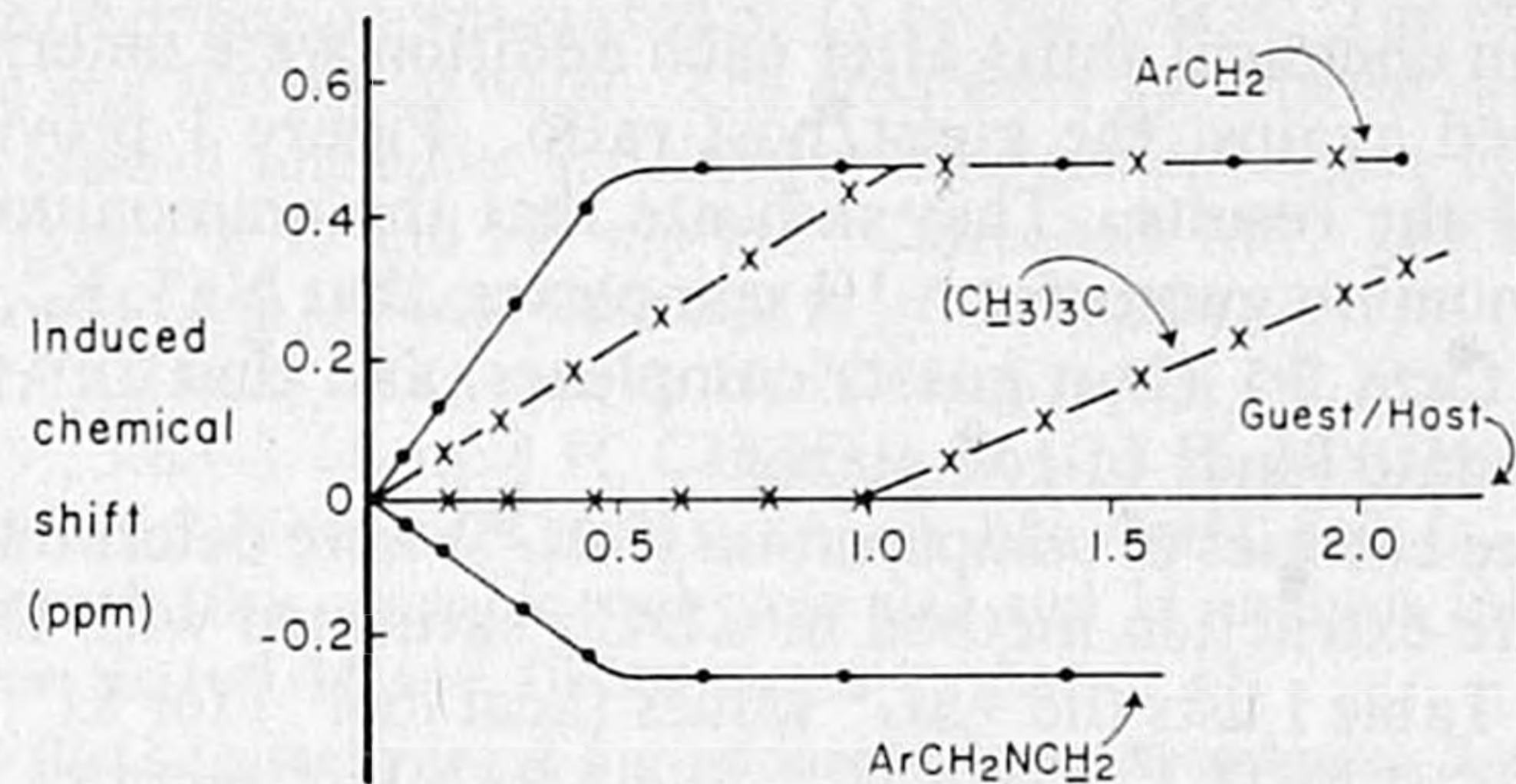


Figure 1. Stoichiometry of complexation: guest/host ratio vs. induced chemical shift for U(PU)₂Y (**4**); (•) K⁺; (×) (CH₃)₃CNH₃⁺.

Table I. Free Energies of Binding of Picrate Salt Guests to Hosts at 25 °C in CDCl₃ Saturated with D₂O^a

host	cation of guest	$K_a \times 10^{-5}$, M ⁻¹ (M ⁻²)	$-\Delta G^\circ$, kcal mol ⁻¹
U(AU) ₂ X (1)	Li ⁺	3 × 10 ⁸	~18.3
	Na ⁺	2 × 10 ⁶	16.5
	K ⁺	1 × 10 ⁴	12.4
	Rb ⁺	2 × 10 ³	11.4
	Cs ⁺	4 × 10 ³	11.8
	NH ₄ ⁺	5 × 10 ³	11.8
	CH ₃ NH ₃ ⁺	7 × 10 ³	12.1
	<i>t</i> -BuNH ₃ ⁺	5 × 10 ⁴	13.2
U(AUCH ₂) ₂ A (2)	Li ⁺	8 × 10 ³	12.1
	Na ⁺	8 × 10 ⁵	15.4
	K ⁺	2 × 10 ⁶	15.6
	Rb ⁺	1 × 10 ⁵	14.2
	Cs ⁺	3 × 10 ⁴	13.1
	NH ₄ ⁺	2 × 10 ⁵	14.4
	CH ₃ NH ₃ ⁺	2 × 10 ⁵	14.4
	<i>t</i> -BuNH ₃ ⁺	3 × 10 ⁴	13.2
U(PU) ₂ X (3)	Li ⁺	17 (1200) ^b	8.5 (11.0) ^c
	Na ⁺	5.3 (290) ^b	7.8 (10.2) ^c
	K ⁺	1.6 (73) ^b	7.1 (9.4) ^c
	Rb ⁺	0.7 (29) ^b	6.6 (8.8) ^c
	Cs ⁺	1.1 (49) ^b	6.9 (9.1) ^c
	NH ₄ ⁺	1.4	7.0
	CH ₃ NH ₃ ⁺	1.6	7.1
	<i>t</i> -BuNH ₃ ⁺	2.3	7.3
U(PU) ₂ Y (4)	Li ⁺	3.8 (300) ^b	7.6 (10.2) ^c
	Na ⁺	2.3 (180) ^b	7.3 (9.9) ^c
	K ⁺	2.7 (290) ^b	7.4 (10.1) ^c
	Rb ⁺	1.4 (90) ^b	7.0 (9.5) ^c
	Cs ⁺	1.4 (80) ^b	7.0 (9.4) ^c
	NH ₄ ⁺	1.4	7.0
	CH ₃ NH ₃ ⁺	2.7	7.4
	<i>t</i> -BuNH ₃ ⁺	20	8.6
U(PU) ₂ Z (5)	Li ⁺	0.25 (13) ^b	6.0 (8.3) ^c
	Na ⁺	0.21 (10) ^b	5.9 (8.2) ^c
	K ⁺	1.9 (110) ^b	7.2 (9.6) ^c
	Rb ⁺	2.7 (150) ^b	7.4 (9.8) ^c
	Cs ⁺	6.2 (580) ^b	7.9 (10.6) ^c
	NH ₄ ⁺	7.4	8.0
	CH ₃ NH ₃ ⁺	17	8.5
	<i>t</i> -BuNH ₃ ⁺	47	9.1
U(PUCH ₂) ₂ A (6)	Li ⁺	3.2 (130) ^b	7.5 (9.7) ^c
	Na ⁺	24 (2100) ^b	8.7 (11.3) ^c
	K ⁺	220 (180000) ^b	10.0 (13.7) ^c
	Rb ⁺	40 (4900) ^b	9.0 (11.8) ^c
	Cs ⁺	14 (1200) ^b	8.4 (11.0) ^c
	NH ₄ ⁺	14	8.4
	CH ₃ NH ₃ ⁺	40	9.0
	<i>t</i> -BuNH ₃ ⁺	93	9.5

^a See Experimental for methods and equations. ^b The values that appear parenthetically are based on K_a' , the association constant for a 2:1 host-to-guest complex (M⁻²). ^c These values are based on K_a' .

(e.g., at C-12 in **4**), the urea methylenes closest to the benzyl protons (e.g., at C-10 in **4**), and the *t*-Bu group were particularly useful in this study. The host was dissolved in CDCl₃ and the guest, dissolved in (CD₃)₂SO, was added in increments. The

(10) Koenig, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553-3566.

(11) The authors warmly thank Professor Thorleif Anthonsen for carrying out these NMR experiments.

changes in chemical shifts after each addition were determined and plotted against the guest/host ratio. Figure 1 provides a sample of the results. They indicate that the ammonium and alkylammonium guests form 1:1 complexes, that Na^+ , K^+ , Rb^+ , and Cs^+ form 2:1 (host:guest) complexes, and that Li^+ forms indeterminate kinds of complexes.

The free energies of complexation ($-\Delta G^\circ$) were determined by the picrate extraction method in CDCl_3 saturated with D_2O at 25 °C.¹⁰ Table I lists the $-\Delta G^\circ$ values (kcal mol^{-1}) for Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ , NH_4^+ , CH_3NH_3^+ , and $t\text{-BuNH}_3^+$ picrates based on an assumed 1:1 complex formation and, in the case of the metal salts, values based on an assumed 2:1 host-guest ratio as well (see Experimental). Values determined earlier for $-\Delta G^\circ$ (1:1 complex formation) for hosts $\text{U}(\text{AU})_2\text{X}$ (**1**) and $\text{U}(\text{AUCH}_2)_2\text{A}$ (**2**) are also listed for purposes of comparison.⁶

Discussion

Yields in Macroring Closure Reactions. Substantially higher yields were observed in the ring closures leading to the hosts containing only cyclic urea units as compared to those containing both anisyl and cyclic urea units. Thus $\text{U}(\text{PU})_2\text{X}$ was produced in 47% vs. $\text{U}(\text{AU})_2\text{X}$ in 7% yields; $\text{U}(\text{PU})_2\text{Y}$ in 73% vs. $\text{U}(\text{AUCH}_2)_2\text{A}$ in 11% or $\text{U}(\text{PUCH}_2)_2\text{A}$ in 55%; $\text{U}(\text{PU})_2\text{Z}$ in 27% vs. $\text{U}(\text{AU})_2\text{Z}$ in no detectable yield. The yield pattern correlates with the degree of organization and compression required for ring closure. The larger the number of conformational degrees of freedom that must be frozen out during ring closure, the lower the yield.

Complexation of Ammonium and Alkylammonium Ions. Hosts with anisyl units separating their cyclic urea sites are much stronger complexing agents than the corresponding hosts in which the methoxyl groups are absent (Table I). Thus $\text{U}(\text{AU})_2\text{X}$ (**1**) binds NH_4^+ , CH_3NH_3^+ , and $t\text{-BuNH}_3^+$ ions with a $-(\Delta G^\circ)_{\text{av}}$ value of 12.4 kcal mol^{-1} , as compared to $\text{U}(\text{PU})_2\text{X}$ (**3**) with a $-(\Delta G^\circ)_{\text{av}}$ value of 7.1 kcal mol^{-1} . Similarly, $\text{U}(\text{AUCH}_2)_2\text{A}$ (**2**) with a $-(\Delta G^\circ)_{\text{av}}$ of 14.0 kcal mol^{-1} exceeds that of $\text{U}(\text{PU})_2\text{Y}$ (**4**) with a $-(\Delta G^\circ)_{\text{av}}$ value of 7.7 kcal mol^{-1} . Even $\text{U}(\text{PUCH}_2)_2\text{A}$ (**6**), with a single methoxyl located in the spacer unit, gives a $-(\Delta G^\circ)_{\text{av}}$ value of 9.0, well in excess of that of its analogue, $\text{U}(\text{PU})_2\text{Y}$ (**4**), with a value of 7.7 kcal mol^{-1} . All of the complexes compared probably are held together by three $^+\text{NH}\cdots\text{O}=\text{C}$ hydrogen bonds, as observed in the crystal structure of $\text{U}(\text{AUCH}_2)_2\text{A}\cdot t\text{-BuNH}_3\text{ClO}_4$.⁶ Thus the non-hydrogen-bonding methoxyls of $\text{U}(\text{AU})_2\text{X}$ and $\text{U}(\text{AUCH}_2)_2\text{A}$ account for about 40% of the free energy of binding by these hosts.

The methoxyl groups probably play several roles in increasing the binding power of the hosts. Corey-Pauling-Koltun molecular model examination of $\text{U}(\text{AU})_2\text{X}$ (**1**) and $\text{U}(\text{AUCH}_2)_2\text{A}$ (**2**) indicates the two anisyl oxygens are wedged in between the three $\text{C}=\text{O}$ groups focusing the orbitals of the unshared electron pairs of the five oxygens roughly on the cavity to be occupied by the guest. The methyl groups attached to the anisyl oxygens diverge from the cavity and shield it on one side from solvation, which further raises the free energy of these hosts. Steric effects in these two hosts force on the three $\text{C}=\text{O}$ groups a tripod arrangement complementary to the three hydrogen bonds of the NH_3^+ groups. Models of $\text{U}(\text{PU})_2\text{X}$ (**3**) and $\text{U}(\text{PU})_2\text{Y}$ (**4**) in which the methoxyl groups are absent are much more conformationally flexible, and the carbonyl groups are open to solvation. Thus the methoxyls force on the cavity the organization (both with respect to location and desolvation of binding sites) required for binding. In other words, the burden of relocating and desolvating the binding sites is placed not on the complexing act but on the synthesis of the host (principle of preorganization).^{12,13}

Comparisons of the free energies of complexation by hosts $\text{U}(\text{PU})_2\text{X}$, $\text{U}(\text{PU})_2\text{Y}$, and $\text{U}(\text{PU})_2\text{Z}$ of guests NH_4^+ , CH_3NH_3^+ , and $t\text{-BuNH}_3^+$ provide a measure of the degree of complementarity of the host-guest relationships. These three hosts differ

mainly in the length of the spacer units that separate two of the three cyclic urea units from one another. Molecular model examinations of the nine complexes indicate the $\text{N}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bonds decrease linearly as the hosts are changed in the order of $\text{U}(\text{PU})_2\text{Z}$, $\text{U}(\text{PU})_2\text{Y}$, and $\text{U}(\text{PU})_2\text{X}$. The values of $-\Delta G^\circ$ of binding by these three hosts to NH_4^+ , CH_3NH_3^+ , or $t\text{-BuNH}_3^+$ decrease in the same order, as anticipated. Interestingly, the magnitude of the difference depends significantly on the guest. For NH_4^+ as guest, the maximum difference is 1 kcal mol^{-1} , for CH_3NH_3^+ it increases to 1.4 kcal mol^{-1} , and for $t\text{-BuNH}_3^+$ it increases to 1.8 kcal mol^{-1} . Furthermore, for each of these three hosts binding these three guests, the $-\Delta G^\circ$ values decrease in the order $t\text{-BuNH}_3^+ > \text{CH}_3\text{NH}_3^+ > \text{NH}_4^+$. This same order is observed for the better binding hosts $\text{U}(\text{AU})_2\text{X}$ (**1**) and $\text{U}(\text{PUCH}_2)_2\text{A}$ (**6**), but not for the best binding host, $\text{U}(\text{AUCH}_2)_2\text{A}$ (**2**). A possible explanation for the dominant order is as follows: The order of steric inhibition of solvation and ion pairing of guests should be $t\text{-BuNH}_3^+ > \text{CH}_3\text{NH}_3^+ > \text{NH}_4^+$. Hosts $\text{U}(\text{AU})_2\text{X}$, $\text{U}(\text{PU})_2\text{X}$, $\text{U}(\text{PU})_2\text{Y}$, $\text{U}(\text{PU})_2\text{Z}$, and $\text{U}(\text{PUCH}_2)_2\text{A}$, whose binding sites are already collected, partially oriented, and somewhat compressed internally, may offer less steric inhibition to complexation than do solvent and counterion. Small van der Waals attractions between the methyl groups of the $t\text{-Bu}$ group and the CH_2ArCH_2 space groups may also contribute to the binding of $t\text{-BuNH}_3^+$.

Complexation of Metal Ions. The 19-membered-ring hosts with the smaller cavities, $\text{U}(\text{AU})_2\text{X}$ (**1**) and $\text{U}(\text{PU})_2\text{X}$ (**3**), bind the smaller ions, Li^+ and Na^+ , better than the larger ions, as expected (*principle of complementarity*). The effect is much more pronounced when the methoxyl groups are present, as in $\text{U}(\text{AU})_2\text{X}$, than when they are absent, as in $\text{U}(\text{PU})_2\text{X}$ (Table I). The methoxyl groups impose high selectivity on $\text{U}(\text{AU})_2\text{X}$, whose $-\Delta G^\circ$ values for Li^+ , Na^+ , and K^+ ions are ~ 18.3 , 16.3, and 12.4 kcal mol^{-1} , respectively. For $\text{U}(\text{PU})_2\text{X}$, the same respective order is observed (11.0, 10.2, 9.4), but the selectivity is reduced from about 3 to <1 kcal mol^{-1} difference between adjacent ions when the methoxyl groups are absent. Not only do the methoxyl groups impose 1:1 complex formation but they also account for 25–35% of the total binding free energy. They provide additional binding sites. They also impose a high degree of conformational immobility on the parts of the macroring and shield the binding sites from solvation, thus providing another example of the *principle of preorganization*. Molecular model examination of $\text{U}(\text{AU})_2\text{X}$ indicates that its cavity is enforced, and, therefore, the compound is a true spherand. However, $\text{U}(\text{PU})_2\text{X}$ possesses conformations in which its parts can fill its cavity, and, therefore, the compound is not a spherand.

Comparisons of the $-\Delta G^\circ$ values of the 20-membered-ring hosts, $\text{U}(\text{AUCH}_2)_2\text{A}$ (**2**), $\text{U}(\text{PU})_2\text{Y}$ (**4**), and $\text{U}(\text{PUCH}_2)_2\text{A}$ (**6**), also demonstrate the importance of the methoxyl groups to strong binding. These hosts exhibit relatively low metal ion selectivities, but slightly favor K^+ binding over the other metal ions. The $-\Delta G^\circ$ values (kcal mol^{-1}) for $\text{U}(\text{AUCH}_2)_2\text{A}$, $\text{U}(\text{PUCH}_2)_2\text{A}$, and $\text{U}(\text{PU})_2\text{Y}$ binding K^+ are 15.6, 13.7, and 10.1, respectively. Thus about 30% of the total binding of $\text{U}(\text{AUCH}_2)_2\text{A}$ is associated with the presence of the methoxyl groups. The methoxyls increase the number of binding sites per host from three to six. They impose some conformational constraints on the various units of the macrocycle, and their methyl groups to some extent shield the binding sites from solvation. Molecular model examination of these hosts shows, however, that both CH_2 and CH_3 groups (when present) can turn inward to fill the cavity, and, therefore, these compounds are not true spherands. Their lack of ion selectivity points to their conformational flexibility and adaptability to various guest diameters.

The 21-membered-ring host, $\text{U}(\text{PU})_2\text{Z}$ (**5**), gave the following $-\Delta G^\circ$ values (kcal mol^{-1}): Cs^+ , 10.6; Rb^+ , 9.8; K^+ , 9.6; Na^+ , 8.2. Thus only a lower order of structural recognition is visible in these values, with the larger cavity favoring the larger ions, as expected. Molecular model examination shows that $\text{U}(\text{PU})_2\text{Z}$ has conformations in which its molecular parts virtually fill its potential cavity and that the compound is not a spherand.

(12) Cram, D. J.; Lein, G. M.; Kaneda, T.; Helgeson, R. C.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 6228–6232.

(13) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106.

Experimental

General. All chemicals were reagent grade. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Methanol, tetramethylethylenediamine (TMEDA) and toluene were dried over 3-Å sieves prior to use. Diisopropylethylamine was distilled from *p*-toluenesulfonyl chloride before use. Commercial solutions of *sec*-butyllithium and *tert*-butyllithium were titrated to a 1,10-phenanthroline end point before use. Medium-pressure chromatography was performed on either a 250 × 25-mm or a 1000 × 25-mm Altec column packed with silica gel 60 (E. M. Merck, particle size 0.040–0.063 mm, 230–400 mesh, ASTM) with flow rates between 6 and 12 mL/min. Gravity chromatograms were run on either silica gel 60 (E. M. Merck, particle size 0.063–0.200 mm) or neutral alumina (MCB, activated alumina, 80–325 mesh). Flash chromatography was conducted on silica gel 60 (E. M. Merck, particle size 0.040–0.063 mm, 230–400 mesh, ASTM). Preparative thin-layer chromatography involved silica gel 60 (E. M. Merck, layer thickness either 0.5 or 2.0 mm). R_f values were determined on thin-layer plates of silica gel 60 (E. M. Merck), layer thickness 0.25 mm. Gel permeation chromatography was performed on a 20 ft × 0.375 in. outer diameter column packed with 200 g of 100-Å Styragel (Waters Associates) with CH₂Cl₂ as eluate at flow rates of 3.5 to 4.0 mL/m. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. A Bruker WP-200 MHz spectrometer was used for all NMR spectra unless otherwise noted. Chemical shifts are reported in ppm downfield from internal (CH₃)₄Si. Coupling constants are reported in Hz. Mass spectra were recorded on an AE-1 model MS-9 double-focusing spectrometer interfaced by Kratos Co. to a Data General Nova 3. The IR spectra were taken on a Perkin-Elmer Model 297 spectrometer. Elemental analyses were determined for all new compounds and were within 0.30% of theory.

1,3-Bis(3-nitrophenyl)urea (7). Over a 4-h period a solution of 15 mL (24.8 g, 0.125 mol) of trichloromethyl chloroformate (diphosgene)⁸ was added dropwise to a refluxing and stirred solution of 50 g (0.362 mol) of 3-nitroaniline and 60 mL (59 g, 0.75 mol) of pyridine in 500 mL of THF. The mixture was cooled to 25 °C, and nitrogen was bubbled through the solution to remove residual phosgene. The precipitate that had formed was collected, washed with ether, and dried. This material was then stirred sequentially with two 400-mL portions of CH₃OH for 15 min to remove pyridinium salts. The final solid was washed with ether and dried under high vacuum to provide 44.7 g of analytically pure **7**. Another 8.05 g was isolated from the filtrates to give a total of 52.8 g (96%): mp 225 °C; M^+ m/e 302; ¹H NMR ((CD₃)₂SO) δ 7.50–7.90 (m, 6 H, ArH), 8.56 (s, 2 H, ArH), 9.44 (s, 2 H, NH). Anal. Calcd for C₁₃H₁₀N₄O₅: C, H, and N.

1,3-Bis(3-nitrophenyl)tetrahydro-2-pyrimidone (8). A mixture of 4 g (13.2 mmol) of diarylurea **7**, 5 mL (9.91 g, 49 mmol) of 1,3-dibromopropane, 0.72 g (2.65 mmol) of benzyltriethylammonium bromide, 217 mL of benzene, and 44 g (1.1 mol) of NaOH in 45 mL of water was stirred for 48 h at 55 °C (maintaining this temperature is critical). Water was added, the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined, treated with activated charcoal, dried (Na₂SO₄), filtered, and concentrated to an oil. The oil crystallized when treated with ether and petroleum ether to give 3.3 g of crude product, which was recrystallized from CH₂Cl₂-ether to give 1.83 g (40%) of pure **8**: mp 179–180 °C; M^+ m/e 342; ¹H NMR (CDCl₃) δ 2.40 (m, 2 H, CH₂CH₂CH₂), 3.94 (t, 4 H, NCH₂), 7.52 (t, $J = 7.9$ Hz, 2 H, ArH), 7.75 (d, $J = 7.9$ Hz, 2 H, ArH), 8.05 (d, $J = 7.9$ Hz, 2 H, ArH), 8.23 (s, 2 H, ArH). Anal. Calcd for C₁₆H₁₄N₄O₅: C and H.

1,3-Bis(3-aminophenyl)tetrahydro-2-pyrimidone (9). A mixture of 1.40 g (4.1 mmol) of dinitrourea compound **8**, 20 mL of ethanol, 20 mL of water, and 3.0 g of iron powder was heated to a temperature just below reflux. Concentrated hydrochloric acid (1 mL) was added. The mixture was stirred and refluxed for 4 h. The mixture was cooled to 25 °C, and the residual iron powder was dissolved with aqueous hydrochloric acid. The solution was adjusted to pH 4 with Na₂CO₃ (just short of precipitation of iron oxides), and the product was isolated by continuous extraction for 24 h with CH₂Cl₂. Evaporation of the organic layer gave 0.80 g (70%) of **9** as a pale yellow solid, pure enough (¹H NMR) for use directly in the next step. A sample was recrystallized from dimethylformamide-ether to give **9**: mp 112 °C; M^+ m/e 282; ¹H NMR ((C-D₃)₂SO) δ 2.10 (m, 2 H, CH₂CH₂CH₂), 3.65 (t, 4 H, NCH₂), 5.05 (broad s, 4 H, NH₂), 6.33–6.47 (m, 4 H, ArH), 6.51 (t, $J_{meta} = 2.0$ Hz, 2 H, ArH), 6.95 (t, $J_{ortho} = 7.9$ Hz, 2 H, ArH). Anal. Calcd for C₁₆H₁₈N₄O: C and H.

Reduction of **8** to **9** with titanium trichloride in water-acetic acid at 80 °C for 15 h gave only a 50% yield of product.

1,3-Bis[3-(3-chloropropylureido)phenyl]tetrahydro-2-pyrimidone (10). A mixture of 0.75 g (2.66 mmol) of diaminourea compound **9** and 1.2 mL (1.37 g, 11.4 mmol) of 3-chloropropyl isocyanate⁹ in 16 mL of

dimethylformamide was stirred at 25 °C for 3 days. The mixture was poured into 200 mL of water. The precipitate was filtered, washed with water, ethanol, and ether, and dried at high vacuum to give 1.05 g (80%) of a mixture of **10** and **11**: mp 195 °C dec; MS, $M^+ - 2HCl$ for **10**, or M^+ for **11**, m/e 448; ¹H NMR ((CD₃)₂SO) δ 1.90 (m, 4 H, CH₂CH₂CH₂Cl), 2.15 (m, 2 H, NCH₂CH₂CH₂N), 3.22 (m, 4 H, CH₂Cl), 3.63–3.74 (m, 8 H, CH₂N), 6.22 (t, 2 H, HNCH₂), 6.80 (m, 2 H, ArH), 7.15 (m, 4 H, ArH), 7.43 (s, 2 H, ArH), 8.40 (s, 2 H, NH). Compound **10** is unstable and gave a C and H analysis intermediate between that of **11** and **10** but closer to that of **11**.

1,3-Bis[3-(tetrahydro-2-pyrimidonyl)phenyl]tetrahydro-2-pyrimidone (11). To a suspension of 1.05 g (2.02 mmol) of the above mixture of **10** and **11** in 90 mL of dry *tert*-butyl alcohol (distilled from CaH₂) was added 1.20 g (10.7 mmol) of potassium *tert*-butoxide. The mixture was stirred at 25 °C and the reaction was monitored with TLC (R_f of **11**, 0.13; R_f of **10**, 0.23). It was essentially complete in 10 min. The mixture was acidified with hydrochloric acid to pH ~5, and the *tert*-butyl alcohol was evaporated under reduced pressure. The residue was dissolved in 50 mL of CH₂Cl₂ and the solution was washed with water. The aqueous layer was extracted twice with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered, and evaporated to yield a light-yellow solid. This material was recrystallized from CH₂Cl₂-ether to give 0.87 g (96%) of **11**: mp 218–220 °C; M^+ m/e 448; ¹H NMR (CDCl₃) δ 2.03 (m, 4 H, HNCH₂CH₂CH₂NAr), 2.20 (m, 2 H, ArNCH₂CH₂CH₂NAr), 3.38 (t of d, 4 H, CH₂NH), 3.66 (t, 4 H, CH₂NAr), 3.81 (t, 4 H, CH₂NAr), 5.10 (broad s, 2 H, NH), 7.05–7.40 (m, 8 H, ArH). Anal. Calcd for C₂₄H₂₈N₆O₃: C and H.

34,36,37-Trioxo-1,7,11,20,24,30-hexaazaheptacyclo-[28.3.1.1^{2,6}.1^{7,11}.0^{13,18}.1^{20,24}.1^{25,29}]octaconta-35(2),3,5,13(14),15,17,38-(25),26,28-nonaene (3). Sodium hydride, 0.065 g of 60% material (16.4 mmol), was washed with two 10-mL portions of dry THF and suspended in 700 mL of dry THF. The trisurea compound **11** (0.878 g, 1.96 mmol) was added and the mixture was refluxed under N₂ for 4 h. The resulting solution was cooled to -78 °C and 0.550 g (2.0 mmol) of 96% 1,2-bis-(bromomethyl)benzene in 5 mL of dry THF was added under N₂ with stirring. The mixture was stirred at -78 °C for 2 h and allowed to warm to 25 °C. After being stirred at 25 °C for 48 h, the mixture was treated with 5 mL of water, and the solvent was evaporated under reduced pressure. The residue was mixed with water-CH₂Cl₂, and the resulting emulsion was dispersed with a few drops of concentrated hydrochloric acid. The aqueous layer was extracted with three portions of CH₂Cl₂, and the combined organic layers were washed with water and subsequently with a 1 M aqueous solution of NaBr. The solution was dried (MgSO₄), filtered, and evaporated to give a white solid which was chromatographed on a gel permeation chromatograph column with CH₂Cl₂ as the mobile phase. The fraction with a retention volume of 170–220 mL was collected and evaporated under reduced pressure to dryness. The residue was dissolved in 10 mL of CH₂Cl₂ and the solution was washed 5 times with conductivity water. The organic layer was diluted with absolute ethanol, and the solvent was evaporated under reduced pressure. The residue was dried under high vacuum to give 0.502 g (47%) of free host **3**. This material was dissolved in 16 mL of CH₂Cl₂ and 50 mL of ether was added. After 5 min a gel formed which was stirred vigorously for 5 h to give a voluminous white precipitate, which was collected and dried under high vacuum to give **1**: mp 165–175 °C and 295 °C; M^+ m/e 550; ¹H NMR (CDCl₃) δ 2.08 (m, 4 H, ArCH₂NCH₂CH₂CH₂NAr), 2.27 (m, 2 H, ArNCH₂CH₂CH₂NAr), 3.16 (t, 4 H, ArCH₂NCH₂CH₂CH₂NAr), 3.68 and 3.73 (2 × t, 2 × 4 H, ArNCH₂CH₂CH₂NAr and ArCH₂NCH₂CH₂CH₂NAr), 4.83 (s, 4 H, CH₂C₆H₄CH₂), 6.97 (d of d, 4 H, ArH), 7.28 (s, 4 H, *o*-CH₂C₆H₄CH₂), 7.30 (t, $J_{ortho} = 7.5$ Hz, 2 H, ArH), 7.63 (t, $J_{meta} = 2$ Hz, 2 H, ArH). The ¹³C NMR (CDCl₃) spectrum gave δ 22.4 (C 9); 22.7 (C 32); 44.5 (C 12); 48.1, 49.5, 49.5 (C 8, C 10, C 33); 119.9, 120.7 (C 3, C 5); 126.8, 127.3 (C 4, C 35); 128.9, 128.9 (C 14, C 15); 136.1 (C 13); 145.4, 145.4 (C 2, C 6); 156.3 (C 36); 157.4 (C 34). Anal. Calcd for C₃₂H₃₄N₆O₃: C, H, and N.

33,35,37-Trioxo-1,7,11,19,23,29-hexaazaheptacyclo-[27.3.1.1^{2,6}.1^{7,11}.1^{13,17}.1^{19,23}.1^{24,28}]octaconta-34(2),3,5,36(13),14,16,38-(24),25,27-nonaene (4). Sodium hydride, 0.410 g of 60% material (10.3 mmol), was washed twice with THF and mixed in 500 mL of THF with 0.402 g (1.48 mmol) of 1,3-bis(bromomethyl)benzene and 0.660 g (1.47 mmol) of trisurea **11** stirred under nitrogen. The reaction was carried out and the product isolated as in the synthesis of **3** except for the following. The chromatographic fraction collected with 160–220 mL of CH₂Cl₂ contained 0.591 g (71%) of **4**, which did not change on recrystallization from CH₂Cl₂-Et₂O: mp 350 °C; M^+ m/e 550; ¹H NMR (CDCl₃) δ 2.08 (m, 4 H, ArCH₂NCH₂CH₂CH₂NAr), 2.26 (m, 2 H, ArNCH₂CH₂CH₂NAr), 3.27 (t, 4 H, ArCH₂NCH₂CH₂CH₂NAr), 3.73 and 3.81 (2 × t, 2 × 4 H, ArCH₂NCH₂CH₂CH₂NAr and ArNCH₂CH₂CH₂NAr), 4.65 (s, 4 H, CH₂C₆H₄CH₂), 6.8–7.3 (m, 9 H,

ArH and CH₂C₆H₄CH₂), 7.72 (s, 1 H, CH₂C₆H₄CH₂), 7.84 (s, 2 H, ArH). The ¹³C NMR spectrum (CDCl₃) gave δ 22.2 (C 9); 23.0 (C 31); 44.6 (C 12); 48.1, 49.5, 51.0 (C 32, C 8, C 10); 118.8, 119.5 (C 3, C 5); 126.9, 128.5 (C 4, C 34); 127.4, 129.7 (C 15, C 36); 129.0 (C 14); 139.0 (C 13); 144.0, 144.5 (C 2, C 6); 154.7 (C 35); 155.6 (C 33). Anal. Calcd for C₃₂H₃₄N₆O₃: C, H, and N.

32,34,37-Trioxo-1,7,11,18,22,28-hexaazaheptacyclo-[26.3.1.1^{2,6}.1^{7,11}.2^{13,16}.1^{18,22}.1^{23,27}]octaconta-33(2),3,5,35(13),14,16,38-(23),24,26-nonaene (5). This compound was synthesized and isolated by the same method applied to **3** from 0.440 g (0.981 mmol) of trisurea **11**, 0.415 g (10.4 mmol) of 60% NaH, and 0.283 g (1.07 mmol) of 1,4-bis(bromomethyl)benzene in 375 mL of THF. The product appeared in the gel permeation fraction from 180 to 220 mL of CH₂Cl₂, which provided 0.146 g (27%) of material which was recrystallized with little change from CH₂Cl₂-Et₂O to give **5**: mp 370 °C; M⁺ *m/e* 550; ¹H NMR (CDCl₃) δ 2.10–2.30 (m, 6 H, NCH₂CH₂CH₂N), 3.45 (t, 4 H, ArCH₂NCH₂CH₂CH₂NAr), 3.70 and 3.85 (2 × t, 2 × 4 H, ArCH₂NCH₂CH₂CH₂NAr and ArNCH₂CH₂CH₂NAr), 4.55 (s, 4 H, CH₂C₆H₄CH₂), 6.90 (d of d, 4 H, ArH), 7.28 (t, *J*_{ortho} = 8.0 Hz, 2 H, ArH), 7.41 (s, 4 H, CH₂C₆H₄CH₂), 7.61 (t, *J*_{meta} = 2.1 Hz, 2 H, ArH). The ¹³C NMR spectrum gave δ 22.6 (C 30); 22.8 (C 9); 46.3 (C 12); 48.9, 49.2, 52.3 (C 8, C 10, C 31); 119.2, 120.4 (C 3, C 5); 126.5, 128.7 (C 4, C 33); 128.1 (C 14); 137.3 (C 13); 144.2, 144.4 (C 2, C 6); 153.9 (C 32); 155.9 (C 34). Anal. Calcd for C₃₂H₃₄N₆O₃·H₂O: C, H, and N. The sample was dried by prolonged heating under vacuum. Anal. Calcd for C₃₂H₃₄H₆O₃·0.25H₂O: C, H, and N.

33,35,37-Trioxo-36-methoxy-15-methyl-1,7,11,19,23,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{13,17}.1^{19,23}.1^{24,28}]octaconta-34(2),3,5,36-(13),14,16,38(24),25,27-nonaene (6). This compound was synthesized and isolated by the same method applied to **3** from 0.471 g (1.050 mmol) of trisurea **11**, 0.300 g (7.50 mmol) of 60% NaH, and 0.330 g (1.072 mmol) of 2,6-bis(bromomethyl)-4-methylanisole¹⁰ in 400 mL of THF. The product was found in the gel permeation chromatographic fraction of 175–210 mL of CH₂Cl₂, which yielded 0.344 g (55%) of **6**, which changed little upon recrystallization from CH₂Cl₂-Et₂O: mp 354 °C dec; M⁺ *m/e* 594; ¹H NMR (90 MHz, CDCl₃) δ 1.90–2.20 (m, 6 H, NCH₂CH₂CH₂N), 2.30 (s, 3 H, ArCH₃), 3.10 (t, 4 H, ArCH₂NCH₂CH₂CH₂NAr), 3.60 and 3.75 (2 × t, 2 × 4 H, ArCH₂NCH₂CH₂CH₂NAr and ArNCH₂CH₂CH₂NAr), 3.95 (s, 3 H, OCH₃), 4.75 (s, 4 H, ArCH₂), 6.80–7.40 (m, 8 H, ArH), 7.80 (s, 2 H, ArH). The ¹³C NMR spectrum gave δ 20.2 (C 39); 22.0 (C 9); 22.4 (C 31); 44.2 (C 12); 48.2, 48.5, 48.8 (C 8, C 10, C 32); 61.5 (C 40); 118.9, 120.4 (C 3, C 5); 126.5, 128.4, 130.5, 132.6 (C 4, C 34, C 14, C 15); 132.2 (C 13); 144.0, 144.3 (C 2, C 6); 154.1 (C 36); 154.7 (C 35); 157.1 (C 33). Anal. Calcd for C₃₄H₃₈N₆O₄·H₂O: C, H, and N.

Determination of *K*_a and -Δ*G*^o Values. The *K*_a values were determined by the picrate salt extraction technique from D₂O into CDCl₃ at 25 °C reported previously. Complexes involving U(AU)₂X (**1**), U(AUCH₂)₂A (**2**) and the eight cations,¹⁰ and **3–6** with the three ammonium ions form only 1:1 complexes. Accordingly, the *K*_a values have the units M⁻¹ (see Table I). With hosts **3–6** complexing the metal ions, *K*_a values with units M⁻¹ and M⁻² (*K*_a' values) were both calculated and recorded (Table I). Lithium ion forms both types of complexes. Although the other metal ions form only the 2:1 (host:guest) complexes, *K*_a

values with M⁻¹ units are included for comparison purposes. Both *K*_a and *K*_a' values were calculated by application of extraction results obtained as previously described.^{3,10} Equations 1, 2, and 5 define *K*_a, *K*_a', and *K*_d, and eq 3 and 4 were used to calculate *K*_a and *K*_a' values. The starred letters refer to the CDCl₃ layer and the nonstarred to the D₂O layer.

$$K_a = \frac{[M^+ \cdot H \cdot \text{Pic}^-]^*}{[M^+ \text{Pic}^-]^* [H]^*} \quad (1)$$

$$K_a' = \frac{[H \cdot M^+ \cdot H \cdot \text{Pic}^-]^*}{[M^+ \text{Pic}^-]^* [H]^*{}^2} \quad (2)$$

$$K_a = \frac{R^*}{K_d(1 - R^*)\{[G_i] - R^*[H_i^*](V^*/V)\}^2} \quad (3)$$

$$K_a' = \frac{R^*}{2K_d(1 - R^*)^2[H_i^*]\{[G_i] - R^*[H_i^*]V^*/(2V)\}^2} \quad (4)$$

$$K_d = \frac{[M^+ \text{Pic}^-]^*}{[M^+][\text{Pic}^-]} = \frac{AD^d}{\epsilon l [G_i]^2} \quad (5)$$

$$R^* = ([G^*]/[H_i^*])_{\text{equil}} = AD^*/(\epsilon l [H_i^*]) \quad (6)$$

$$R_a^* = ([G^*]/[H_i^*])_{\text{equil}} = \frac{\{[G_i] - AD/(\epsilon l)\}(V/V^*)}{[H_i^*]} \quad (7)$$

The other definitions are as follows: the subscripts *i* refer to initial concentrations, and when absent, the concentrations are those at equilibrium; M⁺ is cation, Pic⁻ is picrate ion, G is guest, H is host, V is volume; R^{*} is the ratio [G^{*}]/[H_i^{*}] at equilibrium obtained from measurements made on the CDCl₃ layer and defined in eq 6; R_a^{*} equals the ratio [G^{*}]/[H_i^{*}] in the CDCl₃ layer calculated from measurements made on the aqueous layer at equilibrium and defined in eq 7; A is the observed absorbance of the picrate ion in CH₃CN; ε is the extinction coefficient of the picrate ion at 380 nm in CH₃CN; D^d is the factor by which the aliquots taken from CDCl₃ layer are diluted in CH₃CN for the *K*_d determination; D^{*} is the factor by which the aliquots taken from the CDCl₃ layer are diluted in the R^{*} determination; D is the factor by which aliquots taken from the aqueous layer are diluted in CH₃CN for the R_a^{*} determination; and *l* is the light path length for the UV cell. Each of the values of *K*_a and *K*_a' recorded in Table I is the average of values obtained from measurements made on the D₂O and CDCl₃ layers. The values based on each layer were in good agreement with one another. A maximum error analysis for this method for determining -Δ*G*^o values by this extraction method has been made.³ They are estimated to be ±3.1% in the present work. Each -Δ*G*^o value is based on two determinations, which were well within the above limits. The very high -Δ*G*^o value of ~18 kcal mol⁻¹ for U(AU)₂X (**1**) binding lithium picrate is only a gross estimate because its higher value pushed it to the edge of the scale.⁷

Registry No. **3**, 88230-23-3; **4**, 88230-24-4; **5**, 88230-25-5; **6**, 88230-26-6; **7**, 1234-21-5; **8**, 88230-27-7; **9**, 88230-28-8; **10**, 88230-29-9; **11**, 88230-30-2; 1,3-dibromopropane, 109-64-8; 3-chloropropyl isocyanate, 13010-19-0.