4-Selenoxo-3,4-dihydroquinazolin-2(1*H*)-one. *o*-Aminobenzonitrile (**2a**; 296 mg, 2.5 mmol), selenium (592 mg, 7.5 mmol), *N*-methylpyrrolidine (0.79 mL, 7.5 mmol), and THF (10 mL) were placed in a 50-mL stainless steel autoclave. The reaction mixture was stirred under carbon monoxide pressure (30 kg/cm^2) at 100 °C for 20 h. After the evacuation of excess carbon monoxide at room temperature, the deposited selenium was filtered off, and the solvent was evaporated in vacuo. The residual solid was recrystallized from THF/pentane to yield 422 mg of **6a** (73%). The sample seemed to contain a small amount of water: pale yellow plates, mp 233–234 °C dec, ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 195.82, 146.97, 137.09, 135.79, 133.32, 123.72, 123.32, 116.04; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 13.48 (br s, 1 H, NH), 11.79 (br s, 1 H, NH), 8.37 (d, J = 8.9 Hz, 1 H, aromatic), 7.75 (t, J = 8.9 Hz, 1 H, aromatic), 7.21 (t, J = 7.7 Hz, 1 H, aromatic), 7.13 (d, J = 7.7 Hz, 1 H, aromatic), 3.27 (s, H_2O); IR (KBr) 3350–2760, 1710, 765, 753 cm^{-1}; MS m/e 226 (M^+). Anal. Calcd for $C_8H_6N_2OSe \cdot {}^1/_4H_2O$: C, 41.85; H, 2.85; N, 12.20. Found: C, 41.69; H, 2.99; N, 12.09. ^{1}H NMR and IR spectra and elemental analysis showed that **6a** contained $^1/_4$ H_2O as a hydrate or 1.95 wt % H_2O as moisture.

In order to obtain an anhydrous sample of **6a**, the sample was dissolved in THF (50 mL) and dried over Na_2SO_4 under nitrogen atmosphere. The solvent was evaporated in vacuo to obtain anhydrous **6a** in 70% (396 mg) yield: pale yellow powder, mp 233–234 °C dec. Anal. Calcd for $C_8H_6N_2OSe$: C, 42.67; H, 2.68; N, 12.44. Found: C, 42.27; H, 2.56; N, 12.30.

6-Chloro-4-selenoxo-3,4-dihydroquinazolin-2(1*H*)-one (6b). 4-Chloro-6-cyanoaniline (**2b**; 381 mg, 2.5 mmol) was reacted under the same conditions, and similar workup as described for the preparation of **6a** gave 334 mg (50%) of **6b**: pale yellow plates; mp 289–290 °C dec; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 194.45, 146.72, 135.94, 135.14, 131.71, 127.59, 124.34, 118.38; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 13.40 (br, 2 H, NH), 8.37 (d, J = 2.9 Hz, 1 H, aromatic), 7.89 (dd, J = 9.6, 2.9 Hz, 1 H, aromatic), 7.21 (d, J = 9.6 Hz, 1 H, aromatic), 4.28 (s, H_2O); IR (KBr) 3240–2900, 1705, 1000, 809 cm^{-1}; MS m/e 262 (M^+). Anal. Calcd for $C_8H_5N_2ClOSe \cdot {}^1/_4H_2O$: C, 36.39; H, 2.10; N, 10.60. Found: C, 36.44; H, 2.27; N, 10.24.

In a similar manner as described above was obtained anhydrous **6b** in 48% (271 mg) yield: pale yellow powder, mp 289–290 °C dec. Anal. Calcd for $C_8H_5N_2ClOSe$: C, 37.02; H, 1.94; N, 10.79. Found: C, 37.00; H, 2.27; N, 10.42.

6-Methoxy-4-selenoxo-3,4-dihydroquinazolin-2(1*H*)-one (6c). 2-Cyano-4-methoxyaniline (**2c**; 370 mg, 2.5 mmol) was reacted under the same conditions. A similar workup as described for the preparation of anhydrous **6a** under dry conditions gave 409 mg (64%) of anhydrous **6c**: pale yellow powder, mp 273.5–274.5 °C dec; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 194.58, 155.36, 146.81, 131.47, 125.13, 123.70, 117.63, 113.71, 55.49; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 12.86 (br, 2 H, NH), 7.93 (d, J = 2.8 Hz, 1 H, aromatic), 7.52 (dd, J = 9.2, 2.8 Hz, 1 H, aromatic), 7.21 (d, J = 9.2 Hz, 1 H, aromatic), 3.87 (s, 3 H, OCH_3); IR (KBr) 3400–3020, 1703, 818, 865 cm^{-1}; MS m/e 256 (M^+). Anal. Calcd for $C_9H_8N_2O_2Se$: C, 42.37; H, 3.16; N, 10.97. Found: C, 42.10; H, 3.30; N, 10.55.

4-Methyl-3,4-dihydro-3,1-benzoselenazin-2(1*H*)-one (12). Reaction of *o*-aminoacetophenone (**8**; 337 mg, 2.5 mmol) with selenium (592 mg, 7.5 mmol) in the presence of *N*-methylpyrrolidine (0.79 mL, 7.5 mmol) in THF (10 mL) under carbon monoxide pressure (30 kg/cm^2) at 100° C for 20 h, followed by a similar workup, gave 352 mg (60%) of **12**: yellow needles, mp 135–136 °C dec; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 166.07, 140.21, 137.49, 129.04, 127.09, 124.75, 119.42, 36.26, 25.21; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 10.70 (br s, 1 H, NH), 6.95–7.61 (m, 4 H, aromatic), 4.55 (q, J = 7.6 Hz, 1 H, CH), 1.75 (d, J = 7.6 Hz, 3 H, CH_3), 3.28 (s, H_2O); IR (KBr) 3280–3150, 1614, 822, 757 cm^{-1}; MS m/e 227 (M^+). Anal. Calcd for $C_9H_9NOSe \cdot {}^1/_2H_2O$: C, 45.97; H, 4.28; N, 5.95. Found: C, 46.22; H, 4.31; N, 6.24.

In a similar manner as described above, anhydrous **12** was obtained in 58% (342 mg) yield: yellow powder, mp 135–136 °C. Anal. Calcd for C_9H_9NOSe: C, 47.80; H, 4.01; N, 6.19. Found: C, 47.90; H, 4.10; N, 6.24.

Reductive Deselenation of 6a with Raney Nickel. In a 100-mL round-bottomed flask fitted with a reflux condenser were placed anhydrous **6a** (130 mg, 0.58 mmol), 2 g of Raney nickel (activity W-5), and ethyl alcohol (30 mL). The mixture was refluxed for 2 h with stirring. After cooling to room temperature, the reaction mixture was filtered, and the solvent was evaporated in vacuo. The residual solid was purified by recrystallization from THF/hexane to give 71 mg (82%) of 3,4-dihydroquinazolin-2-(1*H*)one (**7**): white needles, mp 241–242 °C;[15] ^{1}H NMR (Me_2SO-d_6) δ 9.08 (br s, 1 H, NH), 7.50–6.80 (m, 5 H, aromatic and NH), 4.40 (s, 2 H, CH_2); IR (KBr) 3240, 1720, 1264, 740 cm^{-1}; MS m/e 148 (M^+). Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.92. Found: C, 64.60; H, 5.20; N, 18.95.

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Inhibition of Choline Acetate Hydrolysis in the Presence of a Macrocyclic Polyphenolate[1]

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While there is an increasing number of reports on synthetic enzyme analogs,[2] little attention has been paid so far to the use of host compounds as inhibitors. Rate retardation by complexation of substrates in suitable macromolecular cavities is of interest not only for biological systems but also for potential synthetic applications, e.g., with multifunctional compounds or with parallel reactions that could be made more selective by addition of suitable blocking reagents. It must be noted, however, that inhibition of reactions, which should not be confused with the more common inhibition of catalysts such as enzymes, places much more stringent requirements than catalysis. Whereas even small catalytic effects can be easily recognized, a corresponding rate retardation requires a complex formation which is strong enough to compete with the reaction outside a cavity, or, in other words, a competition between ground-state and—usually much larger—transition-state energy effects. This is likely to be the reason why saturation kinetics for rate retardations with organic substrates to our knowledge have been barely reported.

Recently we have demonstrated[3] that the electrostatic interaction between four negative charges of a macrocyclic polyphenolate H and trimethylammonium derivatives can lead to almost micromolar dissociation constants K in water which partially exceed corresponding constants in biological systems. The present paper describes how the delocalized negative charge in the cyclic cavity not only

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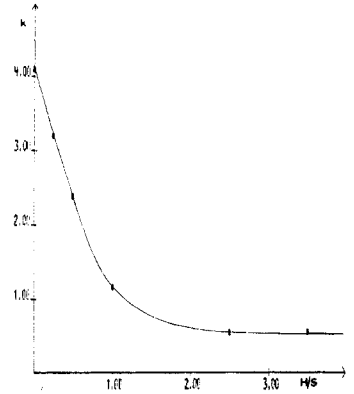
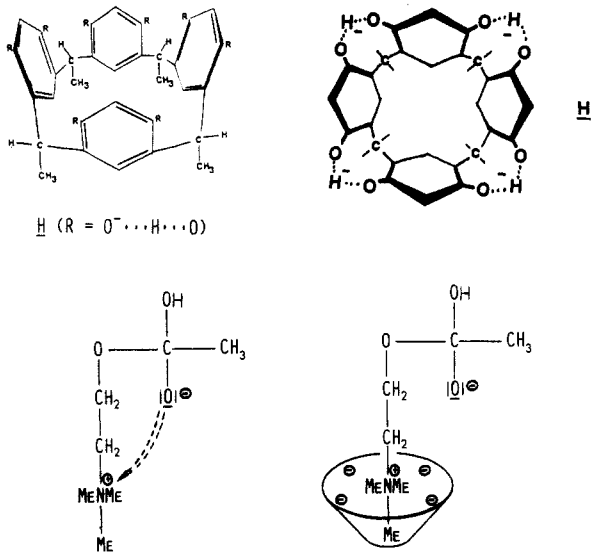


Figure 1. Plot of k_{exp} vs. [H]/[1] (molar ratio) experimental points and theoretical curve; k_{exp} measurements were taken at (60 ± 0.2 °C in H_2O at pH 10.0; k_{exp} in 10^3 s^{-1} units.

provides for binding but also for a destabilization of the hydrolysis transition state of acetylcholine.



The binding and hydrolysis of acetylcholine (1) is an important step in the action of this neurotransmitter at the muscle synapse;[4] the kinetics of the nonenzymatic reaction have also been studied by several workers[5] and are characterized by a strong acceleration by the positively charged ammonium substituent in the vicinity of the ester group as well as by rate retardation upon addition of electrolytes.

In the presence of host H the hydrolysis of acetylcholine (1) to choline (2) and acetic acid (AcOH) followed clean (pseudo-)first-order kinetics up to 80% conversion. The absence of deviations from first order is mainly due to the similar binding constants[3] of educt and product which lead to negligible concentration changes of H during reaction. A plot of the observed rate constants k_{exp} vs. the ratio of [H]/[1] shows a typical saturation effect (Figure 1), if the measurements are performed at a constant ionic strength. As it has been shown that both the binding constants K[3] as well as the hydrolysis rates k_1 of acetylcholine[5a,b] decrease with increasing salt concentrations, the ionic strength was kept at 0.1 M ([H] + [1] + [NaOH] + [NaCl]

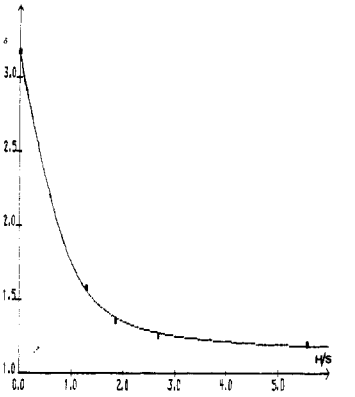


Figure 2. Plot of the methyl proton NMR shifts (ppm) of choline vs. [R]/[S] (molar ratio) and theoretical curve; measurements were taken in D_2O at 60.0 ± 0.5 °C at pH 10.0 with dioxane as internal reference.

= 0.1 M) by adding appropriate amounts of sodium chloride.

The formal treatment of the kinetics is complicated by the binding of both substrate 1 as product 2 (choline) to the receptor ring H, which, however, by comparison to other substrates,[3] can be assumed to have a very similar equilibrium constant K. As the concentrations of the solvent H_2O and the gegenion Cl^- remain essentially constant, the reaction sequence can be simplified as follows:

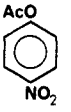
$$1 + H \overset{K}{\rightleftharpoons} [1\cdot H] \xrightarrow{k_2} [2\cdot H] + AcOH \overset{K'}{\rightleftharpoons} 2 + H + AcOH$$

$$1 \xrightarrow{k_1} 2 + AcOH$$

$Me_3N^+CH_2CH_2OOCMe,Cl^-$ (1) $Me_3N^+CH_2CH_2OH,Cl^-$ (2)

With a numerical least-squares curve-fitting program based on a modified SIMPLEX minimization, the unknowns k_2 and K were varied until a fit between observed and calculated rate constants was obtained (see Figure 1).

The retardation of the hydrolysis rate amounts almost to a factor of ten ($k_2 = 4.8 \times 10^{-4}$ s^{-1}; $k_1 = 4.1 \times 10^{-3}$ s^{-1}); it could be attributed to a general destabilization of the negatively charged $B_{Ac}2$-type transition state by the charged cavity. In view of the distance between the carboxyl group and the negative ring a preferable explanation, however, is based on electrostatic attenuation of the known accelerating effect[5a-c] of the charged ammonium substituent. Moreover, we find no significant rate differences between reactions of *p*-nitrophenyl acetate (PNPA) with H and with phenoxide alone; although H is a weak binder



PNPA

for electroneutral substrates[3] such as PNPA, a rate retarding effect of H due to its excess negative charge should also show up in the bimolecular reaction PNPA + H if this would be a significant effect on the $B_{Ac}2$-transition state.

Equilibrium constants such as K values derived from saturation kinetics are often difficult to compare with thermodynamic constants obtained by direct spectroscopic measurements.[6] It is gratifying that the value from the

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kinetic analysis ($K = 11 \times 10^3$ L/mol) compares favorably with the constant $K = (12 \pm 1) \times 10^3$ L/mol, which we obtained by NMR titration under the same conditions. Since acetylcholine hydrolyzes too fast at the minimum pH necessary to keep the host H in solution, we measured the product choline instead, which is justified for the reasons given above. Figure 2 shows the result of a numerical curve fit[7] yielding a K value which is lower than the previously reported[3] because of different temperature and salt concentrations.

Experimental and Computational Details

Preparation and spectroscopic properties of H have been described elsewhere;[8] all other compounds were commercially available.

^{1}H NMR shift titrations were carried out with a Bruker AM 400 system at 400 MHz and were evaluated with a numerical least-squares simulation program.[7] The complexation induced shift (CIS, corresponding to 100% complexation, in ppm) and the association constants K (L/mol) obtained from the analysis of the different choline chloride proton signals were as follows: with CH_3, CIS = 2.09, K = 12 450; with N–CH_2, CIS = 1.14, K = 13 100; with O–CH_2, CIS = 0.52, K = 10 500 (initial concentrations: choline, 2.00×10^{-4} M; H, (0–1.33) $\times 10^{-3}$ M; D_2O at 60.0 ± 1 °C).

Kinetics of choline acetate hydrolysis were followed by continuous titration of the liberated acetic acid with a Metrohm pH-stat apparatus (E 373, E412, E 300), which was connected to a microcomputer-based automatic data aquisition system.[9] At pH 10.00, 60.0 ± 0.2 °C, initial concentration of 1 at 2.00×10^{-3} M, and ionic strength of 0.10 M, the following rate constants ($k \times 10^3$, in s^{-1}) were obtained at different H concentrations (10^{-3} M): [H] = 0.00:4.1 ± 0.2; 0.50:3.2 ± 0.3; 1.00:2.4 ± 0.1; 2.00:1.2 ± 0.1; 5.00:0.6 ± 0.1; 7.00:0.5 ● 0.1.

All linearizations were based on first order and showed correlation coefficients of $r \geq 0.99$.

Hydrolysis kinetics of *p*-nitrophenyl acetate (PNPA) were followed by extinction measurements at λ = 420 nm, where interference with H absorption was small enough (H showed increasing absorption at shorter wavelengths due to oxidation products); the instrument used was a Kontron UV-spectrometer Uvikon 725. At 25 ± 0.2 °C in water/methanol/dioxane [71/24/5% (v/v)], pH 10.00, 0.1 M H_3BO_3/NaOH, and an initial PNPA concentration of 5.0×10^{-4} M, we obtained at different H (10^{-3} M) concentrations the following pseudo-first-order rate constants ($k \times 10^2$ [s^{-1}]): [H] = 0.00:0.20 ± 0.02; 4.0:1.3 ± 0.1; 6.0:1.7 ± 0.1; 8.0:2.0 ± 0.2; 10.0:2.4 ± 0.2. The k values showed a linear increase with [H]; on the basis of the corresponding correlation $k = k_{OH^-} + k_2$[H], where k_{OH^-} is the rate constant in absence of H, a bimolecular rate constant of $k_2 = 2.2 \pm 0.1$ L/(mol s) is obtained from the slope, which is close to the corresponding reported value for the reaction with phenolate alone (k = 1.8 L/(mol s)).[10]

The rate equations can be derived as follows. For S = 1, P = 2, R = H, $[S_0]$ = initial [1], and $K = K'$, we obtain with

$$[S_0] = [S] + [P] + [RS] + [RP] = [S] + [RS] + [A] \quad (1)$$

the following:

$$[RS] + [RP] = \frac{[S_0][R]K}{1 + [R]K} \quad (2)$$

$$[S] + [P] = \frac{[S_0]}{1 + [R]K} \quad (3)$$

$$[S_0] = ([S] + [P])(1 + [R]K) \quad (4)$$

With eq 4 and eq 2, we obtain:

$$K = \frac{[RS] + [RP]}{[R]([S] + [P])} \quad (5)$$

The differential equation for the formation of acetic acid,

$$dA/dt = [S]k_1 + [RS]k_2 \quad (6)$$

can be written as (by using eq 1 and 2)

$$dA/dt = \frac{k_1 + k_2K[R]}{K[R] + 1}([S_0] - [A]) \quad (7)$$

and integrated to

$$k_{exp} = \frac{[R]K}{[R]K + 1}k_2 + \frac{1}{[R]K + 1}k_1 \quad (8)$$

or (with eq 5)

$$k_{exp} = \frac{[RS] + [RP]}{[S_0]}k_2 + \frac{[S] + [P]}{[S_0]}k_1 \quad (9)$$

and

$$[RS] + [RP] = \frac{k_1 - k_{exp}}{k_1 - k_2}[S_0] \quad (10)$$

Furthermore, we can write

$$K = \frac{[RS] + [RP]}{([S_0] - [RS] - [RP])([R_0] - [RS] - [RP])} \quad (11)$$

or

$$[RS] + [RP] = \frac{[R_0] + [S_0] + K}{2} - \left[\frac{([R_0] + [S_0] + K^2}{4} - [R_0][S_0]\right]^{1/2} \quad (12)$$

With a numerical least-squares curve-fitting program based on a SIMPLEX minimization[9c] the unknowns k_2 and K were varied until a fit between the right side of eq 10 and 12 was obtained (see Figure 1).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, Bonn, and the Fonds der Chemischen Industrie, Frankfurt, West Germany.

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Substituent Effects on the Pyrolysis of α-Chloro-*o*-xylenes

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Pyrolysis of α-chloro-*o*-xylene in the gas phase provides an excellent preparative route to benzocyclobutene[1] and has been used in several elegant syntheses.[2] It is generally believed that α-chloro-*o*-xylene undergoes intramolecular 1,4 elimination of HCl to give *o*-quinodimethane as the

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