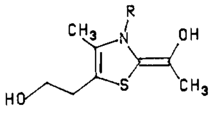
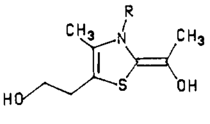
it is also possible that the enzyme could hold the material in a conformation that prevents formation of the enamine double bond and thus retains chirality. However, this would offer no particular mechanistic advantage and so is unlikely in terms of evolution of the catalytic function.



E



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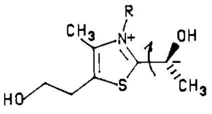

Nonplanar

These *E* and *Z* forms should be produced proportionately from either of the two enantiomers of lactylthiamin. That is, either the *E* or the *Z* form will predominate, but the relative quantities will be independent of the absolute stereochemistry of lactylthiamin. Our results are consistent with the production of one or both of these and further work is necessary to determine the preferred stereochemistry of these systems.[18]

Conclusion

The stereochemical course of the nonenzymic decarboxylation of lactylthiamin under a variety of conditions indicates the preferential formation of a symmetrically solvated achiral intermediate from a chiral reactant to yield a chiral racemic product. The ability of an enzyme to generate a single enantiomer of hydroxyethylthiamin diphosphate from the decarboxylation of lactylthiamin diphosphate is consistent with a mechanism involving stereospecific protonation due to the effects of the enzymic medium. Knowledge of the stereochemistry of the decarboxylation reaction catalyzed by TDP-dependent enzymes as well as studies of the stereospecificity of binding processes will provide detailed information about catalysis in these systems.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada through an operating grant (R.K.) and a summer undergraduate research fellowship (K. Kitamura).

Molecular Design of Calixarene-Based Uranophiles Which Exhibit Remarkably High Stability and Selectivity

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Abstract: For the selective binding of the uranyl ion (UO_2^{2+}) a new class of uranophiles has been designed from calixarenes: they are para-sulfonated calix[*n*]arenes (*n* = 4, 5, 6: $\mathbf{2}_4$H, $\mathbf{2}_5$H, and $\mathbf{2}_6$H, respectively) and their carboxylated derivatives ($\mathbf{2}_4CH_2COOH$, $\mathbf{2}_5CH_2COOH$, and $\mathbf{2}_6CH_2COOH$, respectively). We have found that the cyclic pentamers ($\mathbf{2}_5$H and $\mathbf{2}_5CH_2COOH$) and the cyclic hexamers ($\mathbf{2}_6$H and $\mathbf{2}_6CH_2COOH$) have remarkably large stability constants ($K_{\mathrm{uranyl}} = 10^{18.4-19.2}$ M^{-1}), whereas the cyclic tetramers ($\mathbf{2}_4$H and $\mathbf{2}_4CH_2COOH$) have very small stability constants ($K_{\mathrm{uranyl}} = 10^{3.1-3.2}$ M^{-1}). This trend is very compatible with the X-ray data which show that UO_2^{2+} complexes invariably adopt the coplanar penta- or hexacoordination geometry. Hence, the high stability is better explained by "coordination-geometry selectivity" than by "hole-size selectivity". The selectivity factors ($K_{\mathrm{uranyl}}/K_{M^{n+}}$) for $\mathbf{2}_6$H and $\mathbf{2}_6CH_2COOH$ were evaluated by comparing the K_{uranyl} with the stability constants for competing metal cations ($K_{M^{n+}}$). It was found that *the selectivity factors for these calixarenes are surprisingly large,* 10^{12-17} *as compared with competing* Ni^{2+}, Zn^{2+}, *and* Cu^{2+} *ions*! The remarkably high selectivity is attributed to the moderately rigid skeleton of calix[6]arene which can provide the preorganized hexacoordination geometry for the binding of UO_2^{2+} but cannot accommodate to the square-planar or tetrahedral coordination geometry for other metal cations in an "induced-fit" manner. Thus, calix[5]arene and calix[6]arene, which are easily synthesized from cheap starting materials, serve as excellent basic skeletons for the design of superior uranophiles.

The selective extraction of uranium from sea water has attracted extensive attention from chemists because of its importance in relation to energy problems. In order to design a ligand that can selectivity extract uranyl ion (UO_2^{2+}), one has to overcome a difficult problem: that is, the ligand must strictly discriminate between UO_2^{2+} and other metal ions present in great excess in sea water. A possibly unique solution to this difficult problem is provided by the unusual coordination structure of UO_2^{2+} complexes. X-ray crystallographic studies have established that UO_2^{2+} complexes adopt either a pseudoplanar pentacoordinate or hexacoordinate structure, which is quite different from the coordination structures of other metal ions.[1-6] This suggests that a macrocyclic host molecule having a nearly coplanar arrangement of either five or six ligand groups would serve as a specific ligand for UO_2^{2+} (i.e., as a uranophile). This approach has been investigated by Cram et al.,[7] Tabushi et al.,[8-10] and others.[11,12] For example, Tabushi et al.[9] synthesized a macrocyclic host molecule (**1**) having six carboxylate groups in the ring. Although the stability constant for UO_2^{2+} and **1** is quite large (log $K_{\mathrm{uranyl}} = 16.4$ at pH 10.4 and 25 °C), the selectivity for UO_2^{2+} is not very high (e.g., $K_{\mathrm{uranyl}}/K_{M^{n+}} = 80–210$ for Ni^{2+} and Zn^{2+}) and the synthesis is not easy.[9]

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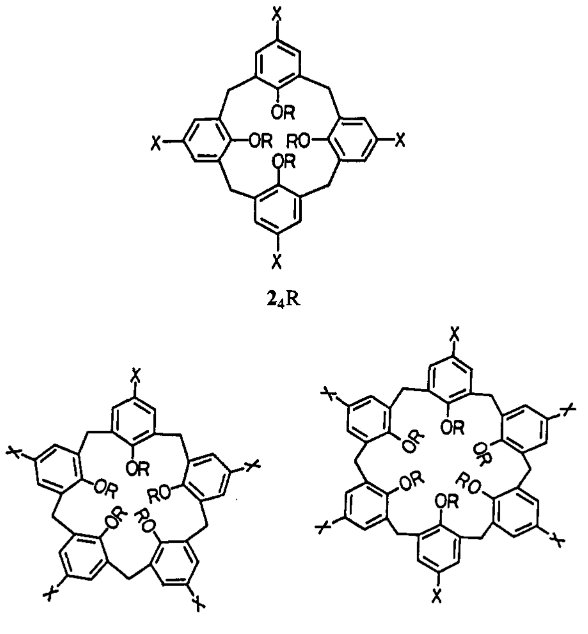
Chart I. Calixarene-Based uranophiles (R = H or CH_2COOH, X = SO_3Na)

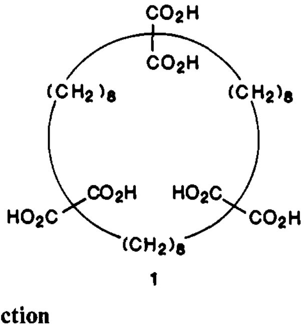


2$_4$R

2$_5$R

2$_6$R

Recently, we have been interested in the functionalization of calixarenes (cyclic oligomers made up of benzene units); the work of Gutsche and co-workers has allowed the facile synthesis of a variety of calixarenes in good yields,[13,14] and they are now expected to be useful in the design of enzyme mimics in totally synthetic systems.[13-17] In the course of our studies,[15-17] we noticed that calix[5]arene and calix[6]arene have an ideal architecture for the design of uranophiles, because the introduction of ligand groups into each benzene unit of these calixarenes exactly provides the required pseudoplanar penta- and hexacoordinate structures.[9] We thus synthesized several water-soluble calixarene derivatives from calix[*n*]arenes (**2**$_n$R: $n = 4, 5, 6$) which are expected to act as uranophiles. We found that the syntheses are quite easy and that these calix[5]arene- and calix[6]arene-based uranophiles have not only the high stability constants ($\log K_{\text{uranyl}} = 18.4$–$19.2$) but also an unusually high selectivity for UO_2^{2+} ($K_{\text{uranyl}}/K_{M^{n+}} = 10^{12}$–$10^{17}$ for Ni^{2+}, Zn^{2+}, and Cu^{2+}). To the best of our knowledge, this is the highest UO_2^{2+} selectivity achieved so far.



1

Experimental Section

Materials. Preparations of calix[6]arene-*p*-hexasulfonate (**2**$_6$H), 5,11,17,23,29,35-hexasulfonato-37,38,39,40,41,42-hexakis(carboxymethoxy)calix[6]arene (**2**$_6CH_2COOH$), and 5,11,17,23,29,35-hexasulfonato-37,38,39,40,41,42-hexamethoxycalix[6]arene (**2**$_6$Me) were described in a previous paper of this series.[16] The preparation of calix[4]arene-*p*-tetrasulfonate (**2**$_4$H) was also described as an intermediate in the synthesis of *p*-nitrocalix[4]arene from *p*-*tert*-butylcalix[4]arene.[18]

5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis(carboxymethoxy)calix[4]arene was synthesized from **2**$_4$H in a manner similar to that described for **2**$_6CH_2COOH$:[16] mp >320 °C, yield 44%, single peak in HPLC; IR(KBr) $\nu_{C=O}$ 1600 cm^{-1}, ν_{SO_3} 1050, 1180 cm^{-1}; ^{1}H NMR (D_2O at 20 °C) δ 4.02 ($ArCH_2$, s, 8 H), 4.42 (OCH_2, br, 8 H), 7.70 (ArH, br, 8 H). The singlet peak of the $ArCH_2Ar$ methylene protons suggests that **2**$_4CH_2COOH$ adopts the alternate conformation at room temperature.

Calix[5]arene-*p*-pentasulfonate (2$_5$**H).** *p*-*tert*-Butylcalix[5]arene was synthesized according to the method of Ninagawa and Matsuda:[19] mp 296 °C (lit.[19] mp 310 °C), yield 4.4%, single peak in HPLC which was different from those of other *p*-*tert*-butylcalixarenes; IR(KBr) ν_{OH} 3260 cm^{-1}, ν_{C-H} 2960, 3030 cm^{-1}, $\nu_{C=C}$ 1600, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (CH_3, s, 45 H), 3.80 ($ArCH_2$, br, 10 H), 7.17 (ArH, s, 10 H), 8.60 (ArOH, s, 5 H); mass spectrum (*m*/*e*) M^+ 810. Anal. $(C_{11}H_{12}O)_5$ C, H. The IR and NMR spectra are in good accord with those in the literature[19,20] and the mass spectrum indicates that the product is the cyclic pentamer.

p-*tert*-Butylcalix[5]arene was debutylated and then converted to **2**$_5$H according to the method described previously:[16] mp >320 °C, yield 68%, single peak in HPLC; IR (KBr) ν_{SO_3} 1050, 1170 cm^{-1}; ^{1}H NMR(D_2O) δ 3.90 ($ArCH_2$, s, 10 H), 7.61 (ArH, s, 10 H). Anal. $(C_7H_5O_4SNa)_5$ C, H.

5,11,17,23,29-Pentasulfonato-31,32,33,34,35-pentakis(carboxymethoxy)calix[5]arene (2$_5$**CH**$_2$**COOH).** This compound was synthesized from **2**$_5$H in a manner similar to that described for **2**$_6CH_2COOH$:[16] mp >320 °C, yield 80%, single peak in HPLC; IR(KBr) $\nu_{C=O}$ 1630 cm^{-1}, ν_{SO_3} 1150, 1200 cm^{-1}. The ^{1}H NMR peaks of the pentasodium salt of **2**$_5CH_2COOH$ were so broad that it was very difficult to determine the chemical shifts. We neutralized the sulfonate groups by treating with ion-exchange resin and then measured the spectrum: ^{1}H NMR (D_2O) δ 4.08 ($ArCH_2$, s, 10 H), 4.3 (OCH_2, br, 10 H), 7.47–7.65 (ArH, m, 10 H). Anal. $(C_9H_6O_6SNa_2)$ C, H.

Determination of the Stability Constants. The stability constants for UO_2^{2+} were evaluated by a displacement method[21] at pH 10.40 (0.010 M carbonate) and 25 °C. An aqueous solution of **2**$_n$R ($(1.6$–$16.8) \times 10^{-4}$ M, 100 μL) was added to uranyl tricarbonate solution (1.51×10^{-3} M, 3 mL) equilibrated to 25 °C, and the progress of the reaction was followed spectrophotometrically. After about 4 h the spectral change reached equilibrium, but we left it at 25 °C for 3 days and then read the equilibrium absorbance. The calculation method is described in the Results and Discussion. We could determine the stability constants for **2**$_5$H, **2**$_5CH_2COOH$, **2**$_6$H, and **2**$_6CH_2COOH$ by this displacement method. On the other hand, those for **2**$_4$H, **2**$_4CH_2COOH$, and **2**$_6$Me were too small to apply the displacement method. Therefore, we employed the simple spectroscopic method. Since the ϵ_{449} could be calculated from the UO_2^{2+} complexes of **2**$_6$H and **2**$_6CH_2COOH$, we estimated the equilibrium concentration of the UO_2^{2+} complexes for **2**$_4$R and **2**$_6$Me assuming that these calixarenes have the same molar absorption coefficient.

The stability constants for competing metal cations (Ni^{2+}, Zn^{2+}, and Cu^{2+}) were determined by a polarographic method[21] at pH 9.50 (0.020 M ammonium), 25 °C, and $\mu = 0.10$ with KCl. The ammonium buffer was used to avoid the precipitation of metal cations in the basic pH region. However, some metal cations precipitated from aqueous solution when the medium pH was enhanced up to pH 10.40. First, the calibration curves for these metal cations were prepared by using the following $E_{1/2}$: −0.92 V for $NiSO_4$ (2×10^{-4}–6×10^{-4} M), −1.10 V for $ZnSO_4$ (1×10^{-4}–3×10^{-4} M), and −0.32 V for $CuSO_4$ (1×10^{-4}–6×10^{-4} M). The height of the reduction wave was decreased on the addition of **2**$_6$H or **2**$_6CH_2COOH$ owing to the complexation with these calixarenes. We thus estimated the change in the uncomplexed metal cations and calculated the stability constants. On the other hand, the stability constants for $MgSO_4$ were too small to determine by the polarographic method. The stability constants have been corrected for the association with NH_3.

Results and Discussion

Spectral Properties and Stoichiometry of the UO_2^{2+} Complexes. Addition of **2**$_6CH_2COOH$ to uranyl tricarbonate ($UO_2(CO_3)_3^{4-}$) solution at 25 °C increased the UV and visible absorption band over a wide wavelength range (225–500 nm) owing to the com-

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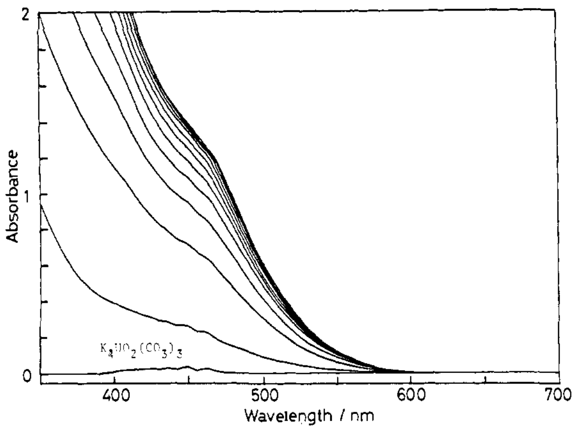

Figure 1. Spectral change for the formation of the $UO_2 \cdot \mathbf{2}_6CH_2COOH$ complex: 25 °C, pH 10.40 (0.01 M carbonate), $[K_4UO_2(CO_3)_3] = 1.51 \times 10^{-3}$ M, $[\mathbf{2}_6CH_2COOH] = 1.68 \times 10^{-3}$ M. The spectra were measured at intervals of 10 min. The first line is for the solution of $K_4UO_2(CO_3)_3$.

petitive association of $\mathbf{2}_6CH_2COOH$ with UO_2^{2+} (Figure 1). The absorption maxima were observed in the UV region in the difference spectrum ($\mathbf{2}_6CH_2COOH + UO_2^{2+}$ in the sample cell and $\mathbf{2}_6CH_2COOH$ in the reference cell): λ_{max} 265 nm (log ϵ 4.44) and 285 nm (shoulder: log ϵ 4.15). This spectrum is similar to that reported for UO_2^{2+} complexes with other macrocyclic uranophiles.[9,10] After a few hours (usually 4–5 h) the spectral change reached equilibrium, and the spectral pattern did not change further (at least for 3 months). A similar spectral change was induced by the addition of $\mathbf{2}_5H$, $\mathbf{2}_5CH_2COOH$, and $\mathbf{2}_6H$, whereas addition of $\mathbf{2}_4H$, $\mathbf{2}_4CH_2COOH$, and $\mathbf{2}_6Me$ scarcely induced any absorbance increase. These results suggest that cyclic pentamers and cyclic hexamers act as excellent ligands for UO_2^{2+} but cyclic tetramers do not. The fact that $\mathbf{2}_6Me$ scarcely affects the spectral pattern of $UO_2(CO)_3^{4-}$ supports the idea that the hydroxy groups or the carboxylate groups (but not the sulfonate groups) on the edge of the calixarenes are responsible for the specific UO_2^{2+} binding. We also added 10^{-3}–10^{-2} M of *p*-hydroxybenzenesulfonate and *p*-carboxymethoxybenzenesulfonate, noncyclic analogues of $\mathbf{2}_nH$ and $\mathbf{2}_nCH_2COOH$, to uranyl tricarbonate solution. They scarcely changed the spectrum, indicating the importance of the cyclic calixarene architecture.

It is known that the kinetic process for the substitution of carbonates in $UO_2(CO_3)_3^{4-}$ by uranophiles is fairly complicated.[22] Therefore, we only dealt with the equilibrium of the competitive displacement. The final absorption spectrum in Figure 1 can be assigned to the calixarene–UO_2^{2+} complex without carbonates (i.e., $UO_2 \cdot \mathbf{2}_nR$), because (i) addition of $\mathbf{2}_6H$ or $\mathbf{2}_6CH_2COOH$ (7.40×10^{-5} M) to uranyl nitrate solution (7.30×10^{-5} M) at 25 °C gives the absorption spectrum identical with that in Figure 1 and (ii) addition of excess sodium carbonate ($\sim 10^{-3}$ M) to this solution does not affect the final absorption spectrum obtained from uranyl nitrate. The results support that intramolecular OH or CH_2COOH groups coordinate to the central UO_2^{2+} ion in preference to intermolecular carbonate ions. This is probably due to the entropic, chelate effect characteristic of cyclic ligands.

The stoichiometry for the uranyl complexes was studied by a continuous variation method. The substitution between uranyl tricarbonate and $\mathbf{2}_nR$ took a few hours at 25 °C. We left the solution at least for 3 days at 25 °C and then determined the equilibrium absorbance. After several selected samples we corroborated that the absorbances do not change further for 3 months. As illustrated in Figure 2, $\mathbf{2}_5H$ and $\mathbf{2}_6H$ gave their maximum absorbances at [calixarenes]/([calixarene] + $[UO_2^{2+}]$) = 0.5. Similarly, $\mathbf{2}_5CH_2COOH$ and $\mathbf{2}_6CH_2COOH$ ([calixarene] + $[UO_2^{2+}] = 1.51 \times 10^{-3}$ M (constant)) gave their maximum absorbances at 0.5 (data not shown here). The results show that these calixarene-based uranophiles form a 1:1 complex with UO_2^{2+} in aqueous solution. On the other hand, stoichiometry for $\mathbf{2}_4R$ could not be evaluated accurately because of the weak absorption band and the precipitation in the high pH region.

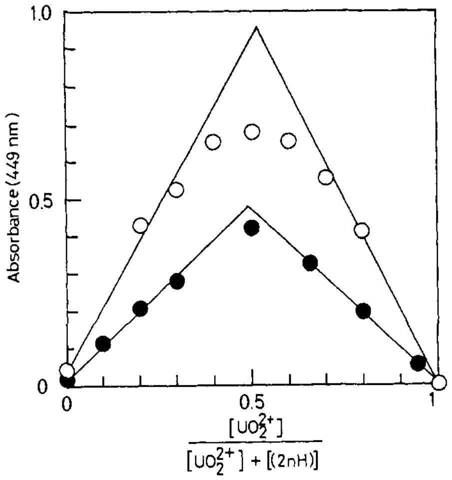

Figure 2. Continuous variation plots for the formation of the UO_2^{2+} complexes: 25 °C, pH 10.40 (0.01 M carbonate); (○) $[\mathbf{2}_6H] + [K_4UO_2(CO_3)_3] = 1.50 \times 10^{-3}$ M; (●) $[\mathbf{2}_5H] + [K_4UO_2(CO_3)_3] = 6.20 \times 10^{-4}$ M.

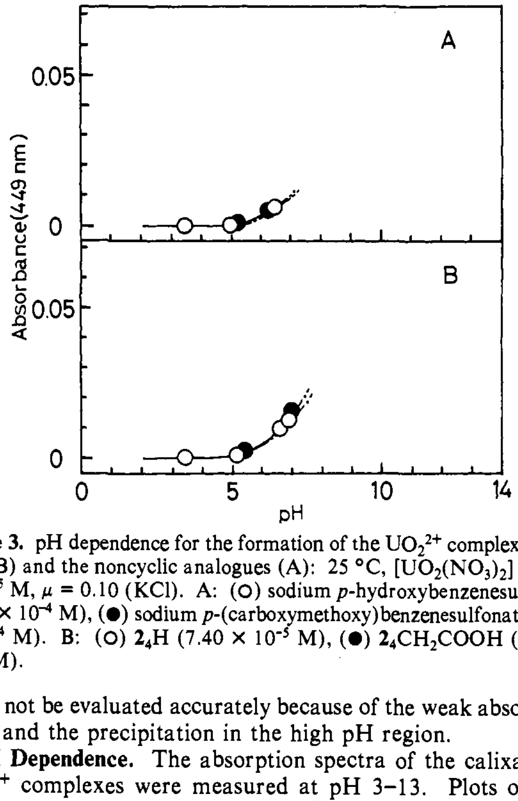

Figure 3. pH dependence for the formation of the UO_2^{2+} complexes with $\mathbf{2}_4R$ (B) and the noncyclic analogues (A): 25 °C, $[UO_2(NO_3)_2] = 7.30 \times 10^{-5}$ M, $\mu = 0.10$ (KCl). A: (○) sodium *p*-hydroxybenzenesulfonate (4.50×10^{-4} M), (●) sodium *p*-(carboxymethoxy)benzenesulfonate (4.60×10^{-4} M). B: (○) $\mathbf{2}_4H$ (7.40×10^{-5} M), (●) $\mathbf{2}_4CH_2COOH$ (7.40×10^{-5} M).

pH Dependence. The absorption spectra of the calixarene–UO_2^{2+} complexes were measured at pH 3–13. Plots of A_{449} (equilibrium absorbance at 449 nm)[23] vs. pH are illustrated in Figures 3–5. Plots for the noncyclic analogues are inserted in Figure 3. The slight increase in the absorbance was observed for $\mathbf{2}_4H$, $\mathbf{2}_4CH_2COOH$, and the noncyclic analogues at pH 5–7, but UO_2^{2+} precipitated above pH 7. This indicates again that these ligands cannot form the stable uranyl complexes in the neutral pH region. In contrast, the absorbances for $\mathbf{2}_5R$ and $\mathbf{2}_6R$ (both R = H and CH_2COOH) sharply increased at pH 5–7 and were almost saturated above pH 7 (except $\mathbf{2}_5H$). One can consider, therefore, that these calixarenes form the stable 1:1 complexes at neutral to basic pH region.

As shown in Figures 4 and 5, the UO_2^{2+} complexes with $\mathbf{2}_5CH_2COOH$, $\mathbf{2}_6H$, and $\mathbf{2}_6CH_2COOH$ gave almost the same A_{449} values in the high pH region ($\epsilon_{449} = 1400 \pm 10$ M^{-1} cm^{-1}). On the other hand, the pH dependence for $\mathbf{2}_5H$ is somewhat different: an additional jump appears at pH 8–10, and the A_{449} in the high

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(22) Tabushi, I., private communication.

(23) This wavelength was chosen because $UO_2(CO_3)_3^{4-}$ has an absorption maximum at this wavelength.

Table I. Determination of K_e and K_{uranyl} for $\mathbf{2}_5\mathrm{CH_2COOH}$ and $\mathbf{2}_6\mathrm{CH_2COOH}$[a]

$10^4[\mathbf{2}_5\mathrm{CH_2COOH}]$ (M)	10^4K_e (M^2)	log K_{uranyl}	$10^4[\mathbf{2}_6\mathrm{CH_2COOH}]$ (M)	10^3K_e (M^2)	log K_{uranyl}
1.61	8.05	18.40	1.68	1.72	18.74
3.22	8.08	18.41	3.36	1.71	18.73
4.83	8.06	18.41	6.72	1.70	18.73
6.45	8.11	18.41	10.07	1.72	18.74
8.06	8.13	18.41	13.43	1.83	18.76
9.67	8.37	18.42			

[a] pH 10.40 with 0.010 M carbonate, 25 °C, $[\mathrm{K_4UO_2(CO_3)_3}] = 1.51 \times 10^{-3}$ M.

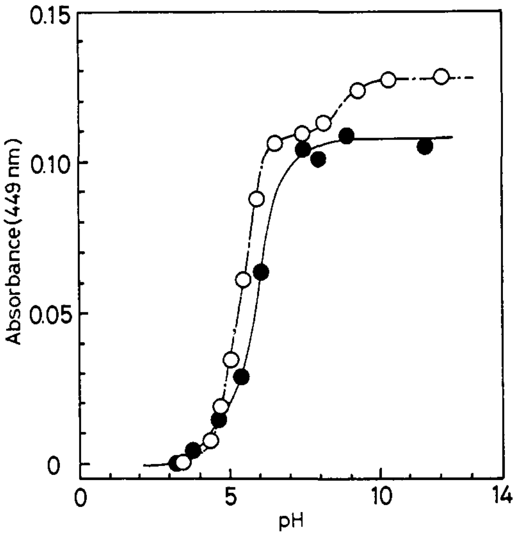

Figure 4. pH dependence for the formation of the UO_2^{2+} complexes with $\mathbf{2}_5$R (7.40×10^{-5} M): 25 °C, $[\mathrm{UO_2(NO_3)_2}] = 7.30 \times 10^{-5}$ M, $\mu = 0.10$ (KCl). (○) $\mathbf{2}_5$H, (●) $\mathbf{2}_5\mathrm{CH_2COOH}$.

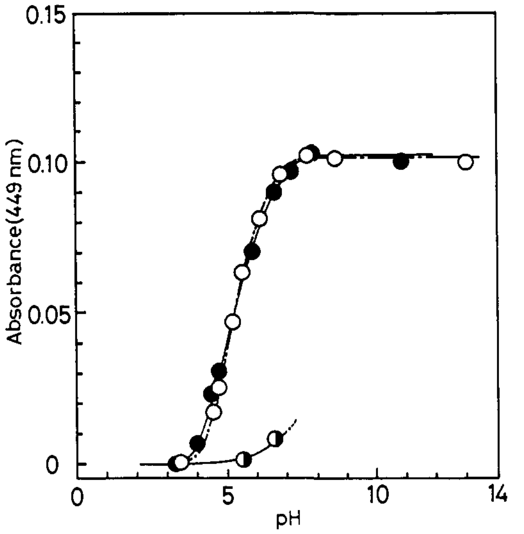

Figure 5. pH dependence for the formation of the UO_2^{2+} complexes with $\mathbf{2}_6$R (7.40×10^{-5} M): 25 °C, $[\mathrm{UO_2(NO_3)_2}] = 7.30 \times 10^{-5}$ M, $\mu = 0.10$ (KCl). (○) $\mathbf{2}_6$H, (●) $\mathbf{2}_6\mathrm{CH_2COOH}$, (◑) $\mathbf{2}_6$Me.

pH region is greater than those for other calixarenes. In like fashion, the UO_2 complexes with $\mathbf{2}_5\mathrm{CH_2COOH}$, $\mathbf{2}_6$H, and $\mathbf{2}_6\mathrm{CH_2COOH}$ gave similar absorption spectra at pH 10.4, but the spectrum for $\mathbf{2}_5$H was somewhat different from others. We also noticed that $\mathbf{2}_5$H gives an absorption spectrum and an A_{449} similar to other calixarene–UO_2^{2+} complexes at pH 6–7. It is now clear that above pH 7 $\mathbf{2}_5\mathrm{CH_2COOH}$, $\mathbf{2}_6$H, and $\mathbf{2}_6\mathrm{CH_2COOH}$ form a single species, but two (or more than two) species are formed from $\mathbf{2}_5$H. Figure 6 shows the potentiometric titration of the UO_2^{2+} complexes with $\mathbf{2}_5$H and $\mathbf{2}_6$H. It is seen from Figure 6 that the titration of the OH groups in $\mathbf{2}_6$H is complete by pH 7. On the other hand, the $\mathbf{2}_5\mathrm{H}\cdot\mathrm{UO_2^{2+}}$ complex still consumes NaOH above pH 7 and the amount exactly corresponds to 1 mol of the OH group (i.e., $^1/_5$ mol of $\mathbf{2}_5$H). In conclusion, one can envisage the

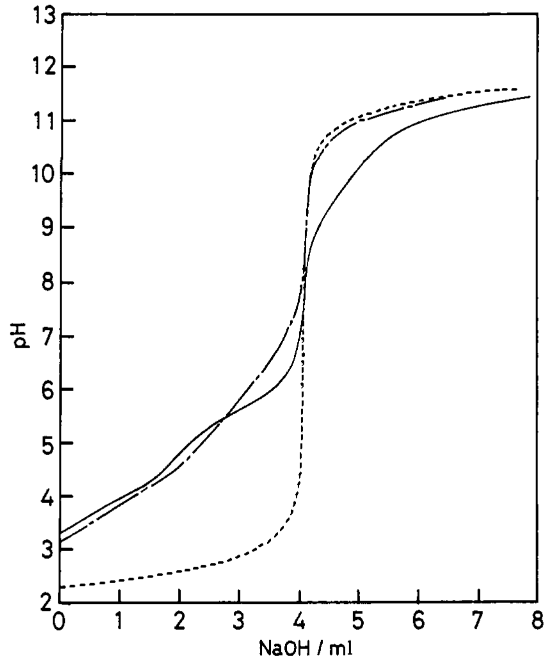

Figure 6. Potentiometric titration of $UO_2\cdot\mathbf{2}_5$H (—) and $UO_2\cdot\mathbf{2}_6$H (–··–) by NaOH (0.106 M): 25 °C, $[\mathrm{UO_2(NO_3)_2}] = [\mathbf{2}_5\mathrm{H}] = 8.8 \times 10^{-5}$ mol/80 mL of water or $[\mathrm{UO_2(NO_3)_2}] = [\mathbf{2}_6\mathrm{H}] = 8.5 \times 10^{-5}$ mol/80 mL of water. The titration was started after addition of a small amount of dilute HCl. The dotted line indicates the blank titration.

following pH dependence for the $\mathbf{2}_5\mathrm{H}$–UO_2^{2+} complex: Below pH 7 four OH groups are dissociated and one OH group remains undissociated. At pH 8–10 the last OH group is dissociated to form the fully saturated pentacoordination complex. At present, it is not yet clear why all the OH groups are dissociated at one time in $\mathbf{2}_6$H while one OH group remains undissociated in $\mathbf{2}_5$H.

Determination of the Stability Constants.[24] UO_2^{2+} is known to form a stable carbonate complex, $UO_2(CO_3)_3^{4-}$, and the stability constant ($K_{carbonate} = [UO_2(CO_3)_3^{4-}]/[UO_2^{2+}][CO_3^{2-}]^3$) is estimated to be $10^{21.5}$ M^{-3} at 25 °C and pH 10.4.[25] When $\mathbf{2}_n$R is added to the uranyl tricarbonate solution, the competitive displacement of carbonate by $\mathbf{2}_n$R takes place and reaches equilibrium after a few hours. The foregoing results establish that this process is expressed by eq 1. Thus, one can estimate the displacement equilibrium constants (K_e) from the spectral changes. Finally, the stability constants for UO_2^{2+} ($K_{uranyl} = [UO_2\cdot\mathbf{2}_nR]/[UO_2^{2+}][\mathbf{2}_nR]$) can be determined by eq 2. We varied the

$$UO_2(CO_3)_3^{4-} + \mathbf{2}_nR \overset{K_e}{\rightleftharpoons} UO_2\cdot\mathbf{2}_nR + 3CO_3^{2-} \qquad (1)$$

$$K_{uranyl} = K_eK_{carbonate} \qquad (2)$$

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[24] The most typical method to determine the stability constant is the pH titration. However, this method is not suitable to the present system for the following reasons: (i) It was very difficult to accurately determine the 5 to 6 pK_a values for the pentamers and the hexamers. (ii) The titration method should not be applied to the system in which the kinetic process for the complex formation is very slow. The slow equilibria (compared with the titration speed) frequently result in wrong stability constants (I. Tabushi, private communication). The complex formation between UO_2^{2+} and uranophiles is very slow and exactly the case, and (iii) when the stability constants were small, uraryl ion precipitated during the titration experiment.

[25] Reference 10 and related papers cited therein.

Table II. Stability Constants (K_{uranyl}) for Calixarene Derivatives and UO_2^{2+} (25 °C)

calixarene	pH	log K_{uranyl}
$\mathbf{2}_4\mathrm{H}$	6.5	3.2[a]
$\mathbf{2}_4\mathrm{CH_2COOH}$	6.5	3.1[a]
$\mathbf{2}_5\mathrm{H}$	10.4	18.9 ± 0.6
$\mathbf{2}_5\mathrm{CH_2COOH}$	10.4	18.4 ± 0.1
$\mathbf{2}_6\mathrm{H}$	10.4	19.2 ± 0.1
$\mathbf{2}_6\mathrm{CH_2COOH}$	10.4	18.7 ± 0.1
$\mathbf{2}_6\mathrm{Me}$	6.5	3.2 ± 0.2
1	10.4	16.4

[a] These values are evaluated by assuming that the extinction coefficients for the tetramers can be approximated by those for the hexamers.

Table III. Selectivity Factors for Uranyl Ion ($K_{\mathrm{uranyl}}/K_{\mathrm{M}^{n+}}$)

calixarene	metal (M^{n+})	log $K_{\mathrm{M}^{n+}}$[a]	$K_{\mathrm{uranyl}}/K_{\mathrm{M}^{n+}}$
$\mathbf{2}_6\mathrm{H}$	UO_2^{2+}	(19.2)	1.0
$\mathbf{2}_6\mathrm{H}$	Mg^{2+}	b	$>10^{17}$
$\mathbf{2}_6\mathrm{H}$	Ni^{2+}	2.2	$10^{17.0}$
$\mathbf{2}_6\mathrm{H}$	Zn^{2+}	5.5	$10^{13.7}$
$\mathbf{2}_6\mathrm{H}$	Cu^{2+}	8.6	$10^{10.6}$
$\mathbf{2}_6\mathrm{CH_2COOH}$	UO_2^{2+}	(18.7)	1.0
$\mathbf{2}_6\mathrm{CH_2COOH}$	Mg^{2+}	b	$>10^{17}$
$\mathbf{2}_6\mathrm{CH_2COOH}$	Ni^{2+}	3.2	$10^{15.3}$
$\mathbf{2}_6\mathrm{CH_2COOH}$	Zn^{2+}	5.6	$10^{13.1}$
$\mathbf{2}_6\mathrm{CH_2COOH}$	Cu^{2+}	6.7	$10^{12.0}$

[a] 25 °C, pH 9.50 with 0.020 M ammonium buffer, $\mu = 0.10$ with KCl, $[M^{n+}] = (0.50–3.00) \times 10^{-3}$ M, $[\mathbf{2}_6\mathrm{R}] = (0.10–6.00) \times 10^{-3}$ M. [b] The stability constants are too small to determine by the polarographic method.

concentration of $\mathbf{2}_n\mathrm{R}$ in the 10^{-4} to 10^{-3} M region and estimated the K_{uranyl} at each $\mathbf{2}_n\mathrm{R}$ concentration. This method allowed the accurate determination of the K_{uranyl}. Typical examples for $\mathbf{2}_5\mathrm{CH_2COOH}$ and $\mathbf{2}_6\mathrm{CH_2COOH}$ are recorded in Table I: we thus obtained log $K_{\mathrm{uranyl}} = 18.4 \pm 0.1$ for $\mathbf{2}_5\mathrm{CH_2COOH}$ and 18.7 ± 0.1 for $\mathbf{2}_6\mathrm{CH_2COOH}$. Similarly, we could determine the K_{uranyl} for $\mathbf{2}_5\mathrm{H}$ and $\mathbf{2}_6\mathrm{H}$ by the displacement method. The results are summarized in Table II.

The K_{uranyl} values for $\mathbf{2}_4\mathrm{R}$ and $\mathbf{2}_6\mathrm{Me}$ could not be determined by the displacement method, because the absorption spectrum of $UO_2(CO_3)_3^{4-}$ scarcely changed upon addition of 10^{-4}–10^{-3} M solutions of these calixarenes. We thus estimated their K_{uranyl} values from Figure 3. The molar absorption coefficient (ϵ_{449}) for the $UO_2\cdot\mathbf{2}_n\mathrm{R}$ complexes has been determined to be 1400 $M^{-1}\ cm^{-1}$ (vide ante). Provided that these calixarenes have the same ϵ_{449}, one can calculate the equilibrium concentrations of $UO_2\cdot\mathbf{2}_4\mathrm{R}$ and $UO_2\cdot\mathbf{2}_6\mathrm{Me}$ at pH 6.5. Although the stoichiometry of these complexes could not be established firmly, we estimated the K_{uranyl} values by assuming the formation of a 1:1 complex. The results are also summarized in Table II.

Examination of Table II reveals that the K_{uranyl} values for $\mathbf{2}_5\mathrm{R}$ and $\mathbf{2}_6\mathrm{R}$ are greater by 2.0–2.3 log units than that for **1** determined under the same conditions.[9] The pH dependences in Figures 4 and 5 indicate that these K_{uranyl} values are almost constant above pH 7 (except for $\mathbf{2}_5\mathrm{H}$). This implies that these calixarene-based uranophiles are capable of binding UO_2^{2+} even in the neutral pH region. On the other hand, the K_{uranyl} values for $\mathbf{2}_4\mathrm{R}$ were dramatically decreased: *they are smaller by about 16 log units than those for* $\mathbf{2}_5\mathit{R}$ *and* $\mathbf{2}_6\mathit{R}$*!* What causes such a large difference in the stability constants? As described in the introduction, X-ray crystallographic studies have established that UO_2^{2+} complexes adopt either a pseudoplanar pentacoordinate or hexacoordinate structure. Likewise, Tatsumi and Hoffmann[26] reported a theoretical calculation that UO_2^{2+} complexes adopt either a pseudoplanar pentadentate (D_{5h}) or hexadentate (D_{6h}) geometry using seven 5f orbitanls and five 6d orbitals. Thus, there are two possible explanations: that is, (i) the ion size of UO_2^{2+} exactly fits the cavity size of $\mathbf{2}_5\mathrm{R}$ and $\mathbf{2}_6\mathrm{R}$ but is too large for the cavity of $\mathbf{2}_4\mathrm{R}$ or (ii) $\mathbf{2}_5\mathrm{R}$ and $\mathbf{2}_6\mathrm{R}$ can provide the ligand groups arranged in a suitable way required for pseudoplanar penta- or hexacoordination on the edge of the calixarenes but $\mathbf{2}_4\mathrm{R}$ cannot. Explanation i is similar to the concept of the "hole-size selectivity" in crown–metal complexation,[27-31] whereas explanation ii may be called the "coordination-geometry selectivity" concept which reminds us of the fact that 18-crown-6 with approximate D_{3d} symmetry shows a high affinity for primary ammonium cations with sp^3 orbitals but 15-crown-5 with lower symmetry does not.[27-31] At present, we believe that explanation ii is more likely, because the cavity size of calixarenes is quite variable as a result of conformational flexibility.[13,14] Furthermore, $\mathbf{2}_6\mathrm{R}$ does not show the large stability constants for transition-metal ions (e.g., Cu^{2+}, Ni^{2+}, Zn^{2+}, etc.), the ion sizes of which are almost comparable with that of UO_2^{2+} (ion radii: Ni^{2+} 0.83 Å, Zn^{2+} 0.74–0.88 Å, Cu^{2+} 0.71–0.87 Å, U^{6+} 0.66–0.87 Å).[32] In any event, it is unambiguous that the markedly large difference in K_{uranyl} is related to the "rigidity" of $\mathbf{2}_n\mathrm{R}$ which would firmly maintain the pseudoplanar coordination geometry resulting from the number of ring members.

Uranyl Ion Selectivity. The selectivity of uranophiles can be evaluated by competitive binding with other metal cations. Most convenient is the spectroscopic method: that is, addition of a competing metal cation (M^{n+}) decreases the absorption band of the UO_2·uranophile complex because of the competitive formation of the M^{n+}·uranophile complex. Solvent extraction from an aqueous solution containing UO_2^{2+} and a large excess of a competiting metal cation is also useful. Tabushi et al.[9] evaluated the uranyl ion selectivity of **1** on the basis of the solvent extraction method. They obtained the following selectivity factors ($K_{\mathrm{uranyl}}/K_{\mathrm{M}^{n+}}$): >31000 for Mg^{2+}, 210 for Ni^{2+}, and 80 for Zn^{2+}.[9]

We first attempted the determination of the selectivity factors for $\mathbf{2}_6\mathrm{H}$ and $\mathbf{2}_6\mathrm{CH_2COOH}$ on the basis of the spectroscopic method. We added a large excess of competing metal cations such as Mg^{2+} (~0.3 M), Zn^{2+} (~10^{-3} M), Ni^{2+} (~10^{-3} M), and Cu^{2+} (~10^{-3} M) at pH 6–8, but none of them affected the absorption spectra of $UO_2\cdot\mathbf{2}_6\mathrm{H}$ and $UO_2\cdot\mathbf{2}_6\mathrm{CH_2COOH}$. This indicates that the K_{uranyl} values for these calixarenes are incomparably greater than the $K_{\mathrm{M}^{n+}}$ for the competing metal cations.[33] Finally, we decided to determine the $K_{\mathrm{M}^{n+}}$ independently on the basis of the polarographic method[21] (25 °C, pH 9.50 with 0.02 M ammonium buffer). We employed pH 9.50 for this experiment, which was different from the pH employed for the determination of the K_{uranyl} (pH 10.40). This is because some of these competing metal cations precipitated at pH 10.40. However, the K_{uranyl} values are almost constant above pH 7 (see Figure 5), so a comparison of the $K_{\mathrm{M}^{n+}}$ and the K_{uranyl} should be significant enough to discuss the selectivity factors. We have found that the $K_{\mathrm{M}^{n+}}$ values are surprisingly small (Table III): for example, Cu^{2+} which is expected to have the greatest stability constant of all metal cations gives log $K_{\mathrm{M}^{n+}}$ = 8.6 for $\mathbf{2}_6\mathrm{H}$ and 6.7 for $\mathbf{2}_6\mathrm{CH_2COOH}$.[34] As a result, $\mathbf{2}_6\mathit{H}$ *and*

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(33) We have synthesized 37,38,39,40,41,42-hexakis(carboxymethoxy)-*p*-*n*-dodecylcalix[6]arene for solvent extraction of UO_2^{2+}. The preliminary solvent extraction data showed that this calixarene also exhibits the high selectivity for UO_2^{2+}. The finding also supports the conclusion that the hydroxy groups on the carboxylate groups (but not the sulfonate groups) are responsible for the specific UO_2^{2+} binding: Shinkai, S.; Shirahama, Y.; Sato, H.; Arimura, T.; Manabe, O., unpublished results.

(34) The $K_{\mathrm{Cu}^{2+}}$ in ref 11 is not corrected for the association with NH_3. We found that the $Cu^{2+}\cdot\mathbf{2}_6\mathrm{CH_2COOH}$ complex produces a yellow color in an aqueous solution (λ_{max} 440 nm). This suggests the formation of the tetrahedral coordinate structure, which is rarely seen for Cu^{2+} complexes. We could determine the $K_{\mathrm{M}^{n+}}$ for Cu^{2+} from a plot of A_{440} vs. $[\mathbf{2}_6\mathrm{CH_2COOH}]$ to be $10^{6.7}$ M^{-1} (25 °C, pH 9.50 with 0.02 M ammonium buffer, $\mu = 0.10$). This value is in good accord with that determined by the polarographic method (Table III).

2_6CH_2COOH exhibit extremely high selectivity factors, $10^{10.6}$–$10^{17.0}$!

Here, it is worth mentioning that the K_{uranyl} values for 2_6H and 2_6CH_2COOH are greater only by 2.3–2.8 log units than that for **1**, whereas the selectivity factors are improved by 10^8–10^{15} log units. This means that the high selectivity factors stem from the unusually low $K_{M^{n+}}$ values: that is, 2_6H and 2_6CH_2COOH are moderately rigid and therefore would firmly maintain the pseudoplanar hexacoordination geometry. This structure is very favorable for the binding of UO_2^{2+} but quite unfavorable for the binding of other metal cations, which usually requires either square-planar or tetrahedral coordination geometry. In 1976 Alberts and Cram[7c] synthesized macrocyclic systems containing one to three β-diketone units and determined the stability constants for several metal cations including UO_2^{2+}. The β-diketone units are linked by the crown-type ethylene oxide chains.[7] The stability constants (25 °C, water:dioxane = 1:1 (v/v)) for a macrocycle containing two β-diketone units are $10^{11.0}$ M^{-1} for UO_2^{2+}, $10^{11.3}$ M^{-1} for Cu^{2+}, $10^{4.8}$ M^{-1} for Ni^{2+}, $10^{9.7}$ M^{-1} for Zn^{2+}, etc.[7] These values are greater by about 1.8 to 6.3 powers of ten than those for the noncyclic analogues, but the significant UO_2^{2+} selectivity was not seen (although their purpose in this paper was not the molecular design of uranophiles). This is probably due to the flexibility of the ring system. In Tabushi's uranophile (**1**), the carboxylate groups are linked by three octamethylene chains, allowing a more flexible conformation. Therefore, it is originally designed so that hexacarboxylate groups can arrange themselves in a suitable way for hexacoordination but also may provide the square-planar or tetrahedral geometry according to an "induce-fit" manner.

Conclusion. We have thus demonstrated that calix[5]arene and calix[6]arene, which can be readily synthesized from cheap starting materials, serve as an excellent basic skeleton for the design of pseudoplanar penta- or hexadentate uranophiles. In general, there are two possible strategies for improving the metal selectivity of macrocyclic ligands: the first one is to enhance the stability constant for the target metal cation and the second one is to lower the stability constants for competing metal cations. If the first strategy is employed, one should design some very rigid macrocycles on the basis of the "hole-size selectivity" rule. Hence, this approach is frequently accompanied by the disadvantage that the dynamic process becomes very slow and is not necessarily recommended for the design of uranophiles. In contrast, the second strategy does not have this disadvantage, and the uranophiles would be applicable as carriers in dynamic processes such as solvent extraction and membrane transport. Calixarenes provide an ideal basic skeleton for the second strategy: they are moderately rigid, allowing the high metal selectivity to be realized, but their conformational freedom still remains. We now believe that modification of calixarenes should lead to a further enhancement in the stability constant and the selectivity factor not only as uranophiles but also more in general as metallocalixarenes.[35,36] Detailed characterization of these and related calixarene derivatives and applications to solvent extraction and immobilization in polymer matrices are now under investigation.

Acknowledgment. We thank Professor T. Kunitake and Professor I. Tabushi for helpful discussions. This research was supported in part by a grant from the Ministry of Education of Japan.

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Reaction of 4-Phenyl-1,2,4-triazoline-3,5-dione with Substituted Butadienes. A Nonconcerted Diels–Alder Reaction

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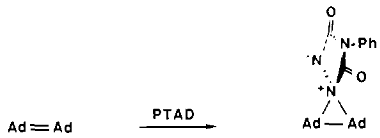
Abstract: The reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with substituted 1,3-butadienes (1,3-butadiene, (*E,E*)-, (*Z,E*)-, and (*Z,Z*)-2,4-hexadiene, and 2,5-dimethyl-2,4-hexadiene) has been investigated. In CH_2Cl_2, 1,3-butadiene, (*E,E*)-2,4-hexadiene, and (*Z,E*)-2,4-hexadiene give the expected Diels–Alder products with high stereospecificity (>200:1). Surprisingly, (*Z,Z*)-2,4-hexadiene gives a mixture of two Diels–Alder products, with the major isomer having the "wrong" stereochemistry. 2,5-Dimethyl-2,4-hexadiene gives mainly (~70%) the ene product. For both (*Z,Z*)-2,4-hexadiene and 2,5-dimethyl-2,4-hexadiene, the reactions proceed via observable intermediates to which we assign diazetidine structures. In MeOH, (*Z,Z*)-2,4-hexadiene and 2,5-dimethyl-2,4-hexadiene give mainly solvent adducts. (*Z,E*)-2,4-Hexadiene gives ~12% MeOH adduct together with the expected Diels–Alder product, while (*E,E*)-2,4-hexadiene and 1,3-butadiene give less than 0.05% of the solvent adducts. A mechanism involving initial formation of an aziridinium imide which subsequently opens to a 1,4-zwitterion can account for all the observations and is consistent with force-field calculations. The proposed mechanism may also hold for reactions of other electrophilic reagents such as $^1O_2$ and polycyanoethylenes.

The Diels–Alder (DA) reaction is one of the most popular synthetic tools because of the high control over regio- and stereochemistry it provides. Because the reaction usually proceeds with complete stereospecificity with respect to both the diene and the dienophile, it is generally believed to be concerted. There are a few exceptions, which are mainly limited to halogenated reactants[1] and DA reactions involving very polar components.[2-4]

Scheme I



Triazolinediones are often used as the dienophile in DA reactions to introduce nitrogen functionality and are among the most reactive dienophiles known.[5,6] Triazolinediones and other azo-

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