

yield. As previously, this acid underwent smooth condensation with the dipeptide L-Ala-D-isoglutamine benzyl ester 13 in the presence of N-hydroxysuccinimide and dicyclohexylcarbodiimide to give the crystalline 24 (mp = 233–234 °C, $[\alpha]^{20}_{D} = +57^{\circ}$, c = 0.4, CH₃OH) in 78% yield.

Finally, hydrogenolysis (Pd-C 10%) of 24 afforded the crystalline 2, our second target molecule (mp 142-143 °C, $[\alpha]^{20}_{D} = +53^{\circ}, c = 4.28, H_2O)$ in 84% yield.

The biological activity of this new class of immunostimulant will be the subject of a forthcoming paper.

Host-Guest Properties of New Water-Soluble Calixarenes Derived from p-(Chloromethyl)calixarenes

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Summary: Water-soluble, cationic, and anionic calix[6]arenes were synthesized from p-(chloromethyl)calix[6]arene as a key intermediate: the formation of aqueous host-guest-type complexes was confirmed by spectroscopic methods.

Sir: "Calixarenes" are cyclic oligomers made up of benzene units like "cyclodextrins" are made up of glucose units.^{1,2} One may expect, therefore, that they can serve as building blocks for designing new functionalized host molecules.²⁻⁴ However, evidence supporting the formation of host-guest complexes in solution has been elusive despite the availability of convenient one-step syntheses of calixarenes.^{1,2,5}

In order to obtain evidence for complexes in aqueous solution, we previously synthesized a series of water-soluble calizarenes that have hydrophilic sulfonate groups on the upper rim of a hydrophobic calizarene cavity.^{6,7} With the aid of hydrophobic forces in water, these compounds form host-guest-type complexes with several organic guest molecules.⁶⁻⁹ The results indicate the capability of calixarenes to act as host molecules in aqueous media. Here,

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Figure 1. Fluorescence spectra of ANS $(1.00 \times 10^{-6} \text{ M})$ in the presence of 3 $[(1.00 \times 10^{-6})-(1.00 \times 10^{-8} \text{ M})]$: 30 °C, pH 9.0 with 0.2 M borate buffer, excitation 365 nm.

we report the synthesis of new water-soluble, cationic, and anionic calixarenes (3 and 5) which are derived from p-(chloromethyl)calix[6]arene (2). As expected, they showed guest-inclusion properties in water, the selectivity of which is governed by electrostatic interactions.

Host molecules 3 and 5 were synthesized from 37,38,39,40,41,42-hexamethoxycalix[6]arene (1)¹⁰ according to the following reaction sequence and identified by IR and NMR spectroscopy as well as elemental analysis.¹¹ It is known that the calixarene conformation can be determined by the ¹H NMR peak for the ArCH₂Ar protons: a sharp singlet indicates the "cone" conformation and split peaks (three pairs of double doublets for calix[6]arene) reveal the "alternate" conformation.^{1,2} Since the ¹H NMR spectra of 3 and 5 show sharp singlets at 4.09 and 3.93 ppm (D₂O at 30 °C), respectively, these calixarenes are conformation.



It is known that some water-soluble calixarenes form micellar aggregates in water.⁷ In order to discuss the molecular recognition ability of calixarenes, one has to estimate the host-guest properties strictly below the cmc (critical micelle concentration). Measurements of electric conductance and surface tension¹² confirmed that in water (containing 1.7 vol % N,N-dimethylformamide (DMF)) at 30 °C neither 3 nor 5 forms the micellar aggregate (up



Figure 2. Emission maximum of ANS $(1.00 \times 10^{-5} \text{ M})$ plotted against host concentrations and against composition of waterethanol mixed solvent: 30 °C, excitation 365 nm, pH 9.0 with 0.2 M borate buffer (only for the left, host-guest system), (O) 3, (\bullet) β -cyclodextrin.



Figure 3. OD_{464} of Methyl Orange (7) (5.00 × 10⁻⁵ M) plotted against host concentrations: 30 °C, pH 9.0 with 0.2 M borate buffer, (O) 3, (O) 5.

to 0.2 M). The relative hydrophobicity of the calizarene cavity was estimated by a fluorescence probe, sodium 1anilinonaphthalene-8-sulfonate (ANS).¹³ As shown in Figure 1, the fluorescence intensity of ANS increased with increasing 3 concentration. This supports the inclusion of ANS in the hydrophobic cavity of 3. In contrast, the fluorescence intensity was scarcely increased by the addition of anionic 5. This is because the electrostatic repulsion overcomes the hydrophobic interaction. A plot of I/I_0 (relative fluorescence intensity) vs [3] (data not shown) shows a saturation curve, from which the association constant (K) was estimated by a Benesi-Hildebrand equation¹⁴ to be 1.2×10^3 M⁻¹. Under the same conditions the K for β -cyclodextrin was estimated to be 94 M⁻¹. Thus, the K for 3 is greater by 12.8-fold than that for β -cyclodextrin. Interestingly, the emission maximum of ANS shifted to shorter wavelengths with increasing 3 concentration. Since a similar hypsochromic shift is observed upon addition of ethanol to aqueous ANS, one can presume the cavity hydrophobicity in a water-ethanol mixed solvent. As shown in Figure 2, the emission maximum (495 nm) in the presence of excess 3 corresponds to 80 vol % ethanol solution. The emission maximum of ANS in the presence of excess β -cyclodextrin appears at 507 nm, which corresponds to 55 vol % ethanol solution. This suggests that a calix[6] arene cavity is more hydrophobic than that of β -cyclodextrin.

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(11) 2: mp 282-284 °C, yield 41%. 3: mp >300 °C, yield 23%, 4: mp 149-151 °C, yield 96%. 5: mp >300 °C, yield 82%.

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In order to obtain insight into the guest selectivity, we determined the K for cationic 6 and anionic 7 using a spectroscopic method. As shown in Figure 3, OD_{464} for Methyl Orange (7) decreased upon addition of 3 but was unchanged after addition of 5. This suggests that cationic 3 includes anionic 7. It is also seen from Figure 3 that 3 forms a 1:1 complex with 7 ($K \approx 7.1 \times 10^4$ M⁻¹). The reverse situration was found for cationic 6, which was selectively complexed by anionic 5 (K = 750 M⁻¹). The results indicate that hydrophobic forces may be generally operative for complex formation in an aqueous system, but the selectivity is crucially governed by the electrostatic force.

The foregoing results demonstrate that *p*-(chloromethyl)calixarene is a useful intermediate to prepare new water-soluble calixarenes and that the charge on the calixarene cavity plays a crucial role in the guest selectivity. Further applications of these water-soluble calixarenes are currently under investigation in this laboratory.

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Free-Radical Alkylations of Enones Involving Proton Transfers¹

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Summary: Radical chain alkylations of the S_{RN} -type are described that involve the abstraction of a proton from intermediate adduct radicals to form radical anions capable of chain propagation by electron transfer to alkylmercury halides. Vinylic S_{RN} processes are described for *o*- and *p*-hydroxycinnamic acids in basic solution.

Sir: Photostimulated chain reactions of alkylmercury chlorides with many α,β -unsaturated ketones, esters, lactones, and amides occur readily in the presence of iodide ion.^{2,3} In these reactions the regioselectively formed β adduct enolyl radicals are reduced to the enolate anions by $I^-/RHgI_2^-$ in processes which regenerate $R^{\bullet,2}$ A similar reaction yielding the additive (reductive) alkylation product is observed with other anions, such as HO⁻ or Me_3CO^- , which can form ate complexes with the mercurial (Table I). On the other hand, α,β -unsaturated compounds such as coumarin react with alkyl radicals by α -attack to generate the benzylic radical, which reacts slowly or not at all with RHgCl. However, a chain reaction can still be achieved because the adduct radical has an acidic α -hydrogen atom. Addition of DABCO in Me₂SO gives rise to substitutive (oxidative) alkylation to form 3-tert-butylcoumarin in 90% yield by the mechanism of Scheme I. Loss of a proton from 1 generates a powerful reducing species ($E_0 = -1.6$ V) which continues the chain by electron transfer to RHgCl (E_0 values for a variety of alkylmercury acetates in MeOH/H₂O are ~ -0.2 V).⁴ In the absence of base, little reaction is observed while in the presence of KI or $KI/K_2S_2O_8$ a complex reaction mixture is formed which includes the coupling product of 1 with a second t-Bu^{*}, 3-tert-butyldihydrocoumarin, a small amount of 3-tert-butylcoumarin, and four (two major and two minor) diastereomeric dimerization products of 1. A similar product distribution but with one of the diastereomers predominating was observed from the reaction with (t-Bu)₂Cu(CN)Li₂ in THF at -78 °C in a process which ap-

 Table I. Photostimulated Reactions of t-BuHgCl with Enones in Me₂SO

		% alky	lation
substrate	conditions ^a	sub- stitutive	additive
PhCOCH=CHCOPh	24 h ^b	tr	10°
PhCOCH=CHCOPh	24 h, KI	0	18°
PhCOCH=CHCOPh	2.5 h, KOH	0	32°
PhCOCH=CHCOPh	17 h, KI, K ₂ S ₂ O ₈	tr	76°
PhCOCH-CHCOPh	PhH, 24 h ^b	tr	4 ^c
PhCOCH—CHCOPh	PhH, 4 h, 2 equiv of t-BuOK	0	52°
(Z)-EtO ₂ CCH=CHCO ₂ Et	20 h ^b	0	37 ^{d,e}
(Z)-EtO ₂ CCH=CHCO ₂ Et	3 h, KI	0	100 ^d
(Z)-EtO,CCH-CHCO,Et	3 h. Na ₂ SO ₄ ^b	0	70 ^{d,e}
(Z)-EtO ₂ CCH=CHCO ₂ Et	i PrHgČl, 17 h	0	43 ^{e√}
Z)-EtO2CCH=CHCO2Et	i-PrHgCl, 3 h, KI, $K_{2}S_{2}O_{3}^{h}$	0	82 ^f
(Z)-EtO,CCH-CHCO,Et	PhH, 20 h ^b	0	48 ^{d,e}
(Z)-EtO ₂ CCH—CHCO ₂ Et	PhH, 20 h, DABCO ^b	0	65 ^{d,e}
CH ₂ =CHCOPh	13 h, DABCO ^b	tr	1100
CH ₂ =CHCOPh	18 h, NaI	0	57°.s
CH ₂ =CHCOPh	18 h, KI, $K_2S_2O_8^h$	0	86**
coumarin	24 h ^b	tr	tr
coumarin	12 h, DABCO	90 ⁱ	tr

^a Reaction of ~0.5 M substrate with 4 equiv of t-BuHgCl and 4 equiv of specified reagents under irradiation from a 275-W fluorescent sunlamp at ~40 °C. Workup with aqueous Na₂S₂O₃. ^b Unreacted substrate recovered. ^ct-BuCH(COPh)CH₂COPh. ^dt-BuCH(CO₂Et)CH₂CO₂Et. ^eSignificant amounts of a 2:1 telomer formed. ^fi-PrCH(CO₂Et)CH₂CO₂Et. ^et-BuCH₂CCPh. ^h2 equivalents. ⁱ3-tert-Butylcoumarin.

Scheme I



parently also proceeds by the intermediacy of 1. The persulfate/iodide system rapidly forms t-Bu[•] by the attack of I[•] and SO₄^{•-} upon t-BuHgCl as evidenced from CIDNP

⁽¹⁾ Electron Transfer Processes. 48. This work was supported by the National Science Foundation (Grant 8717871) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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