Figure 4. Optimized geometries for $H_2CN_2^{+\cdot}$ and $PhCHN_2^{+\cdot}$ calculated by UHF/STO-3G.

24-mL test tube with a rubber septum was purged with argon, and then a 0.1-mL acetonitrile solution of 4.5 mM copper(II) perchlorate was added using a syringe. The solution became colorless within 1 min, and the products were determined similarly by GLC. Oxidation with a tris(*p*-bromophenyl)aminium hexachloroantimonate (6.6 mM) solution was carried out in the same way.

Formation of 1,2-Diphenylcyclohexene (8) from Bis(diazo) Compound 7. An acetonitrile solution of 2.0 mM 7 and 0.2 mM DCA was purged with argon and irradiated (>400 nm) for 5 min. The product 8 was identified by ^{1}H NMR and by GC-MS in comparison to the authentic sample,[58] and the yield determined by GLC was 96%. Similarly, the oxidation of 2.0 mM 7 by copper(II) perchlorate (0.03 equiv) afforded 8 in 95% yield.

ESR Measurement. ESR spectra were measured on a Varian E-112/V7800 spectrometer equipped with a temperature controller. The microwave frequency was measured with a Takeda Riken 5201M frequency counter, and the resonance magnetic field values of the signals were measured with the aid of a Varian E500 NMR G-meter.

A simple two-electrode cell for low-temperature ESR studies developed by Ohya-Nishiguchi[59] was employed. The sample solution was degassed in the reservoir of the cell by repeated freeze–pump–thaw cycles and poured into the quartz tube. No reference electrode was used in the ESR measurements, but the applied potential vs Ag/AgCl could be calibrated from the applied voltage using a Hokuto Denko HA301 potentiostat. The sample was cooled in ESR the cavity and the applied voltage was raised. The ESR spectra were recorded at optimal voltage on steady state.

Theoretical Calculations. The calculations were carried out on FACOM M-780/20 or HITAC M-680H and S-820/80 computers using GAUSSIAN 80[60] or GAUSSIAN 82[61] programs. The structures of π- and σ-PhCHN$_2^{+\cdot}$ were optimized with the UHF/STO-3G[33] procedure, and using the geometry the energies were recalculated with MP2/STO-3G.[34] Both the structures have energy minima in planer C_s symmetry, and the bond lengths and angles are summarized in Figure 4.

The spin densities of σ-H$_2$CN$_2^{+\cdot}$ and H$_2$C=N—O$^\cdot$ were calculated with the UHF/4-31G procedure.[37] The optimized geometries and total energies for σ-H$_2$CN$_2^{+\cdot}$ are as follows: bond lengths, R(C–N) = 1.350 Å, R(N–N) = 1.208 Å, R(C–H$_{syn}$) = 1.079 Å, R(C–H$_{anti}$) = 1.073 Å; bond angles, C–N–N = 124.07°, H$_{syn}$–C–N = 122.21°, H$_{anti}$–C–N = 116.59°; total energy for H$_2$C=N—O$^\cdot$: bond lengths, R(C–N) = 1.288 Å, R(N–O) = 1.289 Å, R(C–H$_{syn}$) = 1.071 Å, R(C–H$_{anti}$) = 1.066 Å; bond angles, C–N–O = 124.21°, H$_{syn}$–C–N = 122.65°, H$_{anti}$–C–N = 117.15°; total energy, –167.984856 au.

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Salt Effects on Supramolecular Complexation and Catalysis[1]

Hans-Jörg Schneider* and Isolde Theis

FR Organische Chemie der Universität des Saarlandes, W-6600 Saarbrücken 11, Germany
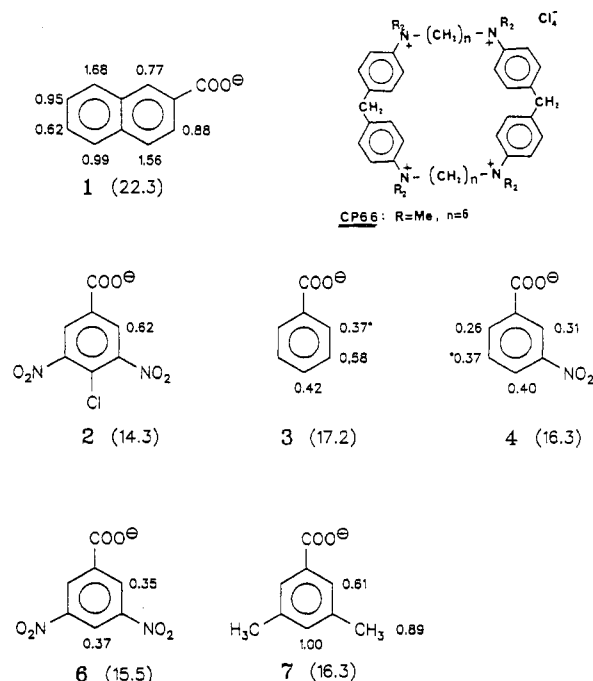
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Complexation equilibria between a positively charged azoniacyclophane (CP66) and naphthalene-2-carboxylate in water show a linear Debye–Hückel correlation with a sensitivity of $m = -1.5$ compared to the $m = -4.1$ for pure ionic complexes observed experimentally and predicted theoretically. The m values can be used as a scale for ionic vs lipophilic van der Waals binding contributions; the latter dominate in the present azoniacyclophane complexes. Complexation-induced NMR shifts (CIS) vary from –0.3 ppm to –1.6 ppm shielding and demonstrate in all cases intracavity inclusion with different geometries. The cyclophane CP66 enhances rates of nucleophilic substitution of 1-chloro-2,6-dinitrobenzoic acid (2) with OH$^-$ by a factor of up to $\sim$2, with NO$_2^-$ by up to $\sim$8. The elimination from 2-(*p*-nitrophenyl)ethyl mesylate to *p*-nitrostyrene under basic conditions is enhanced by up to $\sim$5; the saturation curve obtained in this case indicates a limiting $k_{cat}/k_{un} \cong 10$ and a binary complex constant of $K \approx 15$ M^{-1}. Salt effect studies show that a considerable part of the rate enhancements by macrocyclic polyammonium ions can be due to the increase of ionic strength as a consequence of the multiple charges in the catalyst. The ionic strength/salt effect contribution is large in the reaction of 2 with OH$^-$, but smaller for the other two reactions.

The presence of salts can have a profound effect on the complexation between organic host and guest molecules,[2] as well as on their catalytic properties. This is expected especially for interactions with host structures bearing

Chart I. Complexes of H = CP66 with Guest Molecules 1-7 ($\Delta G°_{cplx}$ (kJ/mol, in Parentheses) and CIS Values (ppm; All Upfield) of the Different Guest Protons[a]

Figure 1. Debye–Hückel correlation of salt effects (NaCl) on equilibrium constants (CP66 + 1 in D_2O, 300 ± 2 K); slope $m = -1.45$; correlation coefficient $r = 0.9992$.

[a] In D_2O at pH = 7.0; $\Delta G°_{cplx}$ values [kJ/mol] extrapolated to ionic strength $I = 0$ with eqs 1 and 2 and $m = -1.5$ (see text). Shifts denoted * had to be obtained from single measurements due to signal overlapping during titration.

multiple charges; the latter are often necessary in order to make systems with large lipophilic cavities sufficiently soluble in water. One of the intriguing aspects of supramolecular catalysis, on the other hand, is to replace organic solvents eventually by water. Several of the enzyme-analogue catalysts described in recent years contain a number of charged nitrogen atoms.[3-6] The simultaneous presence of multiple charges in one macrocyclic host (with concentration c) and the square dependence of the ionic strength I on their number z leads to a strong attenuation

$$I = 0.5\sum_i c_i z_i^2 \tag{1}$$

of those complexations which are based partially or entirely on electrostatic interactions, whereas associations with electroneutral host or guest molecules are only affected by weaker salting-in or salting-out effects.

Model Host–Guest Complexes. Salt Effects on Equilibrium. The guest compounds selected for the present study are presented in Chart I together with related structures which together show clear evidence for intracavity inclusion within the host CP66[7,8] by the complexation induced ^{1}H NMR shifts on 1-7 (see CIS values
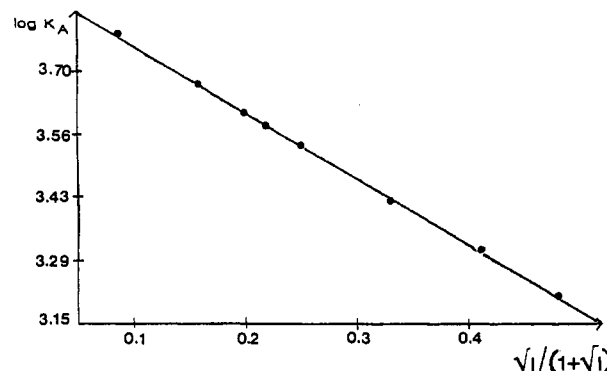
in Chart I). The larger shifts as well as the larger complexation free energy $\Delta G°_{cplx}$ observed with 1 result from the closer contact of the naphthalene (1) compared to the phenyl moieties 2-7 with the cavity walls; the observed CIS values on 1 agree semiquantitatively with the shielding by aromatic ring current and N^+ electrical field effects as calculated for pseudoequatorial inclusion of naphthalene derivatives in CP66.[7] The phenyl derivatives 2-7 show necessarily smaller shifts due to their protons being more remote from the host aromatic ring currents. The smaller CIS on the protons vicinal to the COO^- group are typical for the partial withdrawing of the phenyl rings out of the cavity due to the attraction between the host N^+ and the guest COO^- charges; molecular models show that only the β-naphthoate 1 can exert a close contact between N^+ and COO^- with simultaneous full intracavity immersion of the naphthalene moiety.[9] The presence of nitro substituents needed for the kinetic studies (see below) in 3,5-position to COO^- (2, 6) leads to a decreasing complexation presumably due to distortion of an ideal $N^+\cdots COO^-$ contact and/or due to their hydrophilic nature in contrast to the methyl compound 7.

The salt effect on an equilibrium constant K was studied with the naphthoate 1 and CP66 and substantiated our earlier findings with the 2,4-dinitronaphtholate 1 anion,[2] yielding again a linear correlation between $\log K$ and the Debye–Hückel term $f(I)$ (Figure 1) with a similar slope ($m = -1.45$ vs $m = -0.98^2$). The extended Debye–Hückel equation[10] would predict $m = -4.07$ if the macrocyclic

$$\log K = \log K° + m\sqrt{I}\big/(1 + \sqrt{I}) \tag{2}$$

receptor CP66 and its complex with 1 are treated as normal ions with $z = 4$, $z = 3$, and $z = -1$ for 1. We have indeed observed[2] slopes of $m = -4.1$ (or $m = -3.3$ at higher salt concentration) with a macrocyclic tetraphenolate complex, for which independent evidence[9,12] shows electrostatic interactions to dominate. Other findings such as from systematic comparisons of $\Delta G°_{cplx}$ with charged and electroneutral naphthalene complexes with CP66 have, on the other hand, demonstrated predominantly non-Coulomb, van der Waals-type contributions to binding.[9,12] Obviously, the slope from the then even more surprisingly linear De-

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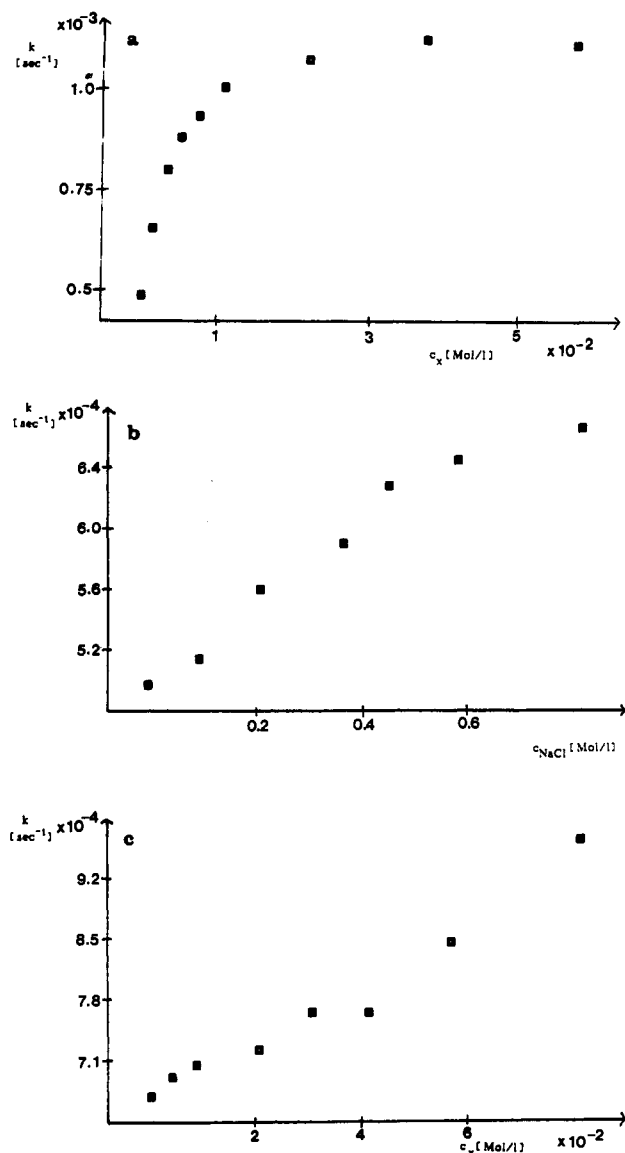
Figure 2. Rate constant k profiles for the reaction of 2 with OH: (a) k as a function of catalyst concentration [CP66]; (b) k as a function of salt concentration [NaCl]; (c) k as a function of catalyst concentration [CP66] at *constant* ionic strength I.

bye–Hückel correlations can be used as an approximate and empirical size indicator for Coulomb contributions to supramolecular complex formation.

Catalysis of Nucleophilic Substitutions.[13] The *basic hydrolysis* of dinitrochlorobenzoate 2 can be conveniently followed by continous UV measurements[5] and was therefore chosen for a kinetic study. The pseudo-first-order rate constants measured with constant [OH$^-$] concentration showed only moderate enhancements with [CP66], however, a saturation phenomenon reminiscent of Michaelis–Menten kinetics (Figure 2a). On the other hand the reaction between substrate and nucleophile, both with negative charge, is also accelerated by NaCl (Table 1). In line with the Bronsted–Bjerrum equation,[10] we find a

$$\log k = \log k_o + 1.02 z_A z_B \sqrt{I} \big/ (1 + \sqrt{I})$$ (3)

correlation between $\log k$ and the ionic strength from the

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Table I. Rate Constants k with 2^a

(A) For the reaction 1 + OH$^-$

[CP66] (10^2 M)	k (10^3 s^{-1})
–	0.49
0.11	0.66
0.29	0.80
0.47	0.885
0.72	0.94
1.06	1.01
2.17	1.07
3.67	1.12
5.68	1.11

(B) For 2 + OH$^-$ at constant ionic strength I

[NaCl] (M)	[CP66] (10^2 M)	k (10^4 s^{-1})
–	–	4.91
0.80	–	6.69
0.76	0.40	6.94
0.72	0.80	7.06
0.60	2.00	7.20
0.50	3.00	7.63
0.40	4.00	7.67
0.24	5.60	8.46
–	8.00	9.66

(C) For the reaction 2 + NO$_2^-$ at constant ionic strength I

[NaCl] (M)	[CP66] (10^2 M)	k (10^4 s^{-1})
–	–	1.42
0.80	–	1.86
0.746	0.50	2.98
0.721	0.81	3.54
0.700	0.995	3.91
0.513	3.00	7.26
0.298	5.01	10.2
0.226	6.00	11.4
–	8.02	14.6

^{a} Reactions in H$_2$O; for 2 + OH$^-$ at 45.0 ± 0.1 °C; for 2 + NO$_2^-$ at 60.0 ± 0.10 °C; concentrations: [2] = 4.00 × 10^{-4} M; [OH$^-$] = [NO$_2^-$] = 0.10 M.

Table II. Rate Constants k for Eliminations with 8^a

|	[CP66] (10^2 M)	k (10^3 s^{-1})
	–	0.60
	0.55	0.98
	1.02	1.24
	3.04	2.40
	4.03	3.06
	5.84	3.54
	7.89	3.63
[NaCl]	0.24	0.49
[TEBAC]	0.24	0.88

^{a} Reactions in H$_2$O at 40.0 ± 0.1 °C, with [8] = 2.2 × 10^{-4} M, [OH$^-$] = 0.2 M; experiments with NaCl and TEBAC (tetraethylbenzylammonium bromide) without CP66.
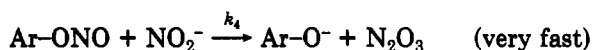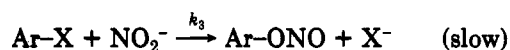
added sodium chloride concentration (Figure 2b). A large part of the rate enhancement by CP66 is therefore due to the ionic strength effect of this host. However, if one keeps the ionic strength constant by addition of suitable amounts of NaCl while varying the catalyst concentrations one still sees moderate rate enhancements due to the macrocycle (Figure 2c). The scatter of the points, the small catalytic efficiency, and the limited solubility of CP66 does not allow one to reach a saturation curve. Furthermore, it must be borne in mind that the ionic strength calculated for the bulk medium can vary substantially from that of the microenvironment.

The *nucleophilic substitution with nitrite* is of particular interest as supramolecular catalysis can also reverse the usual regioselectivity observed with these ambident anions.[6] As shown earlier by Rosenblatt et al.,[14] however,

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(14) Rosenblatt, D. M.; Dennis, W. H., Jr.; Goodin, R. D. *J. Am. Chem. Soc.* **1973**, *95*, 2133.
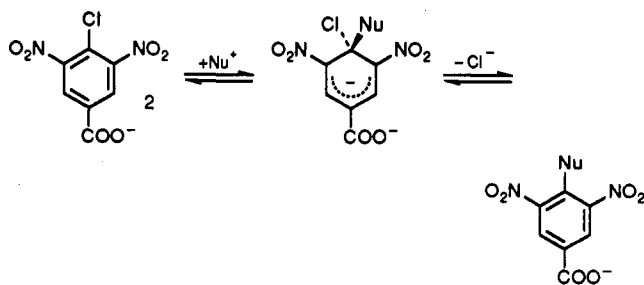
the reaction of nitrite with 2,4-dinitrochlorobenzene leads to the corresponding phenoxide as final product, since the first formed nitro compound $Ar-NO_2$ is converted faster via the nitrite ester Ar–ONO to the phenoxide; the latter reaction also proceeds faster than the Ar–ONO formation:[14]

$$Ar-X + NO_2^- \xrightarrow{k_1} Ar-NO_2 + X^- \quad \text{(slow)}$$

$$Ar-NO_2 + NO_2^- \xrightarrow{k_2} Ar-ONO + NO_2^- \quad \text{(faster)}$$

$$Ar-X + NO_2^- \xrightarrow{k_3} Ar-ONO + X^- \quad \text{(slow)}$$

$$Ar-ONO + NO_2^- \xrightarrow{k_4} Ar-O^- + N_2O_3 \quad \text{(very fast)}$$

Kinetic measurements showed that the appearance of the dinitro phenoxide Ar–O⁻ starts only after about 20% conversion (Figure 3a). This induction period is due to the slow buildup of the nitro derivative $Ar-NO_2$;[14] it was not reported for the micelle-catalyzed reaction by Broxton et al.[13b] After the induction period the observed rates obeyed clean (pseudo-)first-order kinetics.

The catalysis upon addition of the macrocycle CP66 amounts to enhancements of observed rate constants (k_{obs}) vs the uncatalyzed reaction ($\simeq k_{un}$) of up to $k_{obs}/k_{un} \simeq 8$. Again, efficiency as well as solubility of the catalyst were too low for reaching saturation curves (Figure 3b). Measurements with high ionic strength (0.8 M NaCl) in the absence of catalyst lead to rate enhancements of only $k_{obs}/k_{un} \simeq 1.3$, showing almost negligible salt effect in this case.

Carbanionic Elimination. The base-catalyzed reaction from [(p-nitrophenyl)ethyl]-β-sulfonic ester 8 to nitrostyrene was also monitored by UV. The olefin proved to be stable under the reaction conditions, in contrast to styrene itself and other derivatives which polymerized too fast. Both the formation of a largely carbanionic[15] intermediate and the OH⁻ concentration enhancement around the N⁺ atoms of the host compound CP66 (proximity effect) could lead to catalysis. This was indeed observed not only in terms of a rate acceleration reaching $k_{obs}/k_{un} \simeq 5$ but also in terms of Michaelis–Menten type saturation curve (Figure 4). Computer simulation of the rate–concentration profile using a numerical least-squares fit program[15] reproduced the experimentally observed points with an equilibrium constant $K \simeq 15$ M⁻¹ for the binary complex CP66·8—in fact, a ternary complex including associated OH⁻ anions—and a catalytic constant of $k_{cat} \simeq 6.8 \times 10^{-3}$
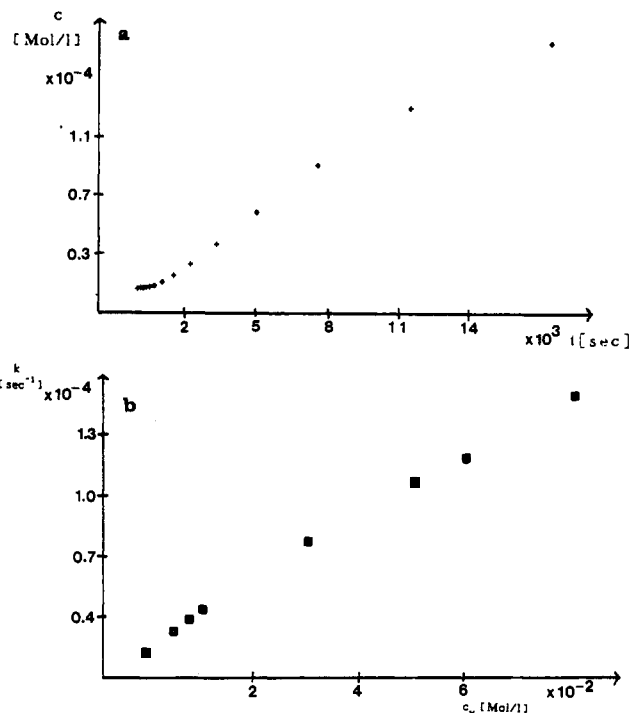

Figure 3. Rate constant k profiles for the reaction of 2 with NO_2^-: (a) k as a function of catalyst concentration [CP66]; (b) the same, however at constant ionic strength I.
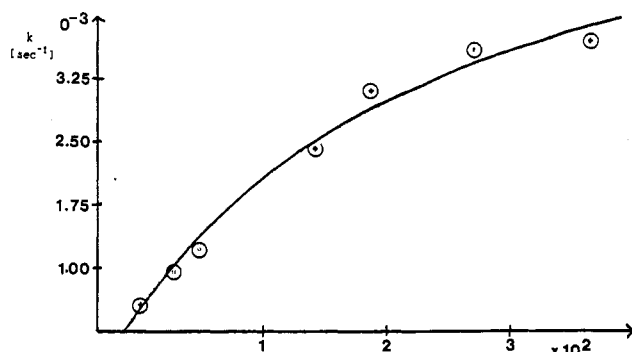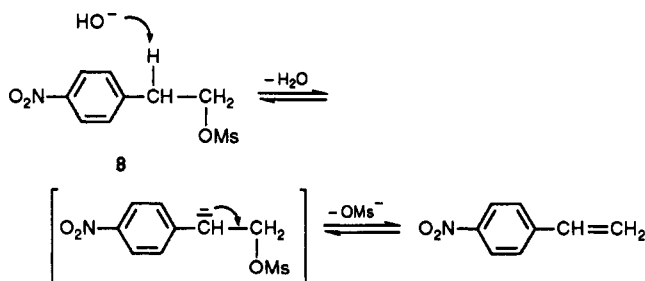

Figure 4. Rate constant k profiles for the elimination reaction of 8; k as a function of catalyst concentration ratio [CP66]/[8]; the computer simulated curve[15] indicates $K \simeq 15$ M⁻¹; $k_{cat} \simeq 6.4 \times 10^{-3}$ s⁻¹.

s⁻¹, indicating a theoretical rate enhancement by a factor of ~10.

Again, the neat salt effects on the reaction were studied by addition of sodium chloride (0.24 M), leading to small rate retardation, and of triethylbenzylammonium chloride (TEBAC), leading to small rate acceleration (Table I). The significantly larger effects observed with CP66 emphasize that the stabilization of negatively charged intermediates and transition states by complexation within suitable endolipophilic macrocycles bearing opposite charges does

(15) Eliminations with *p*-nitrophenyl ethyl derivatives, *p*-X-C₆H₄CH₂CH₂Y, although certainly not representing pure borderline E1cb cases, are expected to proceed largely via anionic transition states; see, e.g., the relatively large Brönsted constants with β = 0.67 for *p*-X = NO₂ compared to β = 0.56 for X = H or β = 0.39 for X = CH₃ (values from: Hadson, R. F. In *Chemical Reactivity and Reaction Paths*; Klopman, G., Ed.; Wiley: London, New York, 1974; p 167). For further references emphasizing the carbanionic character of many elimination reactions see: Bordwell, F. G. *Acc. Chem. Res.* 1972, 5, 374.

hold some promise for supramolecular catalysis. The high polarity of water as well as the high ionic strength around the charges will decrease the favorable electrostatic interactions; in addition, the necessary desolvation of both host and nucleophile or base will limit the achievable catalytic efficiency.

Experimental Section

Complexation constants with CP66 were determined as described previously[2] using NMR titrations in D_2O at pH = 7.0, 300 ± 5 K, with guest compounds 1–7 usually starting with concentrations of $[G]$ = 1.0 × 10^{-3} M and [CP66] = 8.8 × 10^{-3} M. The equilibrium constants K (in 10^{-3} M^{-1} units) were as follows (before/after correction for ionic strength): 1 (7.0/8.2); 2 (0.21/0.32); 3 (0.78/1.05); 4 (0.51/0.71); 6 (0.36/0.53); 7 (0.51/0.72). The titrations were performed by adding the host CP66 solution in usually six to eight increments; the nonlinear least-squares curve fitting[2] of the observed ^{1}H NMR shifts gave K and CIS values (Chart I) which agreed within usually ±5% (in K) for each measurement.

The salt effects on the complexation constant K for 1 with CP66 (Figure 1) were obtained from single measurements at concentrations appropriate for higher complexation degrees[2] by comparing the observed shift changes to the CIS values which were determined independently once for a given salt concentration, assuming a negligible CIS dependence on salt concentration. The ionic strength term calculated from [CP66] and added sodium chloride (see below) varied as follows: 0.09, 0.16, 0.20, 0.22, 0.25, 0.33, 0.41, 0.48; the corresponding K values (in 10^{-3} M^{-1} units) were: 5.97, 4.71, 4.13, 3.80, 3.45, 2.65, 2.06, 1.63. The ionic strength term $\sqrt{I}/(1 + \sqrt{I})$ of the Debye–Hückel eq 1 was calculated for the sum of the ionic host CP66, the guest G, and the added

electrolyte NaCl concentrations with $I = 0.5\sum_i c_i z_i^2$. For the free host H = CP66 (z = 4) we arrive at $I = 10[H]$; for the complex H·G (z = 3) at $I = 6[H·G]$.

Kinetic Measurements. The reactions of 1-chloro-2,6-dinitrobenzoate (2) with either OH^- or NO_2^- were monitored by recording the UV extinction of the resulting phenoxide at 428 nm (Kontron Uvikon 860 UV/vis spectrometer, data registration, and procession with Apple and PC-compatible computers with suitable programs[16]. The temperature was kept constant (±0.02°) by thermostated cells; the compounds were added with syringes from stock solutions. The reactions were usually followed up to 10 half-lives and showed clean (pseudo-)first-order kinetics (with 2 + NO_2 after a 20-min induction period, see above). The elimination reaction from 8 was followed by the UV absorptions at 304.9 nm; independent measurements yielded the extinction coefficients = 3403 M^{-1} cm^{-1} for 8 and 7504 M^{-1} cm^{-1} for the product nitrostyrene; the Lambert–Beer measurements between 1 and 3 [IO^3M^{-1}] showed linear correlations coefficients of $r >$ 0.99.

Compounds were either prepared as described earlier (CP66[17]) or were commercially available (2–7) and recrystallized if their spectroscopic purity (NMR) was found to be <95%. The ester 8 was obtained from 2-(p-nitrophenyl)ethanol and methanesulfonyl chloride in pyridine using standard procedures.

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Multipath Reactions between Intramolecularly Formed Oxazolium Salts and Nucleophiles[†,1]

Alfred Hassner* and Bilha Fischer

*Department of Chemistry, Bar-Ilan University, Ramat Gan 52100, Israel*

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Reaction of 2-(4'-bromobutyl)-5-ethoxyoxazole (1) with nucleophiles led either to S_N2 substitution products or to products with a piperidine skeleton. The latter were shown to arise from an intramolecular ring closure to an oxazolium salt 7, which was faster in the presence of a catalytic amount of NaI and in a polar solvent and for which NMR evidence is presented. The further transformation of 7 to 3–6 apparently involves addition of nucelophiles to 7 to produce 4-oxazoline 8 which opens to azomethine ylide 9. Neutralization of the latter occurred either via a proton shift, an alkyl shift, or via trapping by a dipolarophile (electron poor or electron rich). FMO calculations explain the preferred regiochemistry observed during trapping of ylide 9b.

Oxazolium salts are useful precursors to azomethine ylide intermediates[2,3] and have been generated by intermolecular alkylation of oxazoles. Intramolecular generation of oxazolium salts had not been reported until this study.[4] Although azomethine ylides have not been isolated to date, they are useful synthetic intermediates formed either by elimination of a positively charged group at the α-position of immonium salts or by tautomerization of isolable valence isomers of azomethine ylides.[5] Thus, conventional methods utilize immonium salts,[6] N-oxides of tertiary amines,[7] triazolines,[8] or aziridines[9] as azomethine ylide precursors.

Results

In the course of our studies on intramolecular Diels–Alder cycloadditions of heterodienophiles to oxazoles,[10] we prepared the 5-ethoxyoxazole 1 possessing an ω-bromoalkyl

Scheme I
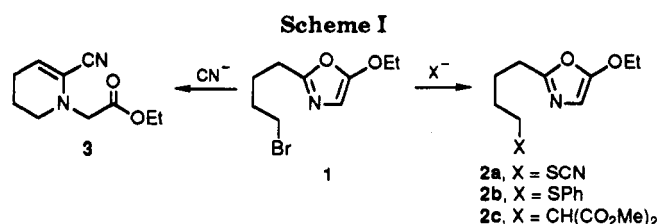
side chain in the 2-position. Such a compound is a potential starting point for intramolecular alkylation of the

(1) Cycloadditions 50. For paper 49 see: Hassner, A.; Murthy, K.S.K. Isr. J. Chem. 1991, 31, 239. Based in part on the Ph.D. thesis of B.F. at Bar-Ilan University.
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