were carried out with 20-100 μM (final concentration) solutions of authentic bis-oxime, glyoxal, and **4b**. Nitroreduction mixtures were added such that the concentration of initial RNO_2 would have corresponded to 50-100 μM. The yield of glyoxal bis-oxime was calculated as 100% (OD(272)/1.72 × 10^4[RNO_2]) where OD(272) was the 90-min reading.

Radiation Chemical Reduction.[8,11] Solutions at pH 7 were prepared with 20 mM phosphate and 100 mM sodium formate. Solutions at pH 4 were prepared with 100 mM sodium formate and the appropriate quantity of HCl. For experiments in D_2O, 99.96% D_2O (Aldrich), sodium deuterioformate (Merck), and either DCl/D_2O or deuteriated phosphate were employed. The latter was obtained by lyophilization (twice) of D_2O/phosphate solutions. Nitroimidazole concentrations were 0.5-1.0 mM. Solutions were degassed by saturation with N_2O and were then placed in sealed vials for irradiations in the γ cell. The reduction stoichiometry was determined as previously described,[8] by following the disappearance of the nitroimidazole UV peak at 326 nm as a function of irradiation time. NMR spectra were obtained on irradiated solutions in D_2O, generally within 1 h of completion. Control experiments established that there is no difference in the spectra obtained at half and full reductions, other than the peaks for unreacted RNO_2. The spectra of pH 7 reduced solutions are unchanged after 4 days.

Electrochemical Reduction. These were carried out in a standard H cell with an agar plug separator. The anode was a 5 cm^2 sheet of platinum foil; this compartment contained 0.5 M NaCl. A mercury pool cathode (12 cm^2 surface area) was used; this was set at a constant potential of -800 mV with reference to a Calomel electrode. Both compartments were continually bubbled with nitrogen during electrolysis. A phosphate buffer was used to maintain a pH in the cathode compartment near neutrality (pH 6.5-7.5), while an acetic acid-acetate (20:1) buffer was used for pH 3.5-4.0. In both cases the pH was continually monitored during the electrolysis and 1 M HCl added where necessary. Current flow depended upon RNO_2 concentration; for solutions of 50 mM RNO_2 the initial current was 50-100 mA. The current drops to the background level (0.1-0.2 mA) on complete RNO_2 consumption. For determination of the reduction stoichiometry, samples were periodically withdrawn, and after the appropriate dilution the RNO_2 concentration determined spectroscopically at 326 nm. Plots of [RNO_2] vs. the number of coulombs passed were linear. NMR spectra of reduced products were recorded after lyophilization, followed by redissolving in D_2O. For the acetate-buffered reductions the pH was adjusted to 1 by the addition of concentrated HCl before lyophilization.

Zinc Reduction. The nitroimidazole (0.2 mM) and ammonium chloride (2 mM) were dissolved in water, and after 15 min of N_2 bubbling, an excess of zinc dust was added. The N_2 bubbling was continued and the mixture stirred. After 30 min the mixture was filtered. The filtrate was lyophilized and taken up in D_2O for NMR analysis.

Reaction of 2-Fluoroimidazole with Hydroxylamine. 2-Fluoroimidazole, as its HCl salt (2 mmol), and hydroxylamine hydrochloride (5 mmol) were dissolved in 5 mL of H_2O, and the pH was adjusted and maintained in the range 3.5-4.0 over a 6-h period. After lyophilization the NMR spectrum was recorded in D_2O. Approximately 10% unreacted fluoroimidazole remains, with 60-70% of the product being represented by the 6.99 ppm signal assigned to the 2-(hydroxylamino)imidazole. Several peaks at 5.0-5.5 ppm (including those for **4c**) account for the remainder. Attempts to separate the hydroxylamine by recrystallization or ion-exchange chromatography failed to improve the purity.

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Calixarenes. 20. The Interaction of Calixarenes and Amines

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Abstract: The interaction of calixarenes and amines in CH_3CN solution is postulated to involve a two-step process, viz., proton transfer from the calixarene to the amine to form the amine cation and the calixarene anion followed by association of the ions to form a complex. The overall association complex for *p*-allylcalix[4]arene and *tert*-butylamine, as a typical example, is about 10^6, the larger part of this arising from the proton transfer, as measured from UV spectral observations, and the smaller part arising from the association of the ions, as measured from ^1H NMR observations. A 2D NOE spectrum of this complex indicates that the methyl groups of the amine and the allyl groups of the calixarene are proximate, in agreement with an *endo*-calix structure for the complex.

The interaction of calixarenes (**1**) and amines is discussed in an earlier paper in this series[1] wherein it is suggested that a proton transfer from calixarene to amine occurs, followed by association of the calixarene anion with the ammonium cation to form an *endo*-calix complex (**3**), as shown in Figure 1. The present paper describes a more detailed study of this phenomenon.

In the present discussion the proton transfer step (K_1) and the "complexation" step (K_2) are treated as discrete processes, as depicted in eq 1, although it is recognized that these might be merged into a single step. Whereas UV spectral measurements, discussed in a later section of this paper, appear to arise primarily as a result of the first step, NMR measurements assess the net

$$ArOH + R_3N \overset{K_1}{\rightleftharpoons} ArO^- + R_3NH^+ \overset{K_2}{\rightleftharpoons} ArO^-\cdots{}^+HNR_3 \quad (1)$$

result of both steps and will be discussed first. The calixarene of choice for this investigation was *p*-allylcalix[4]arene (**1a**), because it is more soluble than the more easily accessible *p*-*tert*-butylcalix[4]arene (**1b**). The amines of choice for particular attention were *tert*-butylamine and neopentylamine, because the earlier work[1] had demonstrated a small but reproducible difference in their behavior in the presence of *p*-allylcalix[4]arene. Table I presents the proton chemical shift and relaxation rate values of the amine component that are observed in the ^1H NMR spectra of *tert*-butylamine and neopentylamine in CD_3CN solutions containing equimolar amounts of *p*-allylcalix[4]arene at 16 and -30 °C. Tables II and III show similar data for the calixarene component of these complexes.

Inspection of the data in Table I shows that both *p*-allylcalix[4]arene and trifluoroacetic acid exert a downfield shift on the methyl resonances of *tert*-butylamine and methyl and methylene resonances of neopentylamine. At 16 °C the calixarene is about 90% as effective as trifluoroacetic acid in its influence on *tert*-butylamine and about 55% as effective in its influence on neopentylamine, as judged from the relative values of the chemical shifts. At -30 °C, however, these values come closer to one another, diminishing in the case of *tert*-butylamine to 82% and increasing in the case of neopentylamine to 74-85%. These values might be interpreted as a measure of the extent of proton transfer from the phenol to the amine (assuming 100% proton transfer

(1) Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1985**, *107*, 6063.

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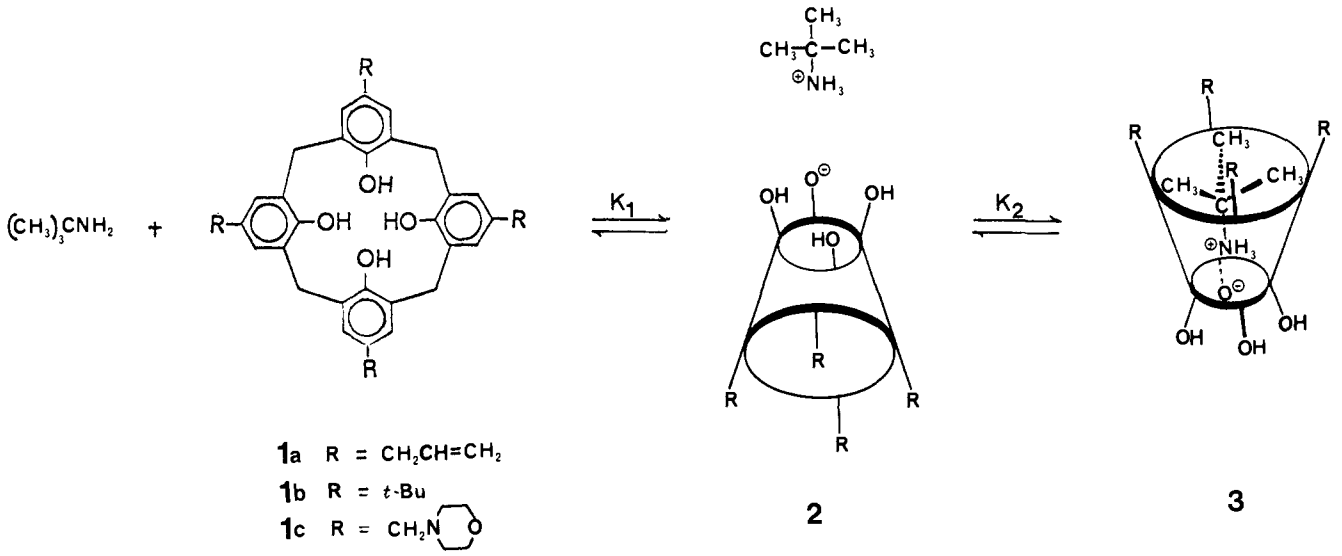
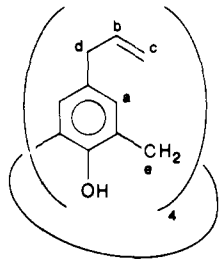


Figure 1. Formation of *exo*-calix and *endo*-calix complexes from amines and calix[4]arenes.

Table I. Chemical Shift and T_1 Values for the Protons in *tert*-Butylamine and Neopentylamine in the Presence of an Equimolar Amount of *p*-Allylcalix[4]arene or CF_3CO_2H at 7×10^{-3} M in CD_3CN

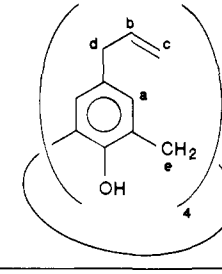
temp, °C	acid	*tert*-butylamine		neopentylamine			
		$\delta(CH_3)$	$T_1(CH_3)$	$\delta(CH_2)$	$\delta(CH_3)$	$T_1(CH_2)$	$T_1(CH_3)$
16	none	1.062	5.507	2.318	0.826	5.548	5.170
	p-allylcalix[4]arene	1.302	0.706	2.569	0.920	2.566	2.586
	CF_3CO_2H	1.337	2.115	2.766	0.982	2.035	2.332
−30	none	1.026	2.745	2.266	0.794	3.158	2.724
	p-allylcalix[4]arene	1.245	0.438	2.611	0.919	0.846	0.857
	CF_3CO_2H	1.292	0.975	2.733	0.941	0.846	0.922

Table II. Chemical Shift Values for Protons in *p*-Allylcalix[4]arene in the Presence of Equimolar Amounts of *tert*-Butylamine and Neopentylamine at 7×10^{-3} M in CD_3CN



temp, °C	position	δ, base			
		none	*tert*-butylamine	neopentylamine	NaOH
16	b	5.837	5.854	5.850	5.857
	c	4.927	4.974	4.976	4.974
	d	3.160	3.126	3.132	3.124
−30	a	6.903	6.753	6.756	6.731
	b	5.744	5.795	5.798	5.797
	c	4.903	4.918	4.912	4.913
	d	3.131	3.071	3.073	3.088
	e	4.119	4.188	4.260	4.268
		3.404	3.122	3.137	3.140

Table III. Relaxation Time Values for Protons of *p*-Allylcalix[4]arene in the Presence of Equimolar Amounts of *tert*-Butylamine and Neopentylamine at 7×10^{-3} M in CD_3CN



temp, °C	position	T_1 values			
		none	*tert*-butylamine	neopentylamine	NaOH
16	a	1.945	1.197	1.720	1.835
	b	4.758	3.772	4.190	4.526
	c	2.994	2.055	2.677	2.939
	d	1.234	0.657	1.073	1.093
−30	a	0.929	0.752	0.802	0.687
	b	2.386	2.079	2.253	1.500
	c	1.327	1.117	1.224	1.242
	d	0.575	0.520	0.492	0.569
	e	0.252	0.194	0.234	0.343
		0.265	0.194	0.234	0.343

for trifluoroacetic acid). However, in aqueous solution the pK values for *tert*-butylamine (10.83) and neopentylamine (10.15) are quite close to one another; yet in the present experiment the chemical shift values for these two amines are quite different. Although it is possible that in acetonitrile solution the difference in pK values between *tert*-butylamine and neopentyl amine is magnified, it seems probable that factors other than inherent basicities come into play in determining the chemical shift values. This is supported by the fact that the pattern noted for the chemical shifts is *not* observed for the relaxation times. Thus, the calixarene is *more* effective than trifluoroacetic acid in reducing the relaxation time and less effective in the case of neopentylamine. This effect is particularly striking at 16 °C where the relaxation time for the methyl groups of *tert*-butylamine is three times shorter with the calixarene than with trifluoroacetic acid. In contrast, the relaxation times for the methyl and methylene groups of neopentylamine are somewhat longer with the calixarene than with trifluoroacetic acid. Here also, the differences between the two amines become less pronounced at −30 °C.

The ^1H NMR data for the calixarene component, as shown in Tables II and III, display trends similar to those in Table I for the amine components. If attention is focused on the aromatic

Table IV. Chemical Shift and Relaxation Time Values for the Protons in Various Amines in the Presence of an Equimolar Amount of *p*-Allylcalix[4]arene or an Excess of Trifluoroacetic Acid

				δ, T_1 values							
				neat	*p*-allylcalix[4]arene			CF_3CO_2H		T_1 reduction factor	
amine		pK_a	% H^+ "transfer"	δ	$(T_1)_a$	δ	$(T_1)_b$	δ	$(T_1)_c$	$(T_1)_a/(T_1)_b$	$(T_1)_a/(T_1)_c$
tert-butylamine		10.83									
16 °C			87	1.062	5.676	1.302	0.706	1.337	2.45	8.04	2.31
−30 °C			72	1.026	2.765	1.245	0.438	1.292	0.975	6.31	3.73
adamantylamine	(H-2)			1.986	5.445			salt insoluble			
	(H-3)			1.624	4.143	1.686	0.881			4.70	
	(H-4)			1.519	4.538	1.801	0.954				
dodecylamine	(H-1)	10.63		2.552	3.131	2.871	0.835	2.898	1.400		
	(H-2)			1.265	2.349	1.266	1.361	1.267	1.733		
	(H-3)			0.874	3.167	0.883	2.814	0.873	2.994		
triethylamine	(H-1)	11.01	85	2.432	4.422	3.002	1.322	3.103	2.780	3.34	1.59
	(H-2)		83	0.950	4.365	1.177	1.761	1.224	2.869	2.47	1.52
morpholine		8.33	50	3.531	5.731	3.684	1.781	3.839	2.258	3.22	2.53
			50	2.716	5.634	2.936	1.609	3.160	2.000	3.50	2.81
piperidine	(H-1)	11.12	85	2.685	5.430	3.014	1.090	3.072	1.963	4.98	2.76
	(H-2)		93	1.421	5.525	1.721		1.743	2.176		
phenylethylamine	(o-H)	9.83		7.259	6.626	7.305	3.694	7.307	4.25	1.79	1.55
	(H-1)		60	2.824	4.560	3.060	1.062	3.166	1.299	4.33	3.51
	(H-2)		58	2.687	4.466	2.857	1.290	2.985	1.513	3.46	2.95
neopentylamine		10.15									
16 °C	CH_2		57	2.318	5.548	2.569	2.566	2.766	2.035	2.16	2.72
	CH_3		60	0.826	5.170	0.920	2.586	0.982	2.332	1.99	2.21
−30 °C	CH_2		74	2.266	3.158	2.611	0.846	2.733	2.733	0.846	3.73
	CH_3		80	0.794	2.724	0.911	0.857	0.941	0.922	3.18	2.95

Table V. Chemical Shift and Relaxation Time Values for the Protons at Positions a, b, c, and d of *p*-Allylcalix[4]arene in the Presence of an Equimolar Amount of Various Amines

		chemical shift values, δ				relaxation time values, T_1			
amine	pK_{BH^+}	a	b	c	d	a	b	c	d
none		6.914	5.837	4.927	3.160	1.945	4.758	2.884	1.234
tert-butylamine	10.83	6.776	5.854	4.974	3.126	1.197	3.772	2.055	0.657
neopentylamine	10.15	6.804	5.850	4.976	3.132	1.720	4.190	2.677	1.073
adamantylamine		6.783	5.856	4.977	3.129	1.411	3.536	2.445	
piperidine	11.12	6.778	5.838	4.980	3.129	1.496	4.205	2.465	0.909
phenylethylamine	9.83	6.820	5.839	4.986	3.142	1.524	4.171	2.523	0.975
morpholine	8.33	6.780	5.835	4.976	3.125	1.677	4.168	2.579	0.975
triethylamine	11.01	6.780	5.835	4.976	3.115	1.677	4.168	2.579	0.975
NaOH (at 16 °C)		6.763	5.857	4.974	3.114	1.835	4.526	2.939	1.093
NaOH (at −30 °C)		6.903	5.744	4.903	3.131	0.929	2.386	1.327	0.575

hydrogen (designated as position *a* in the table), the chemical shift values at 16 °C for the calixarene in the presence of *tert*-butylamine and neopentylamine are seen to be 90% and and 75%, respectively, as large as those for calixarene in the presence of NaOH. As with the amine component, these converge at −30 °C at values corresponding to ca. 85% of that of NaOH. The chemical shifts of the protons at positions b, c, and d show relatively little change upon complexation. Those at position e (observed as a broad resonance at 16 °C but as a pair of doublets at −30 °C), however, show a somewhat greater change, particularly in the presence of neopentylamine. The relaxation times for the protons at positions a, b, c, and d are significantly shorter in the presence of *tert*-butylamine and somewhat shorter in the presence of neopentylamine than in the presence of NaOH, again emphasizing the fact that the interaction with the amines is probably more than a simple proton transfer process.

A few studies of the interaction of amines and phenols in organic solvents has been reported in the literature. The most extensive recent work has been carried out by a group at the University of Wroclaw in Poland[2] who have applied cryoscopic, dielectric, dipole moment, nuclear quadrupole resonance, and infrared spectroscopic measurements to a variety of systems containing phenols and diethylamine in benzene and CCl_4 solutions. The conclusions from these investigations are that (a) the polarity of the hydrogen bond between the phenol and the amine depends on the pK_a of the phenol and (b) monomeric as well as dimeric complexes exist in these solvents. The first of these conclusions finds further support from an ESR study of the 1:1 hydrogen-bonded complexes formed between 2,2,6,6-tetramethylpiperidin-1-oxyl and various phenols in CCl_4 solution[3] in which the free energies of formation of the complexes correlate with the free energies of ionization of the phenols. The second of the conclusions is supported, to an extent, by an X-ray crystallographic study[4] of a complex derived from phenol which shows the complex to be a complicated network in which the phenolate oxygen is involved in multiple hydrogen bonds. Another recent study[5] also provides evidence for the existence of complexes containing phenols and amines in ratios ranging from 3:1 to 1:1. Although these data are commensurate with the process expressed in eq 1, they provide no insight into whether we are dealing with *exo*-calix or *endo*-calix complexes in the present system. As shown in Figure 1, the "*endo*-calix postulate" pictures the ammonium ion inside the cavity of the calixarene. The data in Tables I–III can be accommodated to either of these postulates. To rationalize the differences in relaxation values it simply need

(2) (a) Oszust, J.; Ratajczak, H. *J. Chem. Soc., Faraday Trans. 1* **1981**, *77*, 1209. (b) Oszust, J.; Ratajczak, H. *Ibid.* **1981**, *77*, 1215. (c) Grech, E.; Kaleník, J.; Malarski, Z.; Sobczyk, L. *Ibid.* **1983**, *79*, 2005.

(3) Bullock, A. T.; Howard, C. B. *J. Chem. Soc., Faraday Trans. 1* **1981**, *77*, 137.

(4) Hanson, A. W.; McCulloch, A. W.; McInnes, A. G. *Tetrahedron Lett.* **1982**, *23*, 607.

(5) Barry, J. E.; Finkelstein, M.; Ross, S. D. *J. Org. Chem.* **1984**, *49*, 1669.

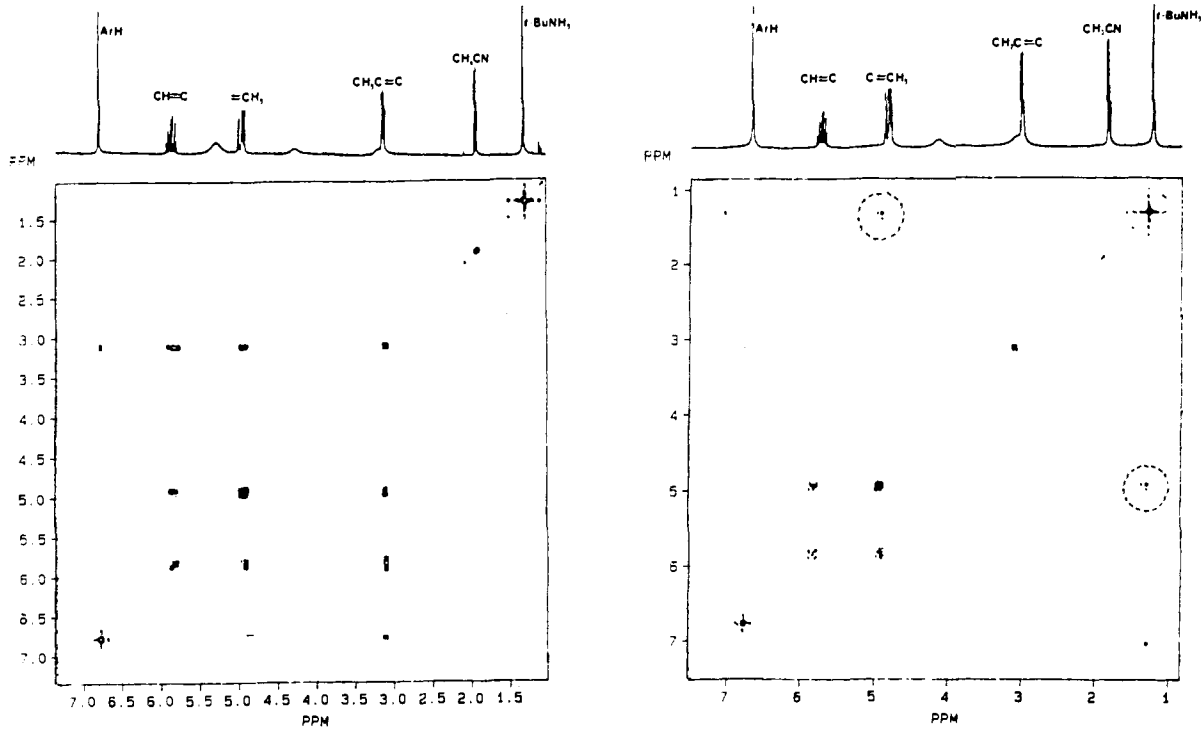


Figure 2. Contour plots of ^{1}H NMR spectra at 300 MHz of a 1:1 mixture of *tert*-butylamine and *p*-allylcalix[4]arene in CD_3CN solution at 17.8 °C: (a) 2D spectrum, (b) 2D NOE spectrum (the small signals on the upper-left to lower-right diagonal arise from leakage).

be postulated that *tert*-butylamine, because it is the stronger base, forms a tighter complex than neopentylamine, thus generating a larger number of higher molecular weight entities. Since all of the compounds in these systems are "small molecules", anything that increases their correlation times (i.e., diminishes the rotational and vibrational rates) will shorten the relaxation times.[6] Lowering the temperature, for example, increases the correlation time, thereby shortening the relaxation time as illustrated by the data in Table III for the T_1 values at 16 and −30 °C. An increase in effective molecular size will have a similar effect. To obtain more information on the relationship between amine basicity and complexation behavior the chemical shifts and relaxation times for several other amines were measured as shown in Tables IV and V.

Table IV shows the chemical shifts, the relaxation times for the protons in the amine component of the complexes, and T_1 reduction factors which are simply the ratios of T_1's in the absence and presence of calixarene or CF_3CO_2H. *tert*-Butylamine shows the highest $(T_1)_a/(T_1)_b$ reduction factor, approximately twice as high as phenylethylamine (taking the highest of its three values), piperidine, and adamantylamine. Although *tert*-butylamine is considerably more basic than phenylethylamine, it is comparable in basicity to adamantylamine and only slightly less basic than piperidine. Triethylamine, which is as basic as piperidine, shows lower $(T_1)_a/(T_1)_b$ reduction factors, viz., 3.34 and 2.47. Morpholine, on the other hand, which is the weakest base in this group, has $(T_1)_a/(T_1)_b$ reduction factors of 3.22 and 3.50, which are comparable to those of piperidine and higher than those of neopentylamine. Thus, it is clear that there is no direct correlation between the basicity of the amine and the way that the relaxation times of its protons are affected by complexation with the calixarene. This conclusion is corroborated, though in less emphatic fashion, by the data in Table V for the chemical shifts and relaxation times of the protons of the calixarene. For example, the relaxation times for the aromatic protons (position a) show no correlation with basicity: neopentylamine reduces T_1 from 1.945 to 1.720, whereas the weaker base morpholine reduces it to 1.677; *tert*-butylamine reduces T_1 to 1.197, whereas the stronger base triethylamine reduces it only to 1.677.

To gain further insight into the structure of amine–calixarene complexes a two-dimensional Nuclear Overhouser Effect experiment (2D NOE) was carried out on an equimolar mixture of *tert*-butylamine and *p*-allylcalix[4]arene in CD_3CN. The two-dimensional technique was the method of choice because it is more efficient than the conventional one-dimensional technique, and it provides a complete set of NOEs between all closely spaced protons. Also, the 2D technique obviates the adverse effects of limited selectivity of radio frequency irradiation of individual resonances. As an additional check, however, one-dimensional NOE difference spectral determinations were also made as well as a simple 2D HOMCOR NMR determination which showed no cross resonances arising from the *tert*-butylamine protons and the calixarene protons. The spectrum, pictured in Figure 2, shows a moderately strong pair of off-diagonal signals with the coordinates δ = ca 1.2 (methyl groups of *tert*-butylamine) and δ = ca. 5 (terminal protons of allyl groups of calixarene), indicating an interaction between these groups. Since the NOE effect is a through-space phenomenon that arises only if groups are proximate, one is forced to the conclusion that in the *tert*-butylamine:*p*-allylcalix[4]arene complex the amine is close to the allyl groups. Although the ^{1}H NMR data in Tables I–V are commensurate with either the *exo*-calix or *endo*-calix postulate, the NOE data provide strong evidence for the latter. Thus, a possible sequence of events involves the initial proton transfer followed by formation of an *exo*-calix complex which, through partial or complete conformational inversion of the calixarene, transforms into an *endo*-calix complex in a manner reminescent of a Venus fly trap capturing its prey, as depicted in Figure 1.[7] It is interesting to note that a 2D NOE spectrum of *p*-allylcalix[4]arene in CD_3CN solution containing 1% CH_3CN is very similar in appearance to Figure 2b. It shows a pair of off-diagonal resonances with coordinates at δ = ca. 1.9 (methyl group of CH_3CN)

(6) Cf. for example, the discussions by Colebrook and Hall: (a) Colebrook, L. D.; Hall, L. D. *Can. J. Chem.* **1980**, *58*, 2016. (b) Hall, L. D. *Chem. Soc. Rev.* **1975**, *4*, 401.

(7) We are indebted to a referee for altering our mindset concerning the cone conformation by suggesting that the 1,2-alternate and/or 1,3-alternate conformations might be more likely candidates because of the better contact they can provide between the anionic and cationic centers while still allowing approximation of the guest molecule and the allyl groups of the calixarene. The increase in the coalescence temperature in the ^{1}H NMR spectra of the calixarene:amine complexes noted earlier,[1] however, seems to be more easily interpreted in terms of cone conformations.

Table VI. Association Constants and Molar Absorptivities (Parenthetical Values) for Calixarene–Amine Interactions

	tert-butylamine	neopentylamine	*tert*-amylamine	*n*-butylamine
p-allylcalix[4]arene				
equation 2	1.3×10^4 (4640)	9.7×10^3 (3830)	1.4×10^4 (3630)	2.4×10^4 (3610)
equation 3	4.7×10^4 (4310)	3.0×10^4 (3530)	5.0×10^4 (3440)	9.6×10^4 (3470)
p-*tert*-butylcalix[4]arene				
equation 2	2.2×10^4 (2720)	2.6×10^4 (1960)		
equation 3	4.8×10^4 (2550)	6.0×10^4 (1850)		
p-morpholinomethylcalix[4]arene				
equation 2	8.9×10^2 (4360)			
equation 3	4.0×10^2 (4990)			
p-*tert*-butylbishomooxacalix[4]arene				
equation 2	2.0×10^3 (2530)	2.4×10^3 (2610)		
equation 3	1.7×10^4 (2520)	1.4×10^4 (2520)		
p-*tert*-butylcalix[6]arene				
equation 2	3.7×10^5 (5990)	8.0×10^5 (6000)		
equation 3	8.0×10^5 (6000)	8.0×10^5 (6210)		

and δ = ca. 5 (terminal protons of allyl groups of calixarene), commensurate with the residence of an acetonitrile molecule *inside* the cavity of the macrocycle, i.e., an *endo*-calix complex.

The initial investigation of the amine–calixarene interaction[1] seemed to indicate a fairly large association constant for the formation of the complex. In the hope of obtaining a quantitative estimate of its magnitude, UV measurements were made on dilute solutions containing several different calixarenes and amines in various ratios, a representative example of which is illustrated in Figure 3 where the ratio of neopentylamine to *p*-allylcalixarene is changed from 0 to 10, resulting in a change from an absorption pattern showing a major peak at 280 nm and a flat shoulder at 290 nm to one possessing a single, more intense, peak at 292 nm and a new, less intense, peak at ca. 310 nm. Solutions of *p*-allylcalix[4]arene in acetonitrile, chloroform, or methylene chloride show λ_{max} at 286–287 nm with a molar absorptivity of ca. 8650. Only in the case of the acetonitrile solution, however, does the addition of base cause a red shift and an increase in molar absorptivity. It is interesting to note that an alcohol solution of the calixarene displays a spectrum rather similar to that of the base-treated acetonitrile solution as also does a solution in acetonitrile–water (80:20).

To obtain the dissociation constants for calixarenes in the presence of amines, absorptivities were measured at various ratios of calixarene to amine and the data were analyzed by the Hildebrand–Benesi expression[8] (eq 2), where [H] is the concentration

$$\frac{[H]}{\Delta A_{311}} = \frac{1}{K_a \epsilon_{HG}[G]} + \frac{1}{\epsilon_{HG}} \qquad (2)$$

of calixarene, [G] is the concentration of amine, [HG] is the concentration of the calixarene–amine complex, A_{311} is the absorptivity at 311 nm (absorptivity of parent calixarene essentially zero at this wavelength), ϵ_{HG} is the molar absorptivity of the calixarene–amine complex, and K_a is the equilibrium constant for the reaction

$$H + G \rightleftharpoons HG$$

A computer-assisted curve fitting for the plot of $[H]/A_{311}$ vs. $1/[G]$ gave values for K_a and ϵ_{HG} shown in Table VI.

The data were also analyzed by a computer program[9] using eq 3 where $[H]_0$ and $[G]_0$ are the initial concentrations of calixarene and amine, l is the path length of the UV cell, and $\Delta\epsilon$ has the same meaning as ϵ_{HG} in the Hildebrand–Benesi equation. Although the K_a values obtained from these two treatments differ

$$K_a = \frac{[H]_0[G]_0 l \Delta\epsilon}{\Delta A_{311}} - ([H]_0 + [G]_0) + \frac{A_{311}}{l\Delta\epsilon} \qquad (3)$$

somewhat in magnitude, the ϵ_{HG} values match reasonably closely.

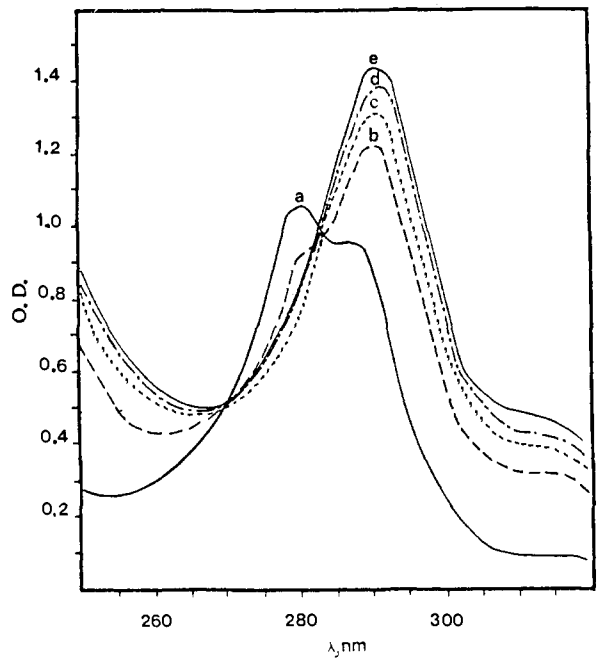


Figure 3. UV spectra of solutions containing various ratios of *p*-allylcalix[4]arene and neopentylamine in CH_3CN solution: (a) calixarene alone, (b) [amine]/[calixarene] = 1.0, (c) [amine]/[calixarene] = 2, (d) [amine]/[calixarene] = 4, (e) [amine]/[calixarene] = 10.

Since the assumption in the Hildebrand–Benesi expression that $[G] - [HG] \cong [G]$ (i.e., $[G] \gg [H]$) was not well satisfied in the present measurements[10] and since the computer program using eq 3 does not depend on this assumption, the values for K_a obtained from the latter are thought to be more accurate.

The values of K_a for *p*-allylcalix[4]arene and *p*-*tert*-butylcalix[4]arene with the four amines shown in Table VI vary by approximately a 3-fold factor, and the values of ϵ_{HG} vary by a slightly smaller factor. It is interesting to note, however, that the variations in these two parameters do not necessarily run in parallel. For example, *p*-allylcalix[4]arene with *n*-butylamine shows a higher K_a value than with *tert*-butylamine but a lower ϵ_{HG} value. Similarly, *p*-*tert*-butylcalix[4]arene with neopentylamine shows a higher K_a but a lower ϵ_{HG} value than does *p*-allylcalix[4]arene with *tert*-butylamine. We interpret this to mean that whereas the K_a value is dependent only on the acidity and basicity of the calixarene and amine, respectively, the ϵ_{HG} value is dependent on other factors as well, including the nature of the complex between the phenolate and ammonium ions. Thus, the considerably smaller ϵ_{HG} values for *p*-*tert*-butylcalix[4]arene with *tert*-butylamine and neopentylamine as compared with *p*-allylcalix[4]arene might arise from a looser complex, this the result

(8) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
(9) Drago, R. S. *Physical Methods in Chemistry*; Saunders: Philadelphia; 1977; pp 89–91. We are indebted to Professor Andrew Maverick for calling our attention to this program and for providing help in using it.
(10) See a discussion by Bergeron and Roberts: Bergeron, R. J.; Roberts, W. P. *Anal. Biochem.* **1978**, *90*, 844.

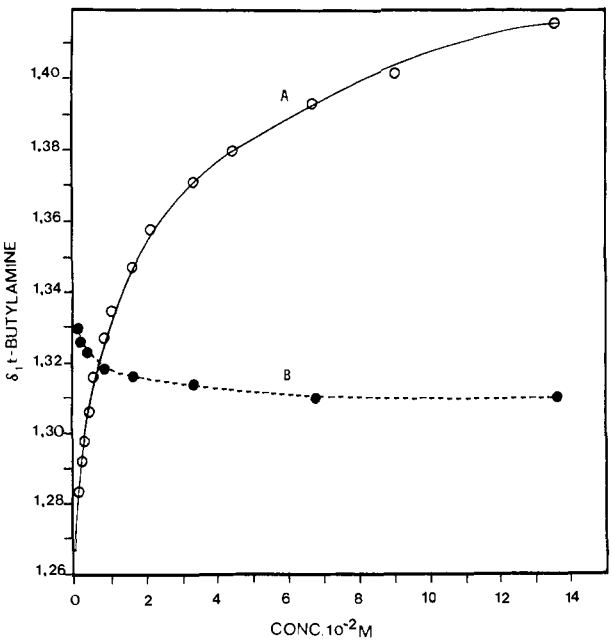


Figure 4. ^{1}H NMR chemical shift values for the CH_3 protons of *tert*-butylamine over the concentration range 1–140 × 10^{-3} M in the presence of (a) an equimolar amount of *p*-allylcalix[4]arene and (b) an excess of CF_3CO_2H.

of the smaller and probably less accessible cavity (if in the cone conformation) or cleft (if in the 1,3-alternate conformation) in *p-tert*-butylcalix[4]arene.

The pK_{BH^+} for *tert*-butylamine is 10.83 in aqueous solution. Using the association constant of 4.7 × 10^4 shown in Table VI, we calculate that the pK_a for the calixarene is approximately 6.2. Böhmer[11] has determined the pK_a's of a pair of mononitrocalix[4]arenes in aqueous solution and has obtained values of 4.3 and 6.0, which represent a reduction of 2.85 and 1.15 units, respectively, from the pK_a of *p*-nitrophenol. The value of 6.2 for *p*-allylcalixarene represents a reduction of 3.8 p*K* units from that of *p*-allylphenol which is assumed to have a pK_a close to that of phenol (pK_a = 10). This increment agrees approximately with the values obtained by Böhmer even though solvents of widely differing character are involved in the two sets of measurements. The fact that pyridine fails to effect proton transfer with calix[4]arenes[1] is also in accord with these K_a values, because the pK_{BH^+} of pyridine is only 5.25.

The interaction of amines with three other calixarenes was also briefly explored. *p*-Morpholinocalix[4]arene (**1c**) was found to be ca. 100 times less acidic than *p*-allylcalix[4]arene, presumably the result of its existence as a zwitterion[12] (i.e., the proton transfer to the external amine is from the protonated morpholino moiety rather than the phenolic moiety). The molar absorptivity of the *tert*-butylamine:*p*-morpholinocalix[4]arene interaction, nevertheless, is about the same as that for the *tert*-butylamine:*p*-allylcalix[4]arene interaction, suggesting that similar complexes are formed. *p-tert*-Butylbishomooxacalix[4]arene,[13] on the other hand, has a value comparable to that of *p*-allylcalix[4]arene but shows a considerably lower molar absorptivity, suggesting less effective complex formation. *p-tert*-Butylcalix[6]arene[13] shows higher K_a values as well as higher molar absorptivities than any of the other calixarenes that were studied, suggesting that more effective complexation occurs in this case. The complexation characteristics of calix[6]arenes will be considered in more detail in a separate communication.

In an attempt to provide a continuum from the UV measurements (which are carried out in very dilute solutions) to the NMR measurements (which are carried out in more concentrated solutions), NMR determinations were made on equimolar mixtures of *p*-allylcalix[4]arene and *tert*-butylamine over a concentration range from 10^{-3} to 2.8 × 10^{-1} M. Although *p*-allylcalix[4]arene by itself is soluble only to the extent of 5 mg/g of CD_3CN, in the presence of amine the solubility increases to ca 160 mg/g of CD_3CN. Figures 4 and 5 show plots of the chemical shifts of the *tert*-butylamine protons as a function of concentration, and Figure 4 also shows the results of a similar study with CF_3CO_2H instead of calixarene as the acidic component. The calixarene and CF_3CO_2H plots are reciprocal to one another, the calixarene inducing a continuously increasing downfield shift in the resonance position with increasing concentration of CF_3CO_2H inducing a decreasing downfield shift with increasing concentration. At concentrations above ca. 10^{-2} M, however, the CF_3CO_2H plot is approximately flat, in accord with UV studies which indicate that proton transfer is essentially complete at or below this concentration. Although it is not possible to achieve sufficiently high concentrations to closely approach the asymptote for the calixarene–amine interaction, a reciprocal plot ($1/c$ vs. $1/\delta$) allows a reasonably reliable extrapolation to high concentrations, producing a limiting value of δ = 1.51. From the plot shown in Figure 4 a reasonably reliable extrapolation to infinite dilution can be made, producing a limiting value of δ = 1.26. With these values, the magnitude of K_2 is calculated to be 50 ± 5. In similar fashion, the T_1 values for a 1:1 mixture of calixarene and amine were measured over a concentration range of 3 × 10^{-2} to 28 × 10^{-2}, with the results shown in Figure 5. The extrapolated values for

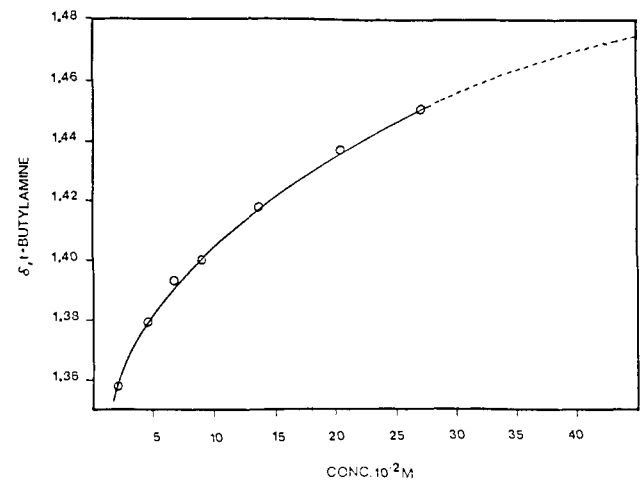


Figure 5. ^{1}H NMR chemical shift values for the CH_3 Protons of *tert*-butylamine over the concentration range 3–30 × 10^{-2} M in the presence of an equimolar amount of *p*-allylcalix[4]arene.

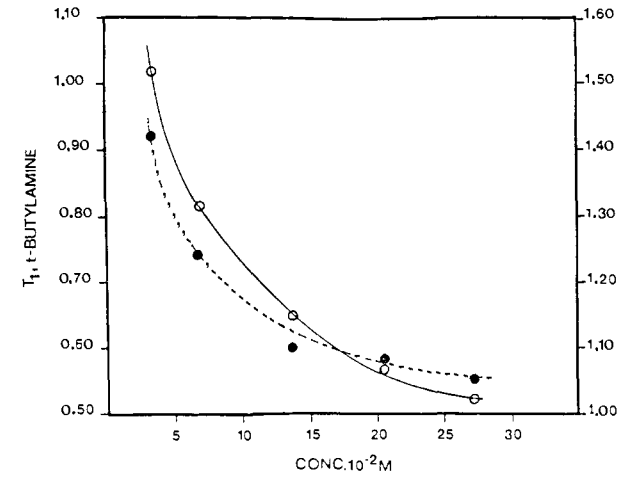


Figure 6. Relaxation times (T_1) for the CH_3 protons of *tert*-butylamine and the aryl protons of *p*-allylcalix[4]arene in a 1:1 mixture over the concentration range 3–30 × 10^{-2} M.

(11) Böhmer, V.; Schade, E.; Vogt, W. *Makromol. Chem., Rapid Commun.* **1984**, *5*, 221.
(12) Gutsche, C. D.; Nam, K. C., unpublished observations.
(13) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

Table VII. Data for Determination of K_1 by Eq 2

[calixarene]/[amine]	ΔA_{311}	[calixarene]/ΔA	[amine]	1/[amine]
1	0.566	3.11×10^{-4}	1.76×10^{-4}	5.68×10^{3}
0.6	0.649	2.71×10^{-4}	2.93×10^{-4}	3.54×10^{3}
0.5	0.680	2.59×10^{-4}	3.52×10^{-4}	2.84×10^{3}
0.37	0.705	2.50×10^{-4}	4.76×10^{-4}	2.10×10^{3}
0.33	0.711	2.48×10^{-4}	5.34×10^{-4}	1.87×10^{3}
0.25	0.736	2.39×10^{-4}	7.04×10^{-4}	1.42×10^{3}

the T_1's at "infinite" concentration are 0.55 and 0.98 for the *tert*-butylamine and calixarene aryl protons, respectively. For the T_1's of the uncomplexes components, the T_1 of *tert*-butylamine in the presence of CF_3CO_2H (2.115) and that of the calixarene in the presence of NaOH (0.0835) were used. With these values the magnitude of K_2 is calculated to be 65 ± 5, in reasonably good agreement with the values calculated from the chemical shift data.

The data obtained in the present study show that the association constants for the interaction of *p*-alkylcalix[4]arenes and amines, as expressed in eq 1, are approximately 10^6. On the basis of the UV and ^{1}H NMR data, these constants are viewed as the product of a proton transfer step, which accounts for the larger fraction of the overall constant, and an *endo*-calix-forming step, which accounts for the smaller fraction.

Experimental Section

The calixarenes used in this study were prepared by methods previously described: calix[4]arene,[14] *p-tert*-butylcalix[4]arene,[15] *p*-allylcalix[4]arene,[14] *p*-morpholinomethylcalix[4]arene,[12] *p-tert*-butylbishomooxacalix[4]arene,[13] *p-tert*-butylcalix[6]arene.[13]

Determination of Spin–Lattice Relaxation Times (T_1). Solutions of *p*-allylcalix[4]arene and the appropriate amine in CD_3CN were used without degassing. Comparisons with degassed samples showed almost imperceptible differences, as has also been noted by other workers.[6a] The T_1 values of the proton resonances were obtained at 300 MHz and 25 °C on a Varian XL-300 spectrometer with the use of the inversion recovery method.[16] To determine the T_1 of a given resonance a series of spectra (each consisting of 8–20 scans) was obtained by using 180°–τ–90° pulse sequences (available in the XL-300 library). The equilibration time (D_1) was chosen to be 3–4 times the longest T_1 of interest (20–24 μs). Data acquisition for various recovery times (D_2) was accomplished by creating an array of D_2 values to cover a range of 0.1–3 times T_1, 8–12 values of D_2 being selected to ensure accurate results. All of the T_1 determinations were repeated 3 times, providing values within 5% of one another.

Table VIII. Data for Determination of K_1 by Eq 3

[H]/[G]	$[H]_0$	$[G]_0$	ΔA_{311}	ϵ_{HG}	K_a
1.0	1.76×10^{-4}	1.76×10^{-4}	0.566	4310	6.6×10^{4}
0.6	1.76×10^{-4}	2.93×10^{-4}	0.649	4310	4.1×10^{4}
0.5	1.76×10^{-4}	3.52×10^{-4}	0.680	4310	4.5×10^{4}
0.37	1.76×10^{-4}	4.76×10^{-4}	0.705	4310	4.2×10^{4}
0.33	1.76×10^{-4}	5.34×10^{-4}	0.711	4310	4.1×10^{4}
0.27	1.76×10^{-4}	6.52×10^{-4}	0.729	4310	5.1×10^{4}
0.25	1.76×10^{-4}	7.04×10^{-4}	0.736	4310	6.1×10^{4}

Determination of the 2D NOE ^{1}H NMR Spectrum of a 1:1 Mixture of *p*-Allylcalix[4]arene and *tert*-Butylamine. A spectral width of 200 Hz was used. The data set consisted of 1024 points in the t_1 dimension and 1024 points in the t_2 dimension; 256 free induction decays were accumulated. The 90° pulse width was 21.55 μs, the mixing time was 0.200 s, and the equilibration time (D_1) was 4.0 s. The value of D_2, set to 0, automatically varies between 0 and the ratio of free induction to spectral width (NI/SW_2). After the double Fourier transformation a folding around (fold T) an axis of the 2D spectrum was performed to increase the sensitivity and discrimination against nonsymmetric data.

Determination of UV Spectra. The UV spectra were measured on a Bausch and Lomb Spectronic 1001 instrument with acetonitrile (Aldrich Gold Label) as the solvent.

Determination of K_1 Values. A typical set of data used for analysis via the Hildebrand–Benesi treatment (eq 2) is shown in Table VII. From these data a slope of 1.68×10^{-8} and an intercept of 2.15×10^{-4} were evaluated with a computer assisted curve fitting program.[17] From these data the values of $K_a = 1.3 \times 10^4$ M^{-1} and $\epsilon_{HG} = 4640$ were calculated.

A typical set of data used for analysis via a computer program using eq 3 is shown in Table VIII. From these data values of $K_a = 4.7 \times 10^4$ M^{-1} and $\epsilon_{HG} = 4310$ were calculated.

Acknowledgment. We are indebted to the National Institutes of Health (Grant GM-23534) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous financial support of this work.

(14) Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802.
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(16) Vold, R. L.; Waugh, J. S.; Klein, M. P.; Phelps, D. E. *J. Chem. Phys.* **1968**, *48*, 3831.
(17) *Curve Fitting* by Interactive Microware, Inc., State College, PA 16801.