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The Kinetics of Atropine and Apoatropine in Aqueous Solutions

WALTER LUND* and TOR WAALER

Farmasøytisk Institutt A, Universitetet i Oslo, Blindern, Oslo 3, Norway

A qualitative and quantitative study of the kinetics of aqueous atropine and apoatropine solutions has been made. The investigation has been carried out in the pH range 1–6, at temperatures 80, 90, and 100°C. The catalytical constants for the hydrogen ion and the hydroxyl ion catalyzed hydrolysis of atropine and for the hydrogen ion catalyzed hydrolysis of apoatropine have been determined. The velocity constant for the dehydration of atropine to apoatropine has been determined at different pH values and temperatures. The activation energy and the frequency factor for the hydrogen ion catalyzed reactions have also been determined. It has been shown that both hydrolysis and dehydration of atropine must be considered when determining the maximum stability of atropine in solution. In addition it is pointed out that the method chosen for the quantitative determination of atropine must be free from interference from apoatropine. The half life of atropine at some pH values and temperatures has been computed from the appropriate constants.

In aqueous solutions atropine is hydrolyzed to tropic acid and tropanol, whilst dehydration with formation of apoatropine can also take place.[1-4] On the other hand dimerization of apoatropine to belladonnine may occur,[5] and the hydrolysis of these compounds must also be considered.[3,6] A complete scheme of all the possible reactions will be as shown in Fig. 1.

Quantitative kinetic studies of aqueous atropine solutions have been made by Zvirblis *et al.*,[7] Kondritzer and Zvirblis,[8] Dušinský,[9] and Struhár.[4] Zvirblis *et al.* and Kondritzer and Zvirblis have investigated the alkaline and acid hydrolysis of atropine. They have not, however, taken into account the possibility of apoatropine formation, in spite of the fact that the methods of analysis used, UV spectrophotometric determination of atropine after extraction of the alkaloids, would give results which would be strongly influenced by the presence of apoatropine. Dušinský and Struhár have investigated the alkaline hydrolysis of atropine. Dušinský has employed an oscillopolarographic

* Present address: Kjemisk Institutt A, Universitetet i Oslo, Blindern, Oslo 3, Norway.

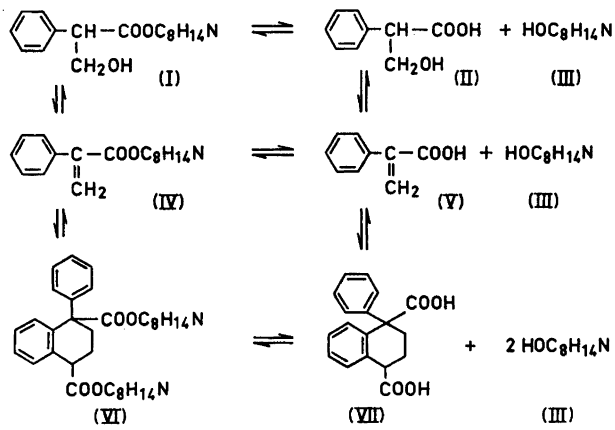

Fig. 1. I atropine, II tropic acid, III tropanol, IV apotropine, V atropic acid, VI belladonnine, and VII isatropic acid.

technique, while Struhár has separated atropine and apoatropine by paper chromatography and determined the amount of atropine colorimetrically, a rather inaccurate method. The most important of the constants for the alkaline hydrolysis of atropine which were found in the investigations mentioned above are given in Table 1. For the acid hydrolysis Kondritzer and Zvirblis have found the catalytical constant to be 1.754×10^{-4}, 3.668×10^{-4}, and 7.350×10^{-4} min^{-1} $mole^{-1}$ l at 70, 80, and 90.3°C, respectively. The authors have also determined the corresponding activation energy and frequency factor; 17.2 kcal/mole and 1.54×10^{7} min^{-1}, respectively.

Table 1. The alkaline hydrolysis of atropine. Previously reported values.

	Atropine form	T (°C)	k_{OH} (sec^{-1}) $mole^{-1}$ l)	E (kcal/mole)	A (sec^{-1})
Zvirblis *et al.*[7]	Unprotonated	25–60	—	7.7	3.6×10^{8}
	Protonated	25–60	—	12.7[a]	3.5×10^{8}
Dušinský [9]	Unprotonated	20	5.1×10^{3}	13.4	1.45×10^{5}
Struhár [4]	Protonated (?)	100	730	21.3	—
		110	888		
		120	2286		

[a] Corrected for the heat of ionization of water (12 kcal/mole at 40°C).

The present investigation was undertaken to study the stability of atropine in aqueous solution, taking into account, if necessary, all the possible reactions in Fig. 1, and to determine if possible the different velocity and catalytical constants and their activation energies. It was decided to work in the pH range 1—6, to study both the hydrogen and hydroxyl ion catalyzed reactions and the reactions in the range where atropine has the maximum stability.[8] In the pH range chosen the alkaloids would be in their protonated form. To obtain measurable reaction velocities the study was carried out at temperatures of 80 to 100°C.

EXPERIMENTAL

Apparatus. A Beckman DU spectrophotometer with quartz cells was used for the quantitative absorbance measurements. Absorbance spectra were recorded with a Beckman DK 2 A recording spectrophotometer. The pH of the solutions was measured with a Beckman Research pH meter using glass and calomel electrodes. The pH meter was standardized against potassium hydrogen phthalate and sodium tetraborate buffers.[10] To determine the pH at 80—100°C, the pH was measured at 25°, and then corrected to the desired temperature by means of an experimental pH/temperature curve. The ampoules were placed in paraffin baths where the temperature was kept constant ±0.1°C.

Materials. Atropinum sulfuricum cryst. and *Apoatropinum hydrochlorid purum* were obtained from E. Merck AG and Fluka AG, respectively. Their purities were controlled by comparing their extinction coefficients with those of the respective bases. The bases were made by recrystallization from cyclohexane/petrolether (m.p. atropine base 115—116.5, apoatropine base 61.5—62.5°C). *dl-Tropasäure purum* was obtained from Fluka AG, while *atropic acid* was isolated from hydrolysis of apoatropine. The acids were recrystallized from benzene/petrolether (m.p. 116.5—117.5 and 105.0—106.5°C). *Tropin purum* from Fluka AG, *Bellacristin Reinsubstanz* from E. Merck AG, α- and β-*isatropic acids* and the other chemicals which were of reagent grade, were used without further purification.

Methods of analysis. The qualitative, as well as the quantitative analysis of reaction mixtures was performed by extraction of the alkaloids with chloroform, leaving the salts of the acids in the water phase which had been made alkaline with dilute ammonia. The alkaloids could be removed from the organic phase with dilute sulfuric acid, while the acids could be extracted with ether, when the solution was acidified with dilute sulfuric acid.

The qualitative analysis was performed by means of thin layer chromatography, the solutions first being concentrated by partial evaporation in a rotavapor. The alkaloid fraction was chromatographed with cyclohexane/chloroform/diethylamine (50/40/10) on plates of Kiselgel GF_{254} Stahl (E. Merck AG), and detected with Dragendorff's reagent (after Thies) and 0.05 M sulfuric acid according to Stahl.[11] The acid fraction was chromatographed with cyclohexane/chloroform/acetic acid (60/20/20) using the same type of plate and detected with bromocresol green solution.[11] The solvents were allowed to travel to 10 cm, and the plates were observed using an ultraviolet lamp before spraying. In some cases the qualitative results were checked, observing absorption spectra of the reaction mixture and of the alkaloid and acid fractions of it.

The quantitative analysis of the alkaloids is based on the UV absorption of these compounds, the alkaloids first being separated as described above. Because apoatropine has an extinction value about twenty times greater than that of atropine and belladonnine it was only possible to determine a mixture of these alkaloids when the concentration of apoatropine was low compared to that of the others.[12] In these cases, however, the amount of belladonnine was too small to be measured. In the other experiments only apoatropine could be determined. For the spectrophotometric determination the following procedure was applied: 10.00 ml of the reaction mixture was adjusted to pH 10 with 2 M ammonia and the extraction was carried out with three 10 ml portions of chloroform. Thereafter the chloroform phase was filtered through anhydrous sodium sulfate, the alkaloids extracted with 10.00 ml 0.1 M sulfuric acid and the solution centrifuged.

The extinctions at wavelengths 248.0 and 257.1 nm were measured and the concentration of atropine and apoatropine computed from the equations

$$E_1 = e_{A,1}[A]+e_{AA,1}[AA]$$
$$E_2 = e_{A,2}[A]+e_{AA,2}[AA]$$

where [A] and [AA] stand for the concentration of atropine and apoatropine respectively, E_1 and E_2 are the measured extinction values, and $e_{A,1}$, $e_{A,2}$, $e_{AA,1}$, and $e_{AA,2}$ are the respective extinction coefficients. The coefficients were determined by measuring the extinction of pure atropine and apoatropine solutions.

Procedure. The experiments were carried out by dissolving the different compounds in distilled water, adjusting the pH to the desired value and filling the solutions into 20 ml ampoules. The concentration of the compounds in question was approximately 4×10^{-3} M, except for the apoatropine and the atropic acid solutions where the concentration was one tenth of that. The pH of the solutions was adjusted by means of hydrochloric acid/potassium chloride or hydrochloric acid/sodium acetate, the ionic strength being kept at 0.5. In two cases, respectively, a citrate and a phosphate buffer was used. The ampoules were sealed and placed in paraffin baths at 80, 90, or 100°C. Having been heated the desired time, the ampoules were taken from the baths, cooled, and analyzed as described above.

REACTION KINETICS

It was found that the complete reaction scheme in Fig. 1 could be somewhat simplified under the experimental conditions chosen. The actual mechanism, illustrated in Fig. 2, can be described by the following equations, the velocity constants being the same as those indicated in the figure:

$$-\mathrm{d}[A]/\mathrm{d}t = (k_1+k_2)[A]-k_3[AA] \quad (1)$$

$$-\mathrm{d}[AA]/\mathrm{d}t = (k_3+k_4)[AA]+k_5[AA]^2-k_2[A] \quad (2)$$

These nonlinear differential equations are not easy to solve. In most cases it was found, however, that the dimerization of apoatropine to belladonnine was of little importance, which means that one could regard k_5 equal to zero in eqn. 2. The solution of eqns. 1 and 2 with respect to [A] and [AA] will then be:[13]

$$[A] = A_0C^{-1}((k_3+k_4-s_1)e^{-s_1t}-(k_3+k_4-s_2)e^{-s_2t}) \quad (3)$$

$$[AA] = AA_0\,C^{-1}((k_1+k_2-s_1)e^{-s_1t}-(k_1+k_2-s_2)e^{-s_2t}) \quad (4)$$

$$[AA] = A_0\,C^{-1}k_2\,(e^{-s_1t}-e^{-s_2t}) \quad (5)$$

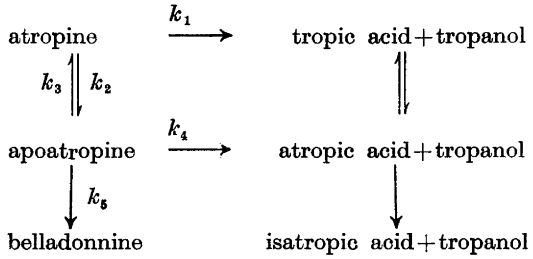

Fig. 2.

where $C=\sqrt{(k_1+k_2-k_3-k_4)^2+4k_2k_3}$, $s_1=\frac{1}{2}(\sum_1^4 k_n-C)$, $s_2=\frac{1}{2}(\sum_1^4 k_n+C)$ and A_0 and AA_0 equal [A] and [AA] at $t=0$. In the general case eqns. 3 and 4 express nonlinear relations between ln[A] and time, and between ln[AA] and time, the slopes of the curves at $t=0$ being equal to k_1+k_2 and k_3+k_4, respectively. If ln[A] or ln[AA] varies linearly with time, this will imply that eqns. 1 and 2 are simplified to:

$$-\mathrm{d[A]}/\mathrm{d}t = (k_1+k_2)[\mathrm{A}] \quad (6)$$

$$-\mathrm{d[AA]}/\mathrm{d}t = (k_3+k_4)[\mathrm{AA}] \quad (7)$$

This was the case in most of the experiments which were carried out. The eqns. 6 and 7 were solved, and k_1+k_2 and k_3+k_4 were computed by means of the method of least squares.[14] Because the quantitative determination of atropine and apoatropine was found to give a small systematic error, the expressions $\ln A_0$ and $\ln AA_0$ in the solutions of eqns. 6 and 7 were also regarded as unknown parameters when the method of least squares was employed.

On the other hand, if one studies the formation of apoatropine from atropine as a function of time, one can use eqn. 5 which can be rewritten

$$[\mathrm{AA}] = f(t,A_0,k_1,k_2,k_3,k_4) \quad (8)$$

To apply the method of least squares to this equation one had to expand the function in a Taylor series. Derivatives of second and higher orders were discarded, and it was assumed that one could find initial values for the unknown parameters.[15,16]

The correction terms that were introduced by this procedure were minimized by repeated computations, the normal equations being solved by means of Gauss' elimination method.[17] All computations were performed using an IBM 1620 computer. The programs were written in Fortran II. Starting with eqn. 8 and treating A_0 and all the velocity constants as unknown, the method did not at first converge. However, paying attention to the fact that A_0, k_1+k_2, and k_3+k_4 were determined beforehand from the studies of variation of atropine and apoatropine with time, eqn. 8 could be simplified:

$$[\mathrm{AA}] = f(t,k_2,k_3) \quad (9)$$

From this equation k_2 was computed, whereas approximate values for k_3 had to be computed from the assumption that $k_3=k_2(k_3+k_4)/(k_1+k_2)$, whereafter the k_2-values were improved by means of the equation $[\mathrm{AA}]=f(t,k_2)$. As initial values for k_2 and k_3 were used $0.25(k_1+k_2)$ and $0.25(k_3+k_4)$, respectively.

In a few of the experiments which started with pure apoatropine solution, it was found that the variation of ln[AA] with time was not linear. This was observed at high temperatures when the pH of the solution was low. A definite explanation for this was not found. The assumption that this was due to dimerization of apoatropine to belladonnine could not be verified in the present investigation. (The computations were here based on the equation $-\mathrm{d[AA]}/\mathrm{d}t=(k_3+k_4)[\mathrm{AA}]+k_5[\mathrm{AA}]^2$). The nonlinearity was therefore assumed

to be due to the hydration of atropine, and k_3+k_4 was determined from the slope of the curve at $t=0$.

As seen from the preceding discussion of the reaction kinetics, the velocity constants k_1, k_2 and k_3+k_4 can be determined.

RESULTS

Qualitative. To decide which of the reactions in Fig. 1 actually took place under the experimental conditions chosen, atropine, apoatropine, belladonnine, tropic acid, and atropic acid, respectively, were dissolved in distilled water, the pH was adjusted to the desired value, and the solutions were filled into ampoules and placed in paraffin baths. After a long time the solutions were analysed as described previously. It was confirmed that atropine was hydrolyzed to tropic acid as well as dehydrated to apoatropine, and that apoatropine was hydrolyzed to atropic acid, hydrated to atropine and dimerized to belladonnine. The formation of atropic acid and isatropic acid from tropic acid, and formation of tropic acid and isatropic acid from atropic acid were also confirmed. However, belladonnine was found to be stable, neither isatropic acid nor apoatropine being found. From the experiments showing the decrease of atropine and apoatropine as a function of time it was found that the equilibrium between the alkaloids and the respective acids was almost completely displaced to the right in Fig. 1. Because too small an amount of isatropic acid was available, a possible formation of atropic acid from isatropic acid was not studied. The actual reaction scheme should be as illustrated in Fig. 2.

Quantitative. To study the velocities of the reactions of the alkaloids in Fig. 2, atropine and apoatropine solutions of different pH values were made, the solutions were filled into ampoules and placed in paraffin baths at temperatures of 80.0, 90.0, and 100.0°C. At definite time intervals ampoules were taken from the baths and the amounts of atropine and apoatropine present

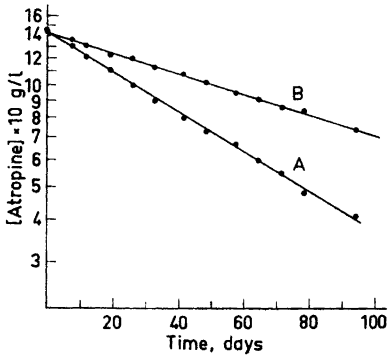

Fig. 3. The atropine concentration drawn in logarithmic scale as a function of time. These experiments were carried out at 90°C at pH values 1.98 (A) and 2.23 (B), respectively.

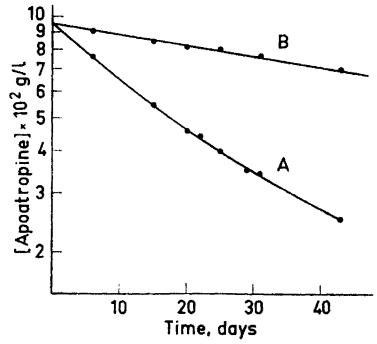

Fig. 4. The apoatropine concentration drawn in logarithmic scale as a function of time. These experiments were carried out at 90°C at pH values 1.07 (A) and 2.02 (B), respectively.

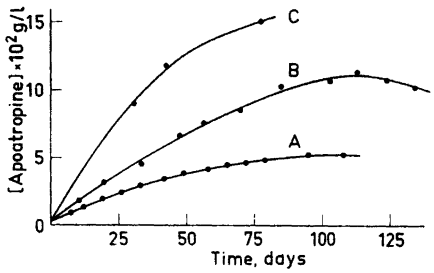

Fig. 5. The formation of apoatropine from atropine drawn as a function of time. These experiments were carried out at 90°C at pH values 2.23 (A), 2.75 (B), and 3.00 (C), respectively.

were determined as described previously. The first ampoule in a series was analyzed as soon as the solution had come to the bath temperature. By the described procedure, one could follow the decrease of atropine and apoatropine with time, and the formation of apoatropine from atropine as a function of time. When the decrease of atropine and apoatropine was represented by plotting the logarithm of the alkaloid concentration as a function of time, curves like those given in Figs. 3 and 4 were obtained.

The formation of apoatropine from atropine resulted in curves like those in Fig. 5. In most cases ln[A] and ln[AA] varied linearly with time. However, at high temperatures and low pH values, a nonlinear relationship between ln[AA] and time was found, as illustrated in Fig. 4.

From the decrease of atropine and apoatropine with time and the formation of apoatropine from atropine, the velocity constants k_1, k_2, and k_3+k_4

Table 2. Velocity constants for the hydrolysis (k_1) and dehydration (k_2) of atropine at different pH values and temperatures.

T (°C)	pH	k_1+k_2 (h^{-1})	k_1 (h^{-1})	k_2 (h^{-1})
100	1.08	1.00×10^{-3}		
	1.38	5.0×10^{-3}		
	2.08	8.8×10^{-4}	8.3×10^{-4}	5.0×10^{-5}
	2.96	4.1×10^{-4}	2.8×10^{-4}	1.38×10^{-4}
90	1.98	5.5×10^{-4}	5.3×10^{-4}	2.2×10^{-5}
	2.23	2.8×10^{-4}	2.5×10^{-4}	3.1×10^{-5}
	2.54	1.83×10^{-4}	1.42×10^{-4}	4.2×10^{-5}
	3.00	1.71×10^{-4}	8.3×10^{-5}	8.8×10^{-5}
80	0.70	4.8×10^{-3}		
	0.89	3.0×10^{-3}		
	1.41	1.04×10^{-3}	1.04×10^{-3}	7.9×10^{-6}
	1.86	3.5×10^{-4}		
	3.00	6.3×10^{-5}	2.9×10^{-5}	3.3×10^{-5}
	4.00	9.6×10^{-5}	4.2×10^{-5}	5.4×10^{-5}
	5.28	1.54×10^{-3}	1.38×10^{-3}	1.83×10^{-4}
	5.88	4.7×10^{-3}	4.5×10^{-3}	2.1×10^{-4}

Table 3. The sum of the velocity constants for the hydrolysis (k_4) and hydration (k_3) of apoatropine at different pH values and temperatures.

T (°C)	pH	k_3+k_4 (h^{-1})
100	1.09	2.8×10^{-3}
	1.37	1.58×10^{-3}
	2.08	5.9×10^{-4}
90	1.07	1.58×10^{-3}
	1.34	8.8×10^{-4}
	2.02	3.0×10^{-4}
80	0.98	8.3×10^{-4}
	1.74	2.2×10^{-4}
	1.99	1.46×10^{-4}
	3.00	1.92×10^{-4}
	4.30	2.0×10^{-4}
	5.40	2.3×10^{-4}

were determined as described previously. The results of the computations are given in Tables 2 and 3.

pH dependence. All the velocity constants determined vary with pH and temperature. If the velocities of the different reactions are catalyzed by hydrogen and hydroxyl ions, one can write

$$k=k_0+k_H[H^+]+k_{OH}[OH^-] \quad (10)$$

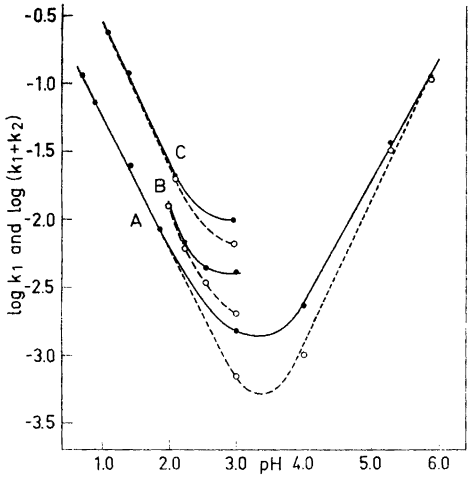

Fig. 6. The variation of log k_1 (dashed curve) and log (k_1+k_2) (full drawn curve) with pH at 80° (A), 90° (B), and 100°C (C).

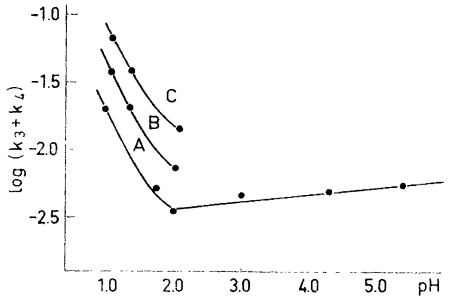

Fig. 7. The variation of log (k_3+k_4) with pH at 80° (A), 90° (B), and 100°C (C).

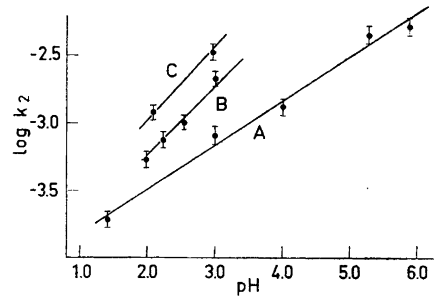

Fig. 8. The variation of log k_2 with pH at 80° (A), 90° (B), and 100°C (C).

where k_H and k_{OH} are the respective catalytical constants, and k_0 stands for the catalysis by other ions and molecules in the solution, whose concentrations do not vary. In Figs. 6, 7, and 8 log k for the different velocity constants is drawn as a function of pH.

From Fig. 6 is seen that log k_1 and log (k_1+k_2) vary linearly with the pH except in the pH range 2—4. The hydrolysis of atropine is catalyzed by hydrogen ions at pH values below 2

$$k_1 = k_{H,1}[H^+]$$

and by hydroxyl ions at pH values above 4

$$k_1 = k_{OH,1}[OH^-]$$

From these equations $k_{H,1}$ and $k_{OH,1}$ were determined. The constants are given in Table 4. From the curve at 80° it is seen that k_0 (eqn. 10) must be small. This was proved by the fact that the curve could be described by the equation

$$k_1 = k_{H,1}[H^+]+k_{OH,1}[OH^-] \quad (11)$$

In the calculations $[H^+]$ and $[OH^-]$ were set equal to 10^{-pH} and $K_w/[H^+]$, respectively. The activity product K_w at 80, 90, and 100°C was computed from the equation given by Harned and Owen,[18] the values 2.53×10^{-13}, 3.81×10^{-13}

Table 4. The catalytical constants for the hydrolysis of atropine and apoatropine at different temperatures.

Constant	pH range	$T=80$°C	$T=90$°C	$T=100$°C
$k_{H,1}$ (h^{-1} $mole^{-1}$ l)	<2	2.40×10^{-2}	5.17×10^{-2}	1.20×10^{-1}
$k_{H,4}$ (h^{-1} $mole^{-1}$ l)	<2	7.92×10^{-3}	1.86×10^{-2}	3.42×10^{-2}
$k_{OH,1}$ (h^{-1} $mole^{-1}$ l)	>4	2.46×10^{4}		
k_3+k_4 (h^{-1})	2.0—5.4	1.92×10^{-4}		

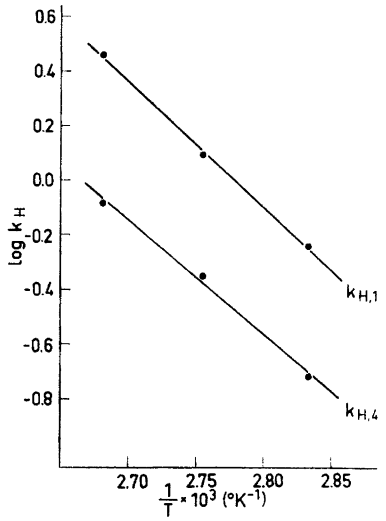

Fig. 9. Temperature dependence of the catalytical constants for the hydrogen ion catalyzed hydrolysis of atropine and apoatropine respectively. Log k_H *vs.* reciprocal of the absolute temperature.

and 5.50×10^{-13}, respectively, being obtained. In the pH range 2—4 in Fig. 6, the values of k_1 and k_1+k_2 are distinctly different.

From Fig. 7, where log (k_3+k_4) is plotted as a function of pH, it is reasonable to assume that the hydrolysis of apoatropine too is catalyzed by hydrogen ions at pH values below 2. A possible explanation for the slight nonlinearity could be the hydration of apoatropine to atropine. Making this assumption, $k_{H,4}$ was calculated by means of the equation $k_4=k_{H,4}[H^+]$. The values are given in Table 4. In the pH range 2—5.4, log (k_3+k_4) varies only slightly with pH, which should imply that the reaction is not catalyzed by hydroxyl ions to any great extent. The mean value of the velocity constant k_3+k_4, determined in this pH range, is given in the last line in Table 4.

In Fig. 8 the variation of log k_2 with pH is drawn. In spite of large deviations in the k_2 values, a linear relationship must be assumed, the dehydration of atropine increasing with increasing pH. This result is rather confusing, the opposite being more usual. The experimental results were, however, too limited to allow for any lengthy discussion of this point. The slopes of the lines are distinctly less than one, which means that no relation of the type $k_2=k_{OH,2}[OH^-]$ can hold for the reaction.

Table 5. The activation energy and frequency factor for the hydrogen ion catalyzed hydrolysis of atropine and apoatropine.

Constant	E (kcal mole^{-1})	A (h^{-1})
$k_{H,1}$	20.9	2.0×10^{11}
$k_{H,4}$	19.1	5.8×10^{9}

Temperature dependence. The activation energy (E) and frequency factor (A) for the temperature dependence of the catalytical constants were determined from the Arrhenius equation ($k=A\cdot e^{-E/RT}$). The logarithm of the catalytical constants was drawn as a function of $1/T$, as shown in Fig. 9. The values of E and A are given in Table 5.

DISCUSSION

In the preceding, the velocity constants k_1, k_2, and k_3+k_4 were determined, as well as the catalytical constants $k_{H,1}$ and $k_{H,4}$ for the hydrogen ion catalyzed hydrolysis of atropine and apoatropine, respectively, and $k_{OH,1}$ for the hydroxyl ion catalyzed hydrolysis of atropine. Finally the activation energies $E_{H,1}$ and $E_{H,4}$ and frequency factors $A_{H,1}$ and $A_{H,4}$ for the hydrogen ion catalyzed reactions were determined. k_2, k_3+k_4, $k_{H,4}$, $E_{H,4}$ and $A_{H,4}$ are determined for the first time. With the experimental conditions and procedure chosen, the dimerization of apoatropine to belladonnine (k_5) could not be determined. The hydration of apoatropine to atropine (k_3) could not be determined either, because the methods used for quantitative analysis of the alkaloids made it impossible for a simultaneous determination of atropine and apoatropine to be carried out when the concentration of atropine was small compared to that of apoatropine.

From the results it is seen that the decrease in atropine in the pH range 2—4 is due to both hydrolysis and dehydration. This implies that it is not possible to determine the maximum stability of atropine in solution by computing the minimum velocity from the equation $k_1+k_2=k_{H,(1+2)}[H^+]+k_{OH,(1+2)}[OH^-]$. However, Kondritzer and Zvirblis [8] seem not to be aware of this fact. By the procedure mentioned one finds the minimum value for k_1, provided k_H and k_{OH} have been determined in the pH ranges where $k_1+k_2\sim k_1$, which means at pH<2 and pH>6, respectively.

As mentioned at the beginning of the present paper, some earlier investigations on the stability of atropine failed to take into account the dehydration of atropine. When the investigation is based on UV spectrophotometry one will then introduce an error which is larger than can be explained by the approximation $k_1+k_2=k_1$. This is due to the much stronger absorption of apoatropine relative to atropine. This fact probably explains why Zvirblis *et al.*[7] and Kondritzer and Zvirblis [8] have found smaller values for $k_{OH,1}$, $k_{H,1}$, $E_{H,1}$, and $A_{H,1}$ than those determined in the present investigation.

The constants determined can be applied to the determination of the stability of atropine in aqueous solution. For k_1 a combination of eqn. 11 with the Arrhenius equation gives

$$k_1=A_{H,1}\exp(-E_{H,1}/RT)[H^+]+A_{OH,1}\exp(-E_{OH,1}/RT)[OH^-] \qquad (12)$$

Eqn. 12 includes $A_{OH,1}$ and $E_{OH,1}$. The last one had been determined previously in this laboratory (unpublished results), the value 12.88 kcal/mole being obtained. $A_{OH,1}$ could then be computed from the Arrhenius equation ($k_{OH,1}$ at 80° is known). $A_{OH,1}$ was found to be 2.32×10^{12} h^{-1}. In the ranges pH<2 and pH>6, where $k_1+k_2\approx k_1$, the stability of atropine could be computed from eqn. 12. As the hydrolysis of atropine was a first-order reaction, the half life of

Table 6. Half lives of atropine (h).

T (°C)	pH=2.0	pH=3.0	pH=4.0
100	6.38×10^{2}	1.68×10^{3}	1.11×10^{3}
90	1.31×10^{3}	4.18×10^{3}	2.64×10^{3}
80	2.69×10^{3}	1.11×10^{4}	6.70×10^{3}
50	3.29×10^{4}	2.93×10^{5}	1.49×10^{5}
20	6.55×10^{5}	1.50×10^{7}	6.38×10^{6}

atropine could be computed from $t_{\frac{1}{2}}=\ln2/k_1$. In the pH range 2—6, k_1+k_2 differs from k_1. The dehydration of atropine also being a first-order reaction, the half life of atropine in this pH range was $t_{\frac{1}{2}}=\ln2/(k_1+k_2)$.

The computation of k_2 could not be made by an equation similar to eqn. 12. k_1+k_2 was therefore determined from the curves in Fig. 6. The temperature dependence of k_1+k_2 was found to obey Arrhenius equation, so this equation could be used when extrapolating k_1+k_2 to temperatures outside the range 80—100°C.

Some values for $t_{\frac{1}{2}}$ in the pH range where atropine has its maximum stability, are given in Table 6. The values at pH 4 were found applying eqn. 12 and assuming curves at 90° and 100° to be similar to the one at 80° in Fig. 6.

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