

Protonation and gem-Diol Formation of 1-Azaadamantanones

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Protonation and ketone hydration of 1-azaadamantane-monoketone, -diketone, and -triketone (3,5,7-trimethyl-1-azatricyclo[3.3.1.1^{3,7}]decan-4-one, -4,6-dione, and -4,6,10-trione, respectively) has been studied applying spectrophotometric and stopped-flow techniques. The very fast protonation is coupled to the slow keto/gem-diol transformation. The through bond interaction between the nitrogen and the carbonyl groups influences strongly the basicity of the nitrogen lone pair. gem-Diol formation is favoured by the steric stress in the adamantane skeleton caused by the carbonyl groups.

In 1968 R. Hoffmann discussed the intramolecular interaction of radical lobes separated by a number of intervening σ -bonds.^{1,2} He introduced the concept of 'through bond' and 'through space' interaction as two different types of those long-range interactions of non-conjugated chromophores. Many examples for both types have been found,³⁻¹⁴ although the separation in 'through bond' and 'through space' contributions is often rather arbitrary. 'Through bond' interaction only depends on the orientation of the σ -bonds between the interacting orbitals and the orbitals themselves. These conformational requirements are fulfilled excellently by derivatives of 1-azaadamantanone in which the carbonyl groups are separated from the nitrogen atom by three σ -bonds,⁷ see Fig. 1.

We studied reactions of the derivatives 1-azaadamantanone $C_{12}H_{19}NO$ (1), -diketone $C_{12}H_{17}NO_2$ (2), and -triketone $C_{12}H_{15}NO_3$ (3) (3,5,7-trimethyl-1-azatricyclo[3.3.1.1^{3,7}]decan-4-one, -4,6-dione and -4,6,10-trione, respectively). Mono-, di-, and tri-ketone are abbreviated as AMK, ADK, and ATK, respectively. The 'through bond' interaction is manifested in the weak basicity of the nitrogen lone pair. The compounds under study have been synthesized only recently. New and efficient synthesis pathways had to be developed due to their unusual chemical properties.¹⁵⁻¹⁸ Adamantane and its derivatives show a very rigid conformation, which makes them suitable for the investigation of long-range couplings in NMR spectroscopy.¹⁹ Moreover, these heterocyclic compounds are of interest as potential bioactive species,²⁰⁻²² in the field of molecular recognition,²³⁻²⁵ and as synthetic building blocks in connection with modified Grob fragmentation reactions.²⁶⁻²⁸

Experimental

Under equilibrium conditions UV spectra were recorded with a spectrophotometer Kontron Uvicon 860 in the temperature range from 10 to 80 °C. At elevated pressures up to 1000 bar † a Cary 219 spectrophotometer was used, which was equipped with a high pressure cell. Kinetic experiments were performed using a dual beam UV stopped-flow apparatus with a dead-time of 3 ms, where equal volumes of solutions of the azaadamantanes and of buffer, acid or base were mixed. Slower reactions were followed with a HP 8452A diode-array spectrophotometer equipped with a stopped-flow unit. This instrument allowed us also to record spectra of intermediates. In all photometric measurements 1 cm cuvettes were used, and reference solutions agreed with sample solutions with regard to composition of solvent and concentration of buffer, acid, or base. NMR spectra were recorded with a Bruker AM 300

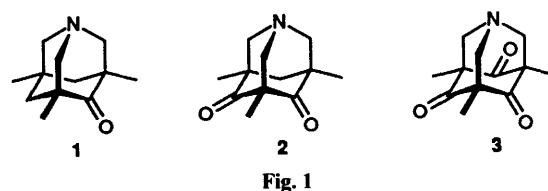


Fig. 1

spectrometer. In all experiments temperature was controlled within ± 0.2 °C. Kinetic results were averaged over at least five determinations.

ATK is not soluble in water, and therefore a mixed solvent had to be used. We chose water-dioxane, 75:25 v/v. In order to avoid disturbances by the schlieren effect, in stopped-flow experiments both solutions had to consist of the same solvent. Some measurements with AMK and ADK were also performed in the mixed solvent.

AMK, ADK, ATK, and 3,5,7-trimethyl-1-azaadamantane were synthesized as described previously.¹⁵⁻¹⁸ Solutions of ADK and ATK were prepared freshly before use, since these compounds decompose slowly with a half-life of about 20 days. The pH value of the solutions was adjusted by the addition of hydrochloric acid, sodium formate, sodium acetate, potassium dihydrogen phosphate, potassium hydrogen phosphate, tris-(hydroxymethyl)aminomethane and sodium hydroxide. All chemicals were of analytical grade; they do not absorb light in the UV range studied. Triply distilled water and 1,4-dioxane 'spectrophotometric grade, 99 + %' were used as solvents, and all solutions were carefully degassed in order to remove carbon dioxide.

pH Values of the solutions were calculated from concentrations and dissociation constants of the buffer compounds and checked with a standard pH electrode. Activity coefficients were estimated by Davies equation²⁹ in aqueous solutions and by the expanded Debye-Hückel equation in the mixed solvent with 57.5 as value for the DK.³⁰ Using Born's equation³¹ we estimated the following values for the dissociation constants in the mixed solvent: 2.75 and 8.5 for phosphate, 4.38 for formate, and 5.39 for acetate. In aqueous solutions the pH values calculated agreed within ± 0.03 with those measured using a glass electrode.

Results

Azaadamantanone-monoketone.—AMK shows an optical absorption with a maximum at 245 nm, which disappears upon protonation of the nitrogen atom. In aqueous solution the photometric titration yields for the dissociation constant $pK_a = 7.14 \pm 0.05$ and for the absorption coefficients $\epsilon(\text{AMK}) = 1080 \text{ cm}^{-1} \text{ dm}^3 \text{ mol}^{-1}$ and $\epsilon(\text{AMKH}^+) = 14 \text{ cm}^{-1} \text{ dm}^3 \text{ mol}^{-1}$ at $\lambda_{\text{max}} = 245 \text{ nm}$. (All values refer to $T = 25$ °C and $p = 1$

† 1 bar = 10^5 Pa.

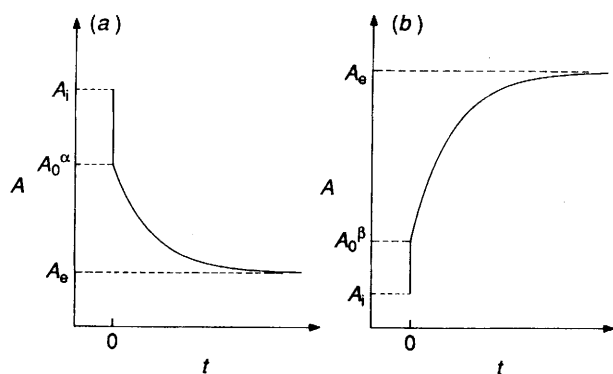


Fig. 2 Change of absorbance (schematically) at stopped-flow experiments; (a) jump starting at pH = 7; (b) jump starting at pH = 2

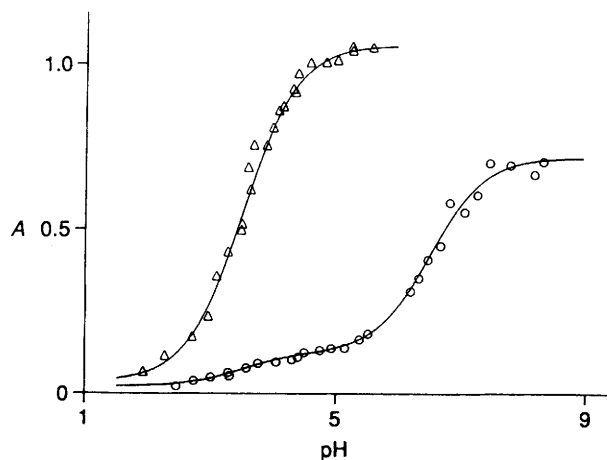


Fig. 3 Absorbances $A_0^\alpha(\Delta)$ and $A_0^\beta(\circ)$ (at $\lambda = 254$ nm) as function of pH for 5×10^{-4} mol dm^3 solution of ADK. The curves are calculated with the constants given in Table 2.

bar, if not indicated otherwise.) The $\text{p}K_a$ value was determined in phosphate buffer between 10 and 60 °C and between 1 and 1000 bar, *i.e.* reaction enthalpy and reaction volume are obtained for the reaction of AMK with H_2PO_4^- . Inserting the temperature dependent values of ΔH^0 and ΔV^0 for the dissociation of dihydrogen phosphate^{32,33} allowed us to calculate the corresponding values for the protonation of AMK: $\Delta H_a^0 = (32 \pm 4)$ kJ mol^{-1} and $\Delta V_a^0 = (6.5 \pm 2.0)$ cm^3 mol^{-1} . Furthermore in water-dioxane, 75:25 v/v we determined $\text{p}K_a = 7.3 \pm 0.2$; *i.e.* the change of the solvent influences the equilibrium only weakly. The kinetics of the reaction could not be followed using the temperature-jump technique, which means that the reaction proceeds in less than 10^{-6} s as expected for *N*-protonation.

The equilibrium of the protonation of 3,5,7-trimethyl-1-aza-adamantane (carrying no carbonyl group) was also measured. We obtained $\text{p}K_a = 10.7$ in aqueous solution, and this compound does not absorb light in the near UV range at $\lambda > 220$ nm.

Azaadamantane-diketone.—In aqueous solution of ADK the absorbance has its maximum at $\lambda_{\text{max}} = 254$ nm. At this wavelength we determined for the dissociation of ADKH^+ $\text{p}K_a = 4.50 \pm 0.02$ with $\epsilon(\text{ADK}) = 2150$ cm^{-1} dm^3 mol^{-1} and $\epsilon(\text{ADKH}^+) = 15$ cm^{-1} dm^3 mol^{-1} . The temperature and pressure dependence of the $\text{p}K_a$ value was measured in acetate buffer. Inserting the values of $\Delta H^0(\text{HAc})$ and $\Delta V^0(\text{HAc}) = -11.4$ cm^3 mol^{-1} for the dissociation of acetic acid^{34,35} yields for the protonation of ADK $\Delta H_a^0 = (47 \pm 8)$ kJ mol^{-1} and $\Delta V_a^0 = (-13 \pm 2)$ cm^3 mol^{-1} .

If acid is added to a neutral solution of ADK, the absorbance decreases slowly with a half life of 1 to 100 s (depending on the

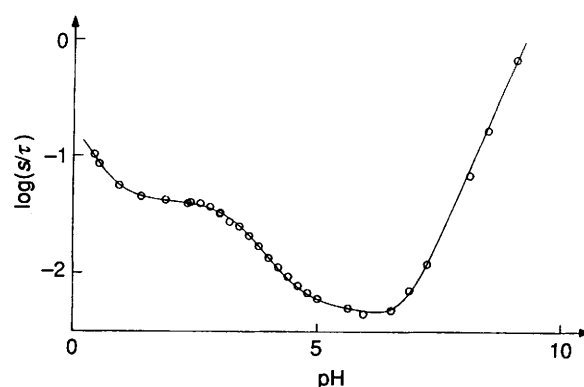


Fig. 4 Logarithm of the reciprocal relaxation time *versus* pH for solutions of ADK. The curve is calculated according to eqn. (9) with the constants given in the text.

final proton concentration). We studied the kinetics of this process using the stopped-flow technique. The measurements were performed either by mixing a neutral solution of ADK with acidic buffer or by mixing a solution containing ADKH^+ at pH = 2 with less acidic buffer. In both cases the absorbance changes in two steps as indicated in Fig. 2. The initial value A_i is calculated from the absorbances of the two solutions to be mixed. A_0 is obtained by re-extrapolating the absorbance to the time of mixing ($t = 0$): A_0^α and A_0^β refer to jumps from pH = 7 to pH < 7 and from pH = 2 to pH > 2, respectively. The difference between A_0 and A_i indicates a very fast reaction at the mixing, which cannot be resolved by the technique applied. The final absorbance A_e is independent of the sign of the pH change, and it agrees with the value from equilibrium titration, *i.e.* the reaction is reversible. The solutions are buffered, and the reaction proceeds under pseudo-first-order conditions. Therefore the change in absorbance is given by eqn. (1).

$$A = (A_0 - A_e) \times \exp(-t/\tau) + A_e \quad (1)$$

A_0^α and A_0^β are plotted in Fig. 3 as function of pH. A_0^α fits to single protonation with $\text{p}K_a = 3.49 \pm 0.05$, whereas A_0^β indicates two protonation steps with $\text{p}K_{a1} = 3.7 \pm 0.2$ and $\text{p}K_{a2} = 6.45 \pm 0.20$. From the temperature dependence of the $\text{p}K$ values we determined the reaction enthalpies $\Delta H_a^0 = 18$ kJ mol^{-1} , $\Delta H_{a1}^0 = 29$ kJ mol^{-1} and $\Delta H_{a2}^0 = 28$ kJ mol^{-1} . Moreover at pH = 1 we determined the temperature and pressure dependence of the absorption coefficient of ADKH^+ $\partial \ln \epsilon(\text{ADKH}^+)/(\partial 1/T) = (-28 \pm 4)$ K and $\partial \ln \epsilon(\text{ADKH}^+)/\partial p = (-1.1 \pm 0.2) \times 10^{-4}$ bar^{-1} . Measurements were also performed in water-dioxane 75:25 v/v, where we obtained $\text{p}K_a = 4.15 \pm 0.05$ and $\text{p}K_a = 3.15 \pm 0.15$.

The reaction is buffer-catalysed. Therefore at constant pH value the relaxation times τ were measured at different buffer concentrations c_B . In Fig. 4 the values of τ extrapolated to $c_B = 0$ are plotted *versus* the pH of the solutions.

In order to identify the structure of the different species, we measured the NMR spectra of ADK in D_2O in the neutral ($\text{H} \gg \text{p}K_a$) and in the acidic ($\text{pH} \ll \text{p}K_a$) range. In neutral solution the spectra of both ^1H NMR and ^{13}C NMR verify the C_2 -symmetry of ADK. (In ^{13}C NMR the 1,3-dicarbonyl system has a chemical shift of 209 ppm.) In acidic solution the ^1H NMR spectra indicate the existence of two different compounds. The spectra of the minor species is very similar to that of the non-protonated ADK, and therefore it can be attributed to the *N*-protonated dicarbonyl ion, whereas the C_2 -symmetry is lost for the predominant species of ADKH^+ . In ^{13}C NMR the predominant species shows the signal of a keto group at 213 ppm and additionally a signal at 101 ppm indicating the existence of a gem-diol group. That means one of the keto

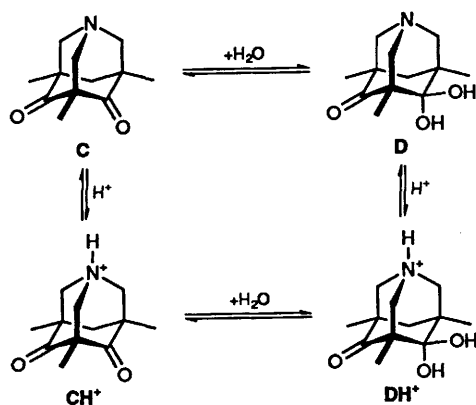


Fig. 5 Reaction scheme for the protonation of ADK and structures of the species involved

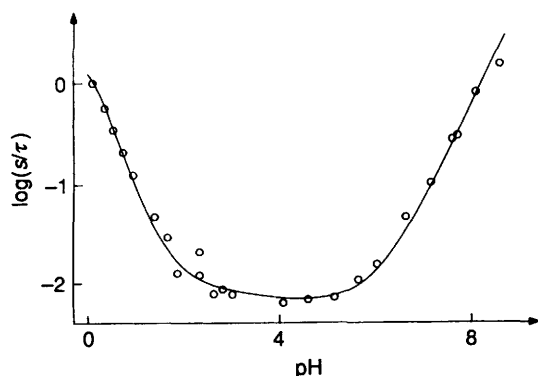


Fig. 6 Logarithm of the reciprocal relaxation time versus pH for solutions of ATK. The curve is calculated according to eqn. (9) with the constants given in the text.

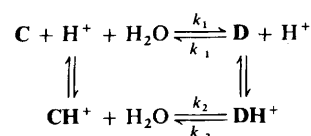
groups of ADK is hydrated. This leads to the reaction scheme in Fig. 5, where keto and gem-diol form are abbreviated as C and D, respectively. The nonprotonated gem-diol has been included for the discussion of the kinetic results, although its concentration is too small to be detected in NMR. The integration of the ^1H NMR signals yields the concentration ratio $[\text{DH}^+]/[\text{CH}^+] = 11 \pm 3$.

Azaadamantane-triketone.—ATK is not soluble in water, and therefore water–dioxane, 75:25 v/v was used as solvent. Acidic solutions of ATK decompose with a half life of approximately 1 h. ATK shows a UV absorption with a maximum at $\lambda = 263$ nm. By optical titration we obtained for the dissociation constant $\text{p}K_a = 1.80 \pm 0.08$ with $\epsilon(\text{ATK}) = 3100 \text{ cm}^{-1} \text{ dm}^3 \text{ mol}^{-1}$ and $\epsilon(\text{ATKH}^+) = 25 \text{ cm}^{-1} \text{ dm}^3 \text{ mol}^{-1}$. Starting with (stable) neutral solutions, stopped-flow experiments yielded results, which agree qualitatively with those obtained for ADK. The pH dependence of A_o^2 fits to a single protonation step with $\text{p}K_a = 0.3 \pm 0.15$. The relaxation times extrapolated to zero buffer concentrations are plotted in Fig. 6. Due to the instability of acidic solutions, reliable values could not be obtained for A_o^2 .

All details of the measurements reported in this paragraph are given in ref. 39.

Discussion

For AMK the only reaction observed is the fast and reversible protonation of the nitrogen atom. For ADK our discussion is based on the reaction scheme presented in Fig. 5, which is abbreviated as Scheme 1, where C (carbonyl) and D (diol) stand for 4,6-dioxo- and 4-oxo-6-(gem-dihydroxy)-1-azaadamantane, respectively. The single equilibria are described by the four



Scheme 1

constants defined in eqns. (2) to (5). Eqn. (6) relates these constants with the overall dissociation constant K_a , which is

$$K_C = \frac{[\text{C}] \times [\text{H}^+]}{[\text{CH}^+]} \quad (2)$$

$$K_D = \frac{[\text{D}] \times [\text{H}^+]}{[\text{DH}^+]} \quad (3)$$

$$K_1 = \frac{[\text{D}]}{[\text{C}]} \quad (4)$$

$$K_2 = \frac{[\text{DH}^+]}{[\text{CH}^+]} = \frac{K_1 \times K_C}{K_D} \quad (5)$$

$$K_a = \frac{([\text{C}] + [\text{D}]) \times [\text{H}^+]}{[\text{CH}^+] + [\text{DH}^+]} = K_C \times \frac{1 + K_1}{1 + K_2} \quad (6)$$

obtained photometrically at equilibrium. In Scheme 1 the horizontally written reactions refer to the ketone hydration, which causes the slow change in absorbance from A_o to A_e in stopped-flow experiments. The vertically written reactions describe the very fast protonation of nitrogen atoms, which cause the rapid change from A_i to A_o . For jumps from pH = 2 (where ADK is completely protonated) to less acidic solution the pH dependence of A_o^2 indicates two protonation reactions, which are attributed to the kinetically decoupled reactions $\text{CH}^+ \rightleftharpoons \text{C} + \text{H}^+$ and $\text{DH}^+ \rightleftharpoons \text{D} + \text{H}^+$. For jumps from neutral to acidic solutions we measure A_o^2 , and the pH dependence of A_o^2 is described by a single protonation step. This indicates that in neutral solution ADK exists nearly exclusively as one of the species C or D. This agrees with the results obtained from NMR measurements, where in neutral solution only the diketo form of ADK is detected, whereas in acidic solutions both keto and gem-diol form are identified (with a predominance of the gem-diol form). This allows us to appoint K_a to K_C . Analogously the two dissociation constants K_{B1} and K_{B2} are attributed to the deprotonation of CH^+ and DH^+ , respectively, i.e. $K_{B1} = K_C$ and $K_{B2} = K_D$. Correspondingly K_a and K_{B1} agree within experimental error. Thus, from the evaluation of A_o we obtain $\text{p}K_C = 3.49 \pm 0.05$ and $\text{p}K_D = 6.45 \pm 0.2$. Together with $\text{p}K_a = 4.50$ the other equilibrium constants can be calculated: $K_1 = (9 \pm 1) \times 10^{-3}$ and $K_2 = 9.1 \pm 1$. This value of K_2 is confirmed by the NMR measurements, where we obtained $K_2 = 11 \pm 3$.

With these values the optical spectra of the different species in Scheme 1 can be determined. Spectra are measured at equilibrium and at $t = 0$ using the diode-array spectrophotometer. In neutral solutions ADK exists at 99% as carbonyl C, and therefore at equilibrium the spectrum of C is obtained. Jumping from a neutral solution to pH = 2 yields the spectrum of CH^+ at $t = 0$. For the protonated ADK we have at equilibrium $[\text{DH}^+]/[\text{CH}^+] = 9/1$, and from the spectrum at pH = 2 we can calculate the spectrum of DH^+ , since that of CH^+ is already known. The same ratio holds for $[\text{D}]/[\text{C}]$ at $t = 0$, when we jump from pH = 2 to pH = 7, and correspondingly we obtain the spectrum of D. The spectra of the four different species are shown in Fig. 7, and the values of λ_{max} , ϵ_C and ϵ_D are summarized in Table 1.

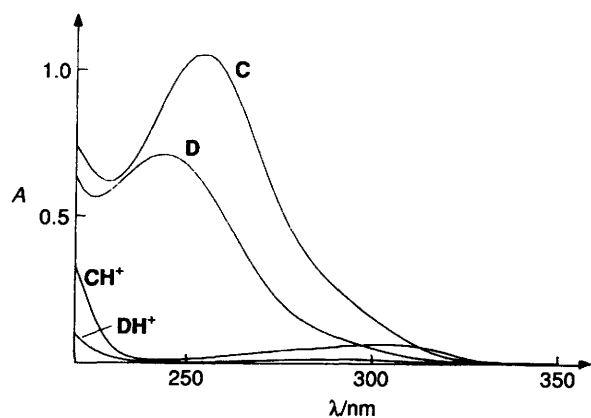


Fig. 7 Spectra of the different species of ADK (see Scheme 1) at concentrations of $5 \times 10^{-4} \text{ mol dm}^{-3}$

Table 1 Spectroscopic data for 1-azaadamantanone 1, -diketone 2, and -triketone 3

Compound	$\lambda_{\text{max}}/\text{nm}$	$\epsilon/\text{cm}^{-1} \text{ dm}^3 \text{ mol}^{-1}$
AMK	245	1080
ADK (keto, gem-diol)	243	1400
ADK (diketo)	254	2150
ATK (triketo)	263 ^a	3100 ^a

^a In water–dioxane 75:25 v/v.

Table 2 Thermodynamic parameters for the reactions of 1-azaadamantanone 1, -diketone 2, and -triketone 3 at 25 °C

	<i>K</i>	<i>pK</i>	ΔH°	ΔS°	ΔV°
			kJ mol^{-1}	$\text{J mol}^{-1} \text{ K}^{-1}$	$\text{cm}^3 \text{ mol}^{-1}$
$K_C(\text{AMK})$		7.14	32	−31	6.5
$K_D(\text{ADK})$		6.5	29	−27	
$K_C(\text{ADK})$		3.5	18	−7	16
$K_C(\text{ATK})$		0.3 ^a			
$K_1(\text{ADK})$	9×10^{-3}		−21	−110	
$K_2(\text{ADK})$	9.1		−33	−90	−3
$K_2(\text{ATK})$	35				

^a In water–dioxane 75:25 v/v.

From the temperature dependent measurements of the absorbances A_o and A_e the reaction enthalpies and entropies are calculated for the single equilibria. For K_2 these parameters are obtainable from the temperature dependence of the absorption in acidic solution, where only CH^+ and DH^+ exist, since the absorption coefficients are known. In a similar way reaction volumes are calculated from the pressure dependent measurements. The results of these calculations are summarized in Table 2.

Finally the relaxation times τ have to be evaluated. The protonation of the nitrogen atoms is very rapid, and equilibrium is always established between **C** and CH^+ and between **D** and DH^+ on the time scale of our experiments. Therefore the rate law for the keto/gem-diol transformation is given by eqn. (7). This reaction is acid/base catalysed, and the rate constants k_i

$$\frac{d([\text{D}] + [\text{DH}^+])}{dt} = k_1[\text{C}] - k_{-1}[\text{D}] + k_2[\text{CH}^+] - k_{-2}[\text{DH}^+] \quad (7)$$

$$k_i = k_i^o + k_i^H \times [\text{H}^+] + k_i^{\text{OH}} \times [\text{OH}^-] \quad (8)$$

consist of three terms, as indicated in eqn. (8). In buffered solutions the integration of the rate law yields eqn. (9).

The relaxation time depends in a very characteristic way on the proton concentration (see Fig. 4), and the fitting of eqn. (9) to the experimental results yields the following seven para-

$$\frac{1}{\tau} = \left(A + B \times [\text{H}^+] + C \times \frac{f_1^2 \times [\text{H}^+]^2}{f_{\text{H}}} + D \times \frac{1}{[\text{H}^+] \times f_1^2} \right) \times \left(\frac{1}{1 + \frac{[\text{H}^+]}{K_D}} + \frac{K_1}{1 + \frac{[\text{H}^+]}{K_C}} \right) \quad (9)$$

with $A = k_{-1}^o + \frac{k_{-2}^{\text{OH}}}{K_D}$; $B = k_{-1}^H + \frac{k_{-2}^o}{K_D}$;

$$C = \frac{k_{-2}^H}{K_D}; \quad D = k_{-1}^{\text{OH}} \times K_W.$$

meters: $\text{p}K_C = 3.48 \pm 0.05$; $\text{p}K_D = 6.56 \pm 0.2$; $K_1 = (6 \pm 2) \times 10^{-3}$; $A = (2.8 \pm 0.3) \times 10^{-3} \text{ s}^{-1}$; $B = (1.8 \pm 0.2) \times 10^4 \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$; $C = (2.6 \pm 0.3) \times 10^4 \text{ s}^{-1} \text{ mol dm}^{-3}$; $D = (6 \pm 1) \times 10^{-10} \text{ s}^{-1} \text{ mol dm}^{-3}$. The last two values allow us to calculate $k_{-2}^H = (7 \pm 1) \times 10^{-3} \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$ and $k_{-1}^{\text{OH}} = (6 \pm 1) \times 10^4 \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$. The values obtained for K_C , K_D and K_1 by this fitting procedure agree well with those obtained from the evaluation of the absorbances A_e and A_o .

Scheme 1 is also used as basis for the discussion of ATK, since the results obtained for ATK agree qualitatively with those for ADK. Again A_e^o fits to a single protonation step. However, A_e^o cannot be measured, and for the evaluation we have to assume that for ATK the concentration of **D** is very small compared to that of **C**, as proven for ADK. Thus the pH dependence of A_e^o can be attributed to the reaction $\text{C} + \text{H}^+ \rightleftharpoons \text{CH}^+$ with $\text{p}K_C = 0.30 \pm 0.15$, and $K_2 = 35 \pm 15$ is calculated from K_2 . The relaxation times are evaluated according to eqn. (9). Inserting the value of K_C and assuming that $K_D(\text{ATK}) = K_C(\text{ADK})$, i.e. $\text{p}K_D = 3.5$, enables us to fit eqn. (9) to the experimental data with $A = (6.5 \pm 0.6) \times 10^{-3} \text{ s}^{-1}$; $B = (28 \pm 2) \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$; $C = (110 \pm 10) \text{ s}^{-1} \text{ mol dm}^{-3}$; $D = (6.5 \pm 1.0) \times 10^{-9} \text{ s}^{-1} \text{ mol dm}^{-3}$. From the last two parameters we obtain $k_{-2}^H = (3.5 \pm 0.4) \times 10^{-2} \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$ and $k_{-1}^{\text{OH}} = (6.5 \pm 1.0) \times 10^5 \text{ s}^{-1} \text{ dm}^3 \text{ mol}^{-1}$.

Conclusions

For 1-azaadamantanones the interaction between the nitrogen lone pair and the carbonyl group (over three intervening σ bonds) leads to a 'sigma coupled transition'.^{7,8,11} In the UV spectra this is indicated by an absorption band with $\lambda_{\text{max}} > 240 \text{ nm}$, which is not observed for azaadamantanones carrying no carbonyl group. Table 1 shows that the interaction between N and CO is enhanced when the molecule contains more than one keto group: λ_{max} increases and $\epsilon(\lambda_{\text{max}})$ is nearly proportional to the number of keto groups. The absorption disappears when the nitrogen atom is protonated, i.e. the through bond interaction is lost when the lone pair of the nitrogen binds to a proton. Analogously this interaction is lost, upon gem-diol formation. Therefore the results obtained for AMK are similar to those for azaadamantane-mono-ketone-mono-diol, see Tables 1 and 2.

The basicity of the nitrogen lone pair is strongly decreased by the through bond interaction. This leads to a change in the $\text{p}K_a$ value of approximately 3 units per carbonyl group from 10.7 (no carbonyl group) to 0.3 (three carbonyl groups).

For substituted amines (e.g. triethylamine) the dissociation volume is close to zero. The increase of the dissociation volume with the number of keto groups indicates that the through bond interaction leads to a poor solvation and therefore to a large molar volume of the azaadamantones. This means the through bond interaction decreases the polarity of the molecules. This explains also the change in the reaction entropy when going from one to two keto groups.

Finally the keto/gem-diol equilibria should be discussed. Here we restrict ourselves to K_2 , since for the protonated species the interference with the through bond interaction has not to be taken into account. Aliphatic carbonyls exist nearly exclusively in the keto form, if there are no inductively electron-attracting substituents.^{36,37} Correspondingly, the gem-diol of AMKH^+ and the di(gem-diol) of ADKH^+ is not found. However, gem-diol formation is observed for ADK and ATK, i.e. for azaadamantones with more than one carbonyl group. For these molecules the two sp^2 carbon atoms cause a great steric strain in the adamantane skeleton, which is reduced by the sp^2/sp^3 transition due to the gem-diol formation. The values of ΔS° , ΔV° , and ΔH° obtained for the gem-diol formation of ADKH^+ are very similar to those for other keto/gem-diol equilibria described in the literature.^{33,38}

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