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The effect of heat, pH and some buffer materials on the hydrolytic degradation of sulphacetamide in aqueous solution

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The hydrolytic degradation of sulphacetamide has been investigated under anoxic conditions over a wide range of pH values and at different temperatures. The sole breakdown product is sulphanilamide. The reaction is essentially independent of pH (measured at 25°) over the range 5 to 11, but is subject to catalysis by buffer constituents. Below pH 4 specific hydrogen ion catalysis occurs. Calculation of activation parameters leads to the conclusion that sulphacetamide solutions can be satisfactorily autoclaved provided they are not subsequently refrigerated.

Aqueous solutions of sulphacetamide are degraded on storage by both oxidative and hydrolytic mechanisms (Clarke, 1965, 1967). Antioxidants such as sodium edetate and sodium metabisulphite have been included in official formulations of the drug to discourage colour development. Sodium metabisulphite, however, increases the hydrolytic deacetylation of sulphacetamide at pH 7·4 (Davies, Meakin & Moss, 1970) to such an extent that sulphanilamide may be deposited from strong solutions of the drug (Anderson & Maudson, 1963; Fletcher & Norton, 1963).

Little is known about the conditions which favour the hydrolysis of sulphacetamide and we report the results of a study into this aspect of the drug's stability.

MATERIALS AND METHODS

Materials

Ammonium sulphamate, *p*-dimethylaminobenzaldehyde, diethylamine, hydrochloric acid and *N*-(1-naphthyl) ethylenediamine dihydrochloride were laboratory reagent grade (BDH): acetone, citric acid, disodium hydrogen phosphate, methanol, potassium chloride, sodium chloride, sodium hydroxide, sodium nitrite were A.R. grade (BDH). Silica gel G (Merck) was used for thin-layer chromatography; oxygen free nitrogen was white spot grade (BOC); glycine and tris(hydroxymethyl)-aminomethane were biochemical grade (BDH). Sulphacetamide sodium B.P. (m.p. 183°) was recrystallized twice from ethanol, sulphanilamide B.P.C. (m.p. 163·5°) was recrystallized twice from water.

Reagent solutions

Ammonium sulphamate 2% w/v in distilled water; *N*-(1-naphthyl) ethylenediamine dihydrochloride 0·1% w/v in distilled water; sodium nitrite 0·1% w/v in distilled water; *p*-dimethylaminobenzaldehyde 1% w/v in equal volumes of concentrated hydrochloric acid and ethanol. Methanolic hydrochloric acid: 1 volume concen-

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trated hydrochloric acid added to 75 volumes of methanol and adjusted to 100 volumes with distilled water.

Buffer solutions

Buffer solutions used for determining the pH profile and temperature dependence of sulphacetamide degradation were: pH range 1·2–3·6, Sørensen's glycine, sodium chloride, 0·1M hydrochloric acid; pH range 3·6–8·0, McIlvaine's citric acid, disodium hydrogen phosphate; pH range 8·4–12·6 Sørensen's glycine, sodium chloride, 0·1M sodium hydroxide.

Buffers used for determining the effect of buffer constituents on sulphacetamide degradation at pH 7·4 were: single double and quadruple strength McIlvaine's citric, acid, disodium hydrogen phosphate (ionic strengths, 0·488, 0·976, 1·952M respectively), single strength McIlvaine's buffer adjusted to ionic strength 1·952M with potassium chloride, and Gomori's tris buffer [0·2M tris (hydroxymethyl) aminomethane, 0·2M hydrochloric acid].

The appropriate standard solutions were prepared according to Documenta Geigy (p. 315). Sulphacetamide sodium was added to the tabulated volume of glycine-sodium chloride solution, or disodium hydrogen phosphate solution and the pH adjusted to the required value by the addition of hydrochloric acid, sodium hydroxide or citric acid solutions as appropriate. All buffered sulphacetamide solutions showed pH drifts of less than 0·1 of a pH unit after heating.

pH measurement

pH measurements were made at 25° with either a Radiometer type 27 meter fitted with a Radiometer type C glass-calomel electrode system (pH 1–11; 0–70°) or a Pye Dynacap meter fitted with a Jena dual glass-calomel electrode system (pH 1–14; 20–120°). The instruments were standardized with 0·05M potassium hydrogen phthalate, 0·05M potassium tetroxalate, 0·025M potassium dihydrogen phosphate–0·025M disodium hydrogen phosphate and 0·01M borax (Schwabe, 1960).

pH measurements at elevated temperatures were made after equilibrating the solutions in a thermostatically controlled water bath ($\pm$0·5°). Apparent pK_a values for 1% solutions of sulphacetamide were determined by potentiometric titration.

Oxygen tension measurement

Oxygen tensions of sulphacetamide solutions were measured using a Radiometer type PHA 927b gas monitor fitted with a Clark type oxygen electrode, standardized with 0·1M borax containing 1% w/v sodium metabisulphite and air saturated water.

Assay method

Sulphacetamide was separated from its degradation product, sulphanilamide, before assay, by thin-layer chromatography. All solutions were then assayed for both sulphacetamide and sulphanilamide content using the following technique.

A 20 $\times$ 20 cm t.l.c. plate spread (0·25 mm) with ether-extracted silica gel G was air dried overnight and activated at 110° for 30 min. Six samples, each of nominal volume 5 μl (true volume 4·84 μl) were applied with an Agla micrometer syringe fitted with a flat tipped, metal needle. Precision of delivery had previously been checked both by direct weighing and tracer techniques and coefficients of variation were 1·22% (30 replicates) and 1·02% (10 replicates) respectively.

The chromatograms were developed in batches at room temperature (20°), using as solvent, acetone–methanol–diethylamine (9:1:1 by volume). This gave excellent separation of sulphacetamide and sulphanilamide, mean R_F values 0·28 and 0·83 respectively. For each run, spots were visualized on one reference plate with *p*-dimethylaminobenzaldehyde solution. Using this as a guide, corresponding areas containing the sulphonamides were scraped into stoppered centrifuge tubes, 5 ml of extracting solvent (methanolic hydrochloric acid for sulphacetamide; methanol for sulphanilamide) were added, the tubes shaken for 10 min and centrifuged at 3500 rev/min for 5 min. Blank areas from each plate were treated similarly.

To the supernatant (3 ml) was added sodium nitrite solution (1 ml) and water (sulphacetamide) or 0·1N hydrochloric acid (sulphanilamide) (3·3 ml). After 5 min ammonium sulphamate solution (1 ml) was added, and 10 min later *N*-(1-naphthyl) ethylenediamine dihydrochloride solution (1 ml). The solutions were adjusted to 10 ml with water and stored in the dark (15 min) to allow colour development. The extinctions of the solutions were then measured at 536 nm using an Unicam SP600 spectrophotometer. The mean values of three assays were used in calculation. Absolute concentrations of the sulphonamides were determined from the extinction coefficients of the pink dyes (sulphacetamide, E (1%, 1 cm) 2104; sulphanilamide, E (1%, 1 cm) 3000) which were calculated with reference to the original sulphonamide.

The percentage residual concentrations obtained from the heating experiments were calculated with respect to the appropriate unheated sulphacetamide solution which was assayed without prior chromatographic separation.

The efficiency of the assay process was checked by the analysis of solutions containing known compositions of sulphacetamide and sulphanilamide (90: 10; 70: 30; 50:50; 30:70); recoveries, calculated as total sulphonamide were 99·3, 99·9, 97·6, 99·9% respectively.

Heating experiments

Although 1% aqueous solutions of sulphacetamide sodium became discoloured when heated under air, the rate of disappearance of the drug was not significantly different from that obtained under anoxic conditions (Tansey, 1969). The formation of colour however, implied additional sequences in the degradation pathway when oxygen was present. Consequently, all data presented in this paper were obtained under anoxic conditions, to eliminate any possible effects of colour-forming reactions.

The effect of pH on the degradation rate of sulphacetamide at 120°. Solutions of sodium sulphacetamide (1%) in buffer over the pH range 1·6–12·6 were bubbled with nitrogen to zero oxygen tension, transferred anoxically to ampoules and sealed (Tansey, 1969). These were heated in an oil bath at 120° ± 0·5°, removed at varying time intervals, chilled in crushed ice and stored at 2° until assayed. Under all conditions, first order kinetics were obeyed, the first order rate constants (k) being computed by means of a least squares regression analysis and used as a measure of the heat sensitivity and to calculate the specific second order rate constants for the hydrogen ion catalysed reaction (k_1) and the hydroxyl ion catalysed reaction (k_5) as defined in equation 6. The values are given in Table 1, and Fig. 1 shows a plot of k against pH.

The effect of temperature. Anoxic solutions containing 1% of sodium sulphacetamide adjusted to pH 7·4 with McIlvaine's buffer were heated for varying periods at temperatures of 99·5°, 110°, 120°, 130° and 140° (all ±0·5°) and assayed as before.

The first order rate constants at each temperature were computed (being respectively 0·627, 1·588, 3·468, 6·644 and 13·370 $\times$ 10^{2} h^{-1}) and used to calculate the activation parameters for the hydrolytic degradation of sulphacetamide (Table 3).

The effect of buffer components. Anoxic solutions containing 1% of sulphacetamide sodium were adjusted to pH 7·4 with hydrochloric acid, single, double and quadruple strength McIlvaine's buffer, ionic strengths 0·488, 0·976 and 1·952M respectively (Elving, Marcovitch & Rosenthal, 1956), single strength McIlvaine's buffer adjusted to ionic strength 1·952M with potassium chloride, and Gomori's tris buffer. The solutions were heated for varying periods at 120° assayed and the various rate constants computed (Table 2).

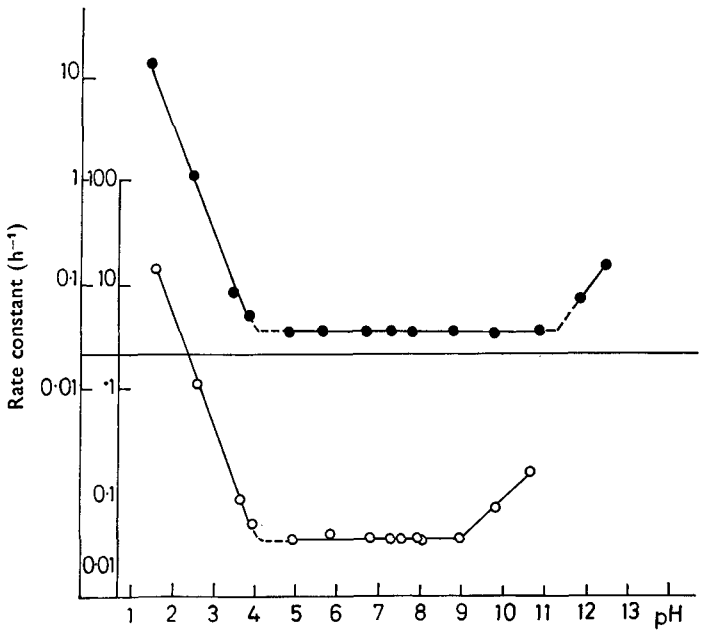


FIG. 1. The effect of pH on the observed first order rate constants for the hydrolysis of sulphacetamide to sulphanilamide at 120° (●, pH value measured at 25°; ○, calculated pH at 120°).

Table 1. *The effect of pH on the reaction rate constants at* 120°.

pH_{25}	pH_{120}	Buffer	Observed 1st order rate constant k (h^{-1}) $\times$ 10^{2}	2nd order rate constant (l. mol^{-1} h^{-1}) [$*k_1$ $**k_5$]
1·61	1·68	GAC	1300·0	378*
2·61	2·72	GAC	104·6	344*
3·65	3·80	GAC	8·104	332*
4·00	4·07	M	4·574	337*
4·95	5·04	M	3·267	—
5·80	5·90	M	3·459	—
6·80	6·91	M	3·364	—
7·40	7·52	M	3·468	—
7·93	8·06	M	3·281	—
8·91	7·35	GAK	3·313	—
9·98	8·22	GAK	3·174	—
11·05	9·08	GAK	3·438	16·90**
12·00	9·85	GAK	6·771	5·63**
12·64	10·37	GAK	14·650	3·74**

Table 2. *The effect of buffer strength on the reaction rate at* 120°.

pH_{25}	Buffer	Ionic strength	Observed 1st order rate constant k (h^{-1}) $\times 10^2$
7·40	Nil	—	2·837
8·36	Nil	—	2·819
7·40	M	0·488	3·468
7·40	M × 2	0·976	4·132
7·40	M × 4	1·952	5·854
7·40	M + KCl	1·952	3·521
7·40	Tris	—	7·619

(pH_{25} are pH values measured at 25° and pH_{120} are the calculated values for 120°, G_{AC}, G_{AK}, M, represent Sørensen's acid glycine, Sørensen's alkaline glycine, and McIlvaine's buffers respectively; M × 2, M × 4 represent double and quadruple strength McIlvaine's buffer.)

Table 3. *Activation parameters for the pH independent hydrolysis of sulphacetamide.*

Compound	Buffer	Activation energy (E) (kJ mol^{-1})	Activation enthalpy (ΔH^*) (kJ mol^{-1})	Activation entropy (ΔS^*) (J mol^{-1} deg^{-1})	Ref.
Sulphacetamide	Nil	≈100	—	—	Anderson, 1967
,,	M	95·9	92·5	—10·9	Data for the effect of temp. (see p. 254)
,,	M + 0·5% S.M.S.	81·6	78·7	—13·4	Davies, Meakin & Moss, 1970
Chloramphenicol	Nil	101·2	99·2	—7·1	Higuchi & others, 1954
,,	A	49·4	46·4	—21·3	,, ,,
,,	B	83·7	80·3	—12·1	Heward, Norton & Rivers, 1970

M = McIlvaine's buffer S.M.S. = sodium metabilsulphite
A = acetate buffer B = borate buffer

DISCUSSION

Throughout all the experiments, only two spots were visualized on the reference plates, at R_F values corresponding to sulphacetamide and sulphanilamide. No traces of diacetylsulphanilamide, previously suggested as a degradation product of sulphacetamide (Fletcher & Norton, 1963; Dickenson: personal communication) were found when chromatograms of the heated solutions were developed in isopropanol–concentrated ammonia–water (90:5:5), which gives good separation of the three compounds (Dickenson: personal communication). The average recovery of total sulphonamide (calculated as sulphacetamide) based on 162 experiments, was 100·2% (coefficient of variation 1·52%). It is therefore reasonable to conclude that under the experimental conditions reported here the degradation of sulphacetamide is solely one of deacetylation to form sulphanilamide.

Such a reaction is analogous to the hydrolysis of carboxylic acid amides. This is subject to acid, base and nucleophilic catalysis, following second order kinetics overall and is first order with respect to amide and catalytic species (Willens & Bruylants, 1951; Johnson, 1967; Hine, 1962; Meloche & Laidler, 1951).

For kinetic interpretation, the rate constant - pH profile should be corrected for temperature effects in view of the large differential between the heating temperatures

(120°) and that of pH measurement (25°). Any pressure effects on the value of k can be ignored, as they are considered negligible at 20 p.s.i. (Whalley, 1964).

Temperature influences the pH of a system largely by its effect on the dissociation constants (K_d) of the constituent weak acids and bases. Over a wide range of temperature the log K_d or pH versus temperature plots are generally parabolic and may be represented by the equations 1 and 2 (Bates, 1954; Robinson & Stokes, 1965).

$$\log K_d = \frac{A_1}{T} + A_2 + A_3T \quad .. \quad .. \quad .. \quad .. \quad (1)$$

$$pH = \frac{B_1}{T} + B_2 + B_3T \quad .. \quad .. \quad .. \quad .. \quad (2)$$

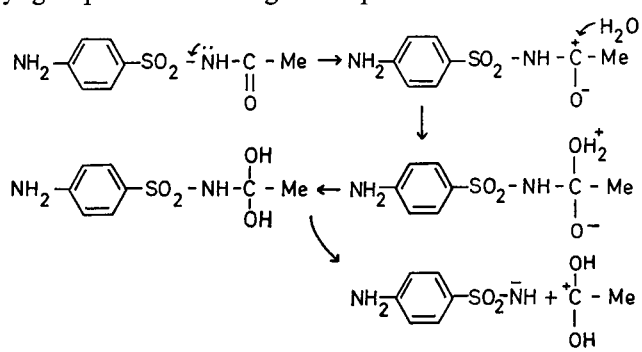
The pH values of a series of 1% sulphacetamide sodium solutions, prepared in Sørensen's acid and alkaline glycine buffers and McIlvaine's buffer, were measured at approximately 10° intervals between 25° and 95° and the data fitted to equation 2 using a multiple regression analysis (System 4 Statistic Scheme, International Computers Ltd.). Multiple correlation coefficients better than 0·8 were obtained in all cases ($r_{tab} = 0{\cdot}707$, $P = 0{\cdot}05$). The computed temperature coefficients (B_1, B_2, B_3) were used to extrapolate the data to 120°. pK_1 (2·13) and pK_2 (5·21) values for sulphacetamide at 120° were similarly obtained from equation 1. Plots of pH_{120} against pH_{25} were found to be rectilinear within a given buffer system, least squares analysis giving equations 3–5.

$pH_{120} = 1{\cdot}0382\ pH_{25} + 0{\cdot}0088$ .. (3) (Sørensen's acid glycine buffer)
$pH_{120} = 0{\cdot}8107\ pH_{25} + 0{\cdot}1251$ .. (4) (Sørensen's alkaline glycine-buffer)
$pH_{120} = 1{\cdot}0142\ pH_{25} + 0{\cdot}0174$ .. (5) (McIlvaine's buffer)

These equations were used to calculate the pH_{120} values for the heated sulphacetamide solutions (Table 1) which are also shown in Fig. 1 plotted against the apparent first order rate constants (k), and it can be seen that a plateau exists over the pH_{120} range 5 to 9.

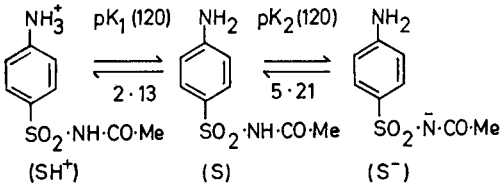
This picture differs from the pH profiles generally associated with the hydrolysis of simple acid amides, where pH independent regions are absent (Bell, 1941). This is attributable to resonance stabilization of the amido-carbonyl group which protects the compounds from attack by weak nucleophiles such as water (March, 1968).

The reactivity found between sulphacetamide and water can be related to the electron withdrawing properties of the sulphonic acid residue, decreasing the availability of the lone pair on the amide nitrogen, thus reducing resonance stabilization of the carbonyl group and facilitating nucleophilic attack.



Similar reasoning involving electron withdrawing substituents on the carbon atoms, can explain the uncatalysed water reactions which occur with other pharmaceutical amides, such as chloramphenicol (Higuchi, Marcus & Bias, 1954) and nicotinamide (Finholt & Higuchi, 1962).

In aqueous solution, sulphacetamide can exist in the protonated (SH^+), neutral (S) and anionic (S^-) forms,



and inspection of Fig. 1 suggests there are five main reactions contributing to the overall hydrolysis rate of sulphacetamide, namely:

$$\left.\begin{array}{ll} SH^+ + H^+ & \xrightarrow{k_1} \\ S + H^+ & \xrightarrow{k_2} \\ S + H_2O & \xrightarrow{k_3} \\ S^- + H_2O & \xrightarrow{k_4} \\ S^- + OH^- & \xrightarrow{k_5} \end{array}\right\} \longrightarrow \text{Sulphanilamide}$$

The overall rate equation (6) is then given by

$$\frac{-dS_T}{dt} = k\,[S_T] = k_1\,[SH^+]\,[H^+] + k_2\,[S]\,[H^+] + k_3\,[S] + k_4\,[S^-] + k_5\,[S^-]\,[OH^-] \quad (6)$$

where S_T represents the total concentration of sulphacetamide, $[SH^+]$, [S], $[S^-]$, $[H^+]$, $[OH^-]$ the concentrations of the various sulphacetamide and catalytic species, k the observed first order rate constant and k_1, k_2, k_3, k_4 and k_5 the corresponding second order rate constants.

The sharp rise in the value of k with decrease in pH_{120} below 4 (Fig. 1) is indicative of an acid catalysed reaction predominating in this area of the log k- pH profile. Hence only the first two terms of the general rate equation (6) will be significantly contributing to the overall reaction velocity. Least squares analysis shows that the log k — pH_{120} relation is rectilinear below pH_{120} 4 ($r = 0{\cdot}9999$ $r_{tab} = 0{\cdot}9500$; $P = 0{\cdot}05$) suggesting that the values of k_1 and k_2 are approximately equal, otherwise a discontinuity should be expected in the curve around the $pK_{1(120)}$ value of 2·13. A similar situation has been reported for the acid catalysed hyrolysis of the protonated and neutral forms of nicotinamide (Finholt & Higuchi, 1962). Under these circumstances equation 6 reduces to equation 7 (Garrett, 1967).

$$\log k = \log k_1 - pH_{120} - \log \gamma \quad .. \quad .. \quad .. \quad (7)$$

where γ is the mean ion activity coefficient. The calculated log k — pH_{120} slope of $-1{\cdot}03$ is in good agreement with equation 7 and is indicative of specific hydrogen ion catalysis in this region. Equation 7 was also used to calculate the specific second

order rate constant (k_1) at the pH values studied experimentally and the values obtained were sufficiently similar to corroborate that specific hydrogen ion catalysis is operative (Table 1).

Above pH_{120} 9, the overall rate equation (6) reduces to equation 8,

$$\log k = \log k_5 - pK_{w(120)} + pH_{120} - \log \gamma \quad .. \qquad .. \qquad (8)$$

and least squares analysis indicates that it is possible to draw a reasonable straight line through the last three points on the right hand side of the log k — pH_{120} profile (Fig. 1) ($r = 0{\cdot}989$, $r_{tab} = 0{\cdot}988$, $P = 0{\cdot}10$). However, the calculated slope of 0·48 is at variance with the theoretical slope of unity required if specific hydroxyl ion catalysis is solely responsible for the observed pH effect (eqn. 8), as is the value of 0·64 obtained when only the last two points, which lie well clear of the plateau region, are considered. We believe that these figures, together with the considerable variation in the k_5 values (Table 1) point to additional hydrolytic mechanisms being operative in these areas. Similar results have been noted for the base catalysed hydrolysis of paracetamol (Koshy & Lach, 1961) and chloramphenicol (Higuchi & others, 1954). Such findings have often been attributed to the presence of buffer constituents, which can influence the kinetics, both through general acid-base or nucleophilic catalysis, and ionic strength effects. Of the buffer components used in this region glycine is the probable catalytic species since it is known to have a significant catalytic effect on other hydrolytic processes (Windheuser & Higuchi, 1962; Johnson, 1967).

Between pH 5–9, where the water reaction is considered to predominate, the presence of more powerful nucleophiles such as the buffer constituents should lead to an increase in the reaction rate (Bender, 1960). Studies at pH 7·4 (Table 2) show that k increases linearly with buffer concentration as would be expected where general acid-base or nucleophilic catalytic effects are operative, and that this is not a primary salt effect is shown by a comparison of the observed first order rate constants obtained in single strength McIlvaine's buffer ($I = 0{\cdot}488$M) with that adjusted to ionic strength 1·952M with potassium chloride ($t_{calc} = 0{\cdot}89$, $t_{tab} = 2{\cdot}31$, $P = 0{\cdot}05$). A similar finding for unbuffered sulphacetamide solution has been reported by Anderson (1966). Such observations are to be expected from theoretical considerations since one of the reacting species (water) forming the activated transition complex is a neutral molecule (Laidler, 1965).

Gomori's tris buffer has a significantly more powerful catalytic effect at pH 7·4 than the McIlvaine system. This is analogous to the effect of 'tris' on the hydrolysis of ethyl dichloroacetate and is compatible with the hypothesis that sulphacetamide undergoes direct nucleophilic attack by 'tris', rather than the latter acting as a general base (Johnson, 1967).

The effect of temperature on the water reaction was studied over the range 99·5 to 140° at pH 7·4. An Arrhenius plot of the log of the observed rate constant against the reciprocal of the absolute temperature was found to be linear ($r = 0{\cdot}9999$, $r_{tab} = 0{\cdot}8783$, $P = 0{\cdot}05$) leading to values of $95{\cdot}9 \pm 4{\cdot}5$ kJ mol^{-1} ($22{\cdot}9 \pm 1{\cdot}1$ kcal mol^{-1}) for the activation energy and $4{\cdot}9 \times 10^7$ ($1{\cdot}2 - 19{\cdot}5 \times 10^7$) s^{-1} for the frequency factor.

Anderson (1967) has reported a value of approximately 100 kJ mol^{-1} (24 kcal mol^{-1}) for the activation energy of sulphacetamide hydrolysis in water. Anderson's data are limited which may account for some of the discrepancy in the values although

the lower value reported here must, in part, be attributable to the slight catalytic effect of the McIlvaine's buffer. These values are larger than those recorded for many amide hydrolyses (Bender, 1960) which only proceed in the presence of hydrogen or hydroxyl ions, but are consistent with water reactions. Comparable values have been calculated from data available in the literature for the pH independent hydrolysis of chloramphenicol (Table 3).

The sulphacetamide data gave a marginally better fit when applied to the absolute rate equation (9), leading to values of $92{\cdot}5 \pm 4{\cdot}5$ kJ mol^{-1} ($22{\cdot}1 \pm 1{\cdot}1$ kcal mol^{-1}) and $-10{\cdot}9 \pm 2{\cdot}5$ J deg^{-1} mol^{-1} ($-2{\cdot}6 \pm 0{\cdot}6$ cal deg^{-1} mol^{-1}) for the activation enthalpy and entropy respectively.

$$K_T = \frac{k_T}{h} \exp. [\Delta S^*/R] \exp. [-\Delta H^*/RT] \quad .. \quad .. \quad (9)$$

(K_T represents the rate constant at temperature T, k the Bolzmann constant, h is Planck's constant, R is the universal gas constant and ΔS^* and ΔH^* represent the entropy and enthalpy of activation, respectively).

The value of $-10{\cdot}9$ J deg^{-1} mol^{-1} for the activation entropy is at variance with the characteristically large negative values (-60 to -120 J deg^{-1} mol^{-1}) associated with the neutral water reactions of carboxylic acid derivatives (Johnson, 1967), but are similar to the figures that we calculate for the chloramphenicol water reaction (Table 3). These entropy values are comparable to that associated with the loss of freedom of a single water molecule ($\approx$22 J deg^{-1} mol^{-1}) and it would therefore appear that there is little difference in the degree of solvation between the initial and transition states in these systems (Schaleger & Long, 1963).

Pharmaceutical implications

Use of the Arrhenius parameters to extrapolate the data to 18° and 25° gives mean values for the rate constants of $1{\cdot}12 \times 10^{-6}$ h^{-1} and $2{\cdot}85 \times 10^{-6}$ h^{-1} respectively leading to $t_{10\%}$ values of 10·7 and 4·2 years, indicating that solutions of sulphacetamide are stable at room temperature.

Similar calculations enable the percentage loss of sulphacetamide resulting from autoclaving solutions at 115° for 30 min to be estimated at 1·1% ($k = 0{\cdot}0223$ h^{-1} at 115°). This would result in the formation of 0·22% sulphanilamide from a 30% sulphacetamide solution. Since the reported solubility of sulphanilamide in water is 0·6% and 0·26% at 20° and 10° respectively (Merck Index, 1968), there seems little reason for not heat sterilizing sulphacetamide solutions, provided they are not subsequently refrigerated.

These conclusions cannot be directly related to the current B.P.C. eye drops of sulphacetamide however, since it has been shown that the sodium metabisulphite, present as an antioxidant has a considerable catalytic influence on the hydrolysis rate of the drug (Davies & others, 1970). As it has also been demonstrated that sodium metabisulphite accelerates photolytic colour development in sulphacetamide solutions (Anderson & Maudson, 1963; Meakin & Davies, unpublished data), the inclusion of this antioxidant in the official eye drops seems open to question.

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