International Journal of Pharmaceutics, 23 (1985) 209–222
Elsevier

IJP 00789

Prodrugs of 5-fluorouracil. III. Hydrolysis kinetics in aqueous solution and biological media, lipophilicity and solubility of various 1-carbamoyl derivatives of 5-fluorouracil

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(Received June 27th, 1984)
(Accepted August 30th, 1984)

Key words: 5-fluorouracil – prodrugs – carbamoyl-5-fluorouracil derivatives – stability – partition coefficients – solubility

Summary

The kinetics of hydrolysis of five 1-carbamoyl-5-fluorouracil derivatives (methyl-, ethyl-, butyl-, phenyl- and N,N-dimethylcarbamoyl derivatives) was studied in aqueous solution of pH 1–14, human plasma solutions and in the presence of rat liver homogenate at 37°C. All the derivatives hydrolyzed to yield 5-fluorouracil in quantitative amounts. The decomposition rates in aqueous solution (pH 1–10) showed a sigmoid pH-dependence which could be ascribed to water-catalyzed or spontaneous hydrolysis of the neutral and anionic forms (pK_a 6.1–6.7). The greater reactivity observed for the anionic form of the derivatives was attributed to intramolecular general base catalysis. The half-lives of hydrolysis of the 1-alkylcarbamoyl derivatives at pH 7.40 and 37°C were 8–11 min and that of the 1-phenylcarbamoyl derivative 5 s, whereas the N,N-dimethylcarbamoyl derivative proved to be highly stable. The hydrolysis was not catalyzed by rat liver homogenates, and human plasma surprisingly showed a pronounced inhibition. This deceleration of the hydrolysis rate was attributed to a non-productive binding to or inclusion of the compounds by plasma proteins. The derivatives were more lipophilic than 5-fluoro-

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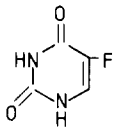
uracil as determined by partition experiments in octanol–aqueous buffer systems and possessed a lower water-solubility.

Introduction

Although 5-fluorouracil (I) remains a clinically important antitumor agent it possesses far from optimal delivery properties. Thus, it shows an incomplete and highly variable bioavailability following oral administration (Cohen et al., 1974; Christophidis et al., 1978; Finch et al., 1979; Fraile et al., 1980; Phillips et al., 1980), largely due to a pronounced first-pass metabolism in the gastrointestinal tract and the liver (Christophidis et al., 1978; Collins et al., 1980; Almersjö et al., 1980). The rectal route of administration appears to be of even less value than the oral one in that no absorption of 5-fluorouracil was observed after giving the drug in the form of a rectal enema (Christophidis et al., 1978).

A promising approach to improve the delivery characteristics of 5-fluorouracil may be the development of prodrugs with enhanced physicochemical properties in regard to delivery. It is thought that by bioreversible derivatization it may be possible to protect the drug against first-pass metabolism and to obtain bio-labile derivatives possessing a higher lipophilicity than the parent drug. The partition coefficient of 5-fluorouracil between octanol and water is only 0.15 (Buur and Bundgaard, 1984a) and this low lipophilicity may be a predominant factor for the poor biomembrane permeability of the drug. Although several types of such masked forms of 5-fluorouracil including 1-carbamoyl derivatives have been described (for references, see Buur and Bundgaard, 1984a) only little information is available on their properties of relevance to delivery, such as the stability and the converting efficiency of the derivatives to the parent 5-fluorouracil as well as lipophilicity and aqueous solubility.

Studies have been undertaken in this laboratory to provide such information with the ultimate goal of identifying prodrugs of 5-fluorouracil with improved delivery



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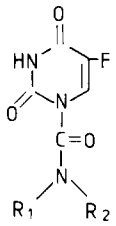


II R_1 = H R_2 = CH_3
III R_1 = H R_2 = CH_2CH_3
IV R_1 = H R_2 = $CH_2CH_2CH_2CH_3$
V R_1 = H R_2 = C_6H_5
VI R_1 = CH_3 R_2 = CH_3

characteristics. In previous studies (Buur and Bundgaard, 1984a and b), various N-acyl and N-alkoxycarbonyl derivatives were assessed as possible prodrug forms. In the present work a series of 1-carbamoyl derivatives (II–VI) have been studied. The kinetics of their conversion to 5-fluorouracil in aqueous solution and in biological media is reported along with determinations of their aqueous solubility and lipophilicity.

Materials and Methods

Apparatus

Ultraviolet spectral measurements were performed with a Shimadzu UV-190 spectrophotometer equipped with a thermostatically controlled cell compartment, using 1-cm quartz cells. ^{1}H-NMR spectra were run on a Varian 360L instrument using tetramethylsilane as zero reference. Readings of pH were carried out on a Radiometer Type PHM 26 meter at the temperature of study. Melting points were taken on a capillary melting-point apparatus or determined by differential scanning calorimetry (DSC) using a Perkin Elmer type DSC-1B apparatus. High-performance liquid chromatography (HPLC) was performed with a system consisting of a Waters pump model 6000A, a variable-wavelength UV-detector Waters type Lambda Max 480 and a 20-μl loop injection valve. The column used, 250 × 4 mm, was packed with LiChrosorb RP-8 (7 μm particles) (E. Merck, Darmstadt). Microanalysis were carried out at Leo Pharmaceuticals, Denmark.

Materials

5-Fluorouracil was purchased from Fluka AG, Switzerland and was used as received. Crystalline human serum albumin was obtained from Sigma Chemicals, St. Louis. The 1-carbamoyl derivatives (II–VI) were prepared by reacting 5-fluorouracil with the appropriate isocyanate or N,N-dimethylcarbamoyl chloride as described by Ozaki et al. (1977). The melting points observed for the compounds by using differential scanning calorimetry are listed in Table 3. By using a capillary melting-point apparatus, the melting points were likely to be overlooked or were even not observable due to thermal dissociation of the derivatives to 5-fluorouracil and isocyanate, cf. Ozaki et al. (1977). The two methods gave identical results only for compounds IV and VI. For some of the derivatives the melting points reported by Ozaki et al. (1977) using the capillary method differ considerably from those found in the present study. The structure of all the derivatives prepared was confirmed by elemental analysis (C, H and N, results within ±0.5% of the theoretical values), UV spectrophotometry, ^{1}H-NMR analysis and by their quantitative transformation to 5-fluorouracil upon hydrolysis (see below).

Kinetic measurements

All rate studies in aqueous buffer solutions were carried out at 37.0 ± 0.2°C and a constant ionic strength (μ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride. The buffers used were hydrochloric acid (pH ≤ 2), acetate (pH 4–5), phosphate (pH 2–3 and 6–8), borate (pH 8.3–10), carbonate (pH 10.5–11.5) and sodium hydroxide (pH > 11.5) and, except in those

experiments in which buffer effects were specifically investigated, the total concentration of the buffers was 0.05 M.

At pH values higher than about 7.5 the reactions were generally followed by direct UV-spectrophotometry and were performed in 2.5 ml aliquot portions of buffer solutions in a thermostated quartz cuvette. The reactions were initiated by adding 25 μl of stock solutions of the derivatives in acetonitrile giving a final concentration of $1-5 \times 10^{-4}$ M. The reaction progress was followed by recording the increase in absorption at 300 nm as a function of time. Pseudo-first-order rate constants were determined from linear plots of $\log(A_\infty - A_t)$ versus time, where A_∞ and A_t are the absorbance readings at infinity and at time, t, respectively.

At pH values lower than about 9 the reactions were followed by using a reversed-phase HPLC procedure (except for compound V where the reaction progress was followed by direct UV-spectrophotometry also in the acidic pH region (decrease in absorption at 266 nm)). Mobile phase systems of 20–65% v/v methanol in 0.01 M acetate buffer of pH 5.0 were used. The flow rate was 1.2 ml $\cdot$ min^{-1} and the column effluent was monitored at 266 nm. For the determination of 5-fluorouracil a solvent system of 5% v/v methanol in 0.01 M acetate buffer of pH 5.0 was used. Quantitation of the compounds was done by measuring the peak heights in relation to those of standards chromatographed under the same conditions. In the kinetic runs the reactions were initiated by adding 100 μl of a stock solution of the derivatives in acetonitrile to 10.0 ml of buffer solution pre-equilibrated at 37°C in screw-capped test tubes, the final concentration in the reaction mixture being about 10^{-4} M. During the experiments the solutions were kept at 37.0 ± 0.2°C in a water-bath and aliquots were removed at suitable intervals and chromatographed. Pseudo-first-order rate constants were calculated from the slopes of linear plots of the logarithm of residual 5-fluorouracil derivative against time.

Stability studies in biological media were performed in 0.05 M phosphate buffer (pH 7.4) containing either human plasma or rat liver homogenate (at 37°C). Preparation of the rat liver homogenate was done in the following way. The livers of rats were homogenized at 0–5°C in a tissue homogenizer, diluted with 0.05 M phosphate buffer of pH 7.40 and centrifuged at 4°C at $600 \times g$ for 10 min. The supernatant was used for the experiments.

The reactions were initiated by adding 50 μl of stock solutions of the derivatives to the pre-heated (37°C) solutions, the initial concentration being about 5×10^{-5} M. At appropriate times samples of 200 or 400 μl were withdrawn and added to 1000 μl of ethanol or 250 μl of 20% trichloroacetic acid, respectively, in order to deproteinize the samples. After mixing and centrifugation for about 2 min, 20 μl of the clear supernatant was subjected to HPLC-analysis as described above.

For reactions performed in phosphate buffer solutions containing varying amounts of human serum albumin (0.5–5%) the HPLC analysis of the remaining carbamoyl derivative was done in a similar way by mixing 200 μl samples with 1000 μl of ethanol followed by centrifugation.

Determination of aqueous solubility, partition coefficients and pK_a values

The aqueous solubility of the derivatives were determined at 22°C by adding

excess amounts to 0.05 M acetate buffer of pH 4.0 as previously described (Buur and Bundgaard, 1984a). The apparent partition coefficients (P) were determined in an octanol–0.02 M acetate buffer (pH 4.0) system as previously described (Buur and Bundgaard, 1984a).

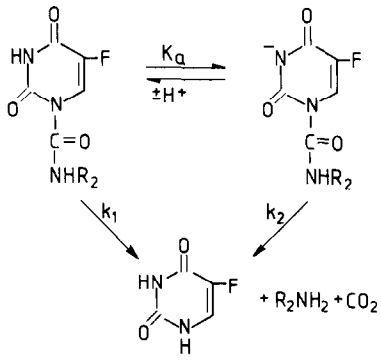
The ionization constants for the derivatives were determined at 22°C and $\mu = 0.5$ by spectrophotometry according to Albert and Serjeant (1971). The wavelength used for the determination of the pK_a values was 236 nm.

Results and Discussion

The kinetics of breakdown of the various 1-carbamoyl-5-fluorouracil derivatives (II–VI) in aqueous buffer solutions was studied over a wide range of pH values at 37°C. At constant pH and temperature the reactions displayed strict first-order kinetics for several half-lives and in all runs 5-fluorouracil was formed in quantitative amounts as evidenced by HPLC analysis. In some cases the decomposition rate was determined using both the direct UV method and the HPLC method and the values of the observed rate constants obtained therefrom agreed within 5%. Variation of buffer concentration at a given pH produced no change in the rate constants, thus revealing no occurrence of general acid–base catalysis by the buffers.

The influence of pH on the rates of hydrolysis of compounds II–V appears from Fig. 1 where the logarithm of the observed pseudo-first-order rate constants (k_{obs}) is plotted against pH. As can be seen log k_{obs} shows a sigmoid dependence on pH up to pH about 10. This shape of the pH–rate profiles can be accounted for by assuming spontaneous or water-catalyzed decomposition of the undissociated and the anionic forms of the derivatives as depicted in Scheme 1. The derivatives are weak acids due to dissociation of the 3-N hydrogen atom, the pK_a values being about 6.7 (see below). According to Scheme 1 the following rate expression can be formulated:

$$k_{obs} = k_1 \frac{a_H}{a_H + K_a} + k_2 \frac{K_a}{a_H + K_a} \qquad (1)$$



Scheme 1

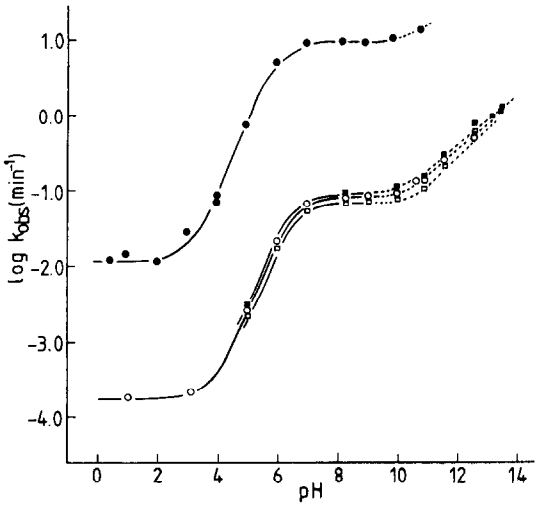


Fig. 1. The pH–rate profiles for the hydrolysis of various 1-carbamoyl derivatives of 5-fluorouracil (5-FU) in aqueous solution ($\mu = 0.5$) at 37°C. ●, 1-Phenylcarbamoyl-5-FU (V); ○, 1-Butylcarbamoyl-5-FU (IV); ■, 1-Ethylcarbamoyl-5-FU (III); □, 1-Methylcarbamoyl-5-FU (II).

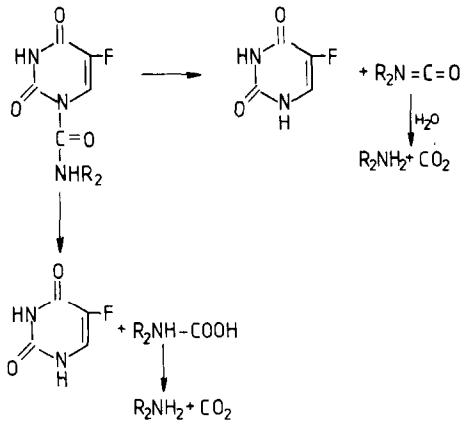
where a_H is the hydrogen ion activity, $a_H/(a_H + K_a)$ and $K_a/(a_H + K_a)$ are the fractions of the compounds in the neutral and anionic form, respectively, K_a is the apparent ionization constant of the compounds and k_1 and k_2 are the first-order rate constants for the spontaneous hydrolysis of the neutral and anionic species, respectively. The values of the rate and dissociation constants derived from Fig. 1 and Eqn. 1 are listed in Table 1. In Fig. 1 the solid curves drawn were constructed from these constants and Eqn. 1 and the good fit observed to the experimental data demonstrates that Eqn. 1 and, accordingly, Scheme 1 adequately describes the hydrolysis kinetics. It should be noted, however, that other kinetically equivalent reactions can

TABLE 1

IONIZATION CONSTANTS AND RATE DATA FOR THE HYDROLYSIS OF VARIOUS 1-CARBAMOYL-5-FLUOROURACIL DERIVATIVES IN AQUEOUS SOLUTION AT 37°C AND $\mu = 0.5$.

Compound	k_1 (min^{-1})	k_2 (min^{-1})	pK_a [a]	
			kin.	UV
II		0.069	6.6	6.7
III		0.091	6.6	6.7
IV	1.7×10^{-4}	0.083	6.6	6.8
V	1.2×10^{-2}	9.1	6.1	
VI				6.7

[a] The kinetically determined pK_a values were obtained at 37°C and $\mu = 0.5$ whereas the values determined by spectrophotometric titration at 236 nm were at 22°C and $\mu = 0.5$.



Scheme 2

equally well account for the pH–rate profiles, e.g. the k_2 reaction is kinetically equivalent to a reaction involving hydroxide ion-catalyzed hydrolysis of the neutral species. As appears from Table 1 the kinetically derived pK_a values agree satisfactorily with those determined by spectrophotometric titration when the temperature difference in the measurements is taken into account.

At pH values above 10 the rate of hydrolysis of the derivatives II–V increases with increasing pH (Fig. 1). The slopes of the pH–rate profiles in this pH range are, however, only about 0.4 and thus, the reactions taking place are not simple hydroxide ion-catalyzed hydrolysis. It should be noted that also at these basic pH values the decomposition of the derivatives was found to give 5-fluorouracil in quantitative amounts.

Considering the mechanism of hydrolysis a pathway involving an unstable isocyanate intermediate (Scheme 2) may be involved as has been documented for the hydrolysis of various carbamates (Williams, 1972; Vontor et al., 1972; Hegarty and Frost, 1973; Hegarty et al., 1974b) as well as for various N-carbamoylimidazoles (Stark, 1965; Hegarty et al., 1974a; Williams and Jencks, 1974; Al-Rawi and

TABLE 2

HALF-LIVES OF HYDROLYSIS OF VARIOUS 1-CARBAMOYL-5-FLUOROURACIL DERIVATIVES IN BUFFER SOLUTIONS (pH 7.40), 80% HUMAN PLASMA AND 20% RAT LIVER HOMOGENATE AT 37°C

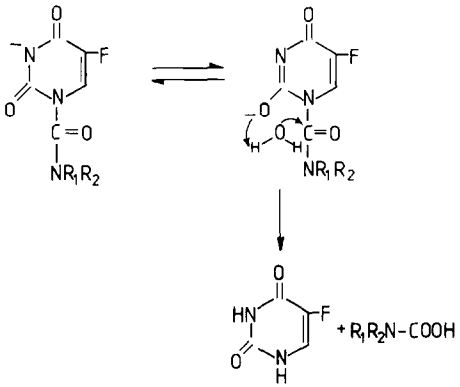
Compound	$t_{1/2}$ (min)		
	Buffer	Human plasma	Rat liver homogenate
II	11.0	20.0	13.8
III	8.7	22.5	11.2
IV	8.0	53.0	11.5
V	0.07	n.d.	n.d.

n.d. = not determined.

Williams, 1979). Such a mechanism is consistent with the 80-fold greater reactivity of the phenyl-substituted derivative (V) as compared with the alkyl derivatives II–IV and with the much reduced reactivity of the N,N-dimethylcarbamoyl derivative VI. At pH 7.4 and 37°C this compound remained fully stable (< 1% decomposition) for 8 h whereas the other derivatives were hydrolyzed with half-lives of 0.07–11 min (Table 2). At pH 13.48 and 37°C a half-life of hydrolysis of compound VI of 108 min ($k_{obs} = 0.0064\ min^{-1}$) was observed which corresponds to about 150-fold greater stability as compared with the monosubstituted methyl derivative II. The derivative VI is structurally unable to yield an isocyanate intermediate and the only mechanism possible is direct nucleophilic attack by hydroxide ions on the carbonyl carbon atom. The 5-fluorouracil anion is a good leaving group (pK_a for the 1-NH group is 8.0 (Berens and Shugar, 1963)) which explains the high reactivity of the carbamoyl derivatives II–V in aqueous solution and which also is compatible with the ElcB elimination mechanism. Hegarty and Frost (1973) have established that for carbamates the ElcB mechanism predominates for compounds with good leaving groups, i.e. pK_a of the alcohol < ca. 12. The present data are, however, insufficient to differentiate between such a mechanism and the alternative mechanism, the normal $B_{Ac}2$ pathway, for example, for esters and amides involving a tetrahedral intermediate (Scheme 2). Support for this mechanism is probably the difference in reactivity of the undissociated and anionic forms of the derivatives IV and V which corresponds to a factor of 5–700. The much greater reactivity of the anionic form may thus be explained in terms of intramolecular general base catalysis as depicted in Scheme 3. In this case the lower reactivity of the dimethylurea derivative VI may be due to increased steric hindrance by the two methyl groups. In the hydrolysis of N_3-acyl derivatives of 5-fluorouracil the anionic forms have also been shown to be much more reactive than the neutral species (Buur and Bundgaard, 1984a) and this may likewise be ascribed to intramolecular catalysis of attack by water on the acyl moiety.

Stability in plasma and liver homogenates

The relative susceptibility of the carbamoyl derivatives to undergo a possible



Scheme 3

enzymatic hydrolysis was studied in vitro at 37°C in 0.05 M phosphate buffer solution (pH 7.40) containing varying concentrations of human plasma or in the supernatant fraction (diluted to 20%) of rat liver homogenate. Under the given reaction conditions strict first-order kinetics was observed (cf. Fig. 2) and the reactions proceeded to give 5-fluorouracil in stoichiometric amounts. The observed half-lives for the hydrolysis in the biological media are listed in Table 2 along with the half-lives of hydrolysis in pure aqueous buffer solution of pH 7.40. As appears from the rate data the presence of human plasma or rat liver homogenate rather surprisingly retards the rate of cleavage of the derivatives. In case of the plasma data this inhibition becomes more pronounced as the alkyl chain length in the derivatives increases, suggesting a non-catalytic binding of the compounds to the plasma proteins. When experiments were performed with varying human plasma concentrations the rate of hydrolysis decreased in a non-linear fashion reaching asymptotically a minimum value with increasing plasma concentration (Fig. 2B). These facts suggest that the observed stabilization of the carbamoyl derivatives (C) by plasma may be accommodated by the reaction mechanism illustrated in Scheme 4:

$$\begin{array}{ccc} C + \text{Protein} & \rightleftharpoons & C\text{–Protein} \\ \downarrow k' & & \downarrow k'' \\ \text{5-Fu} & & \text{5-Fu} \end{array}$$

Scheme 4

where k′ and k″ are the pseudo-first-order rate constants for the hydrolysis of free and protein bound or complexed carbamoyl derivative, respectively. For compound IV the rate constant k″ was found to have a value of about a tenth of that of k′ ($= k_{obs}$ in pure buffer solutions). It appears difficult to give a firm mechanistic explanation for the observed deceleration of the hydrolysis of the derivatives by the plasma. One possibility is that plasma lipoproteins are involved and that the

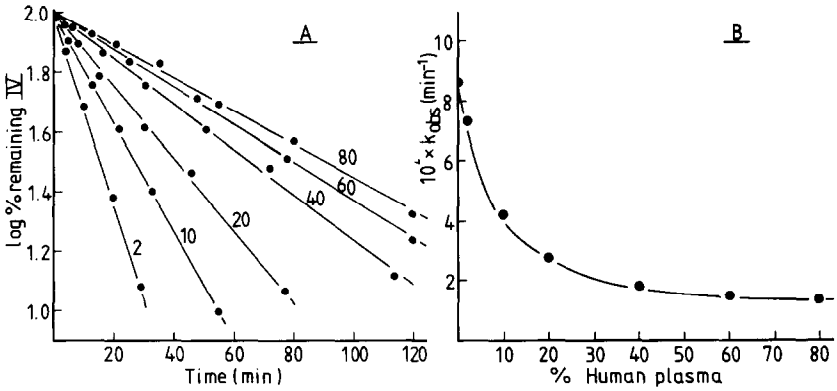


Fig. 2. A: first-order plots for the hydrolysis of 1-butylcarbamoyl-5-fluorouracil (IV) in 0.05 M phosphate buffer of pH 7.40 containing varying concentrations (in %) of human plasma (at 37°C). B: plot of the observed pseudo-first-order rate constants derived from Fig. 2A against the concentration of human plasma.

carbamoyl derivatives may partition into the non-polar core of these proteins and form an inclusion complex in which the compounds are protected against hydrolysis (cf. Scheme 3). Such a mechanism has previously been advanced for the stabilizing effect observed for serum lipoproteins on the degradation of chloroethylnitrosourea (Weinkam et al., 1980).

That binding of the compounds to plasma proteins is a major factor in the observed inhibition of the hydrolysis by plasma was supported by kinetic experiments performed in the presence of human serum albumin (HSA). As can be seen from Fig. 3A the rate of hydrolysis of compound IV at pH 7.40 is decreased in the presence of HSA. At a HSA concentration of 4–5% corresponding to that occurring in plasma the hydrolysis rate constant is decreased to a value of about 0.01 min^{-1} which is close to that observed in 80% plasma solutions (cf. Fig. 2B). The influence of HSA on the rate of hydrolysis may be described in terms of Scheme 4. From this 1 : 1 complexation scheme the following rate expression may be derived:

$$k_{obs} - k' = -\frac{(k_{obs} - k')}{K[HSA]} + (k'' - k') \qquad (2)$$

where K is the apparent formation constant for the complex formed between compound IV and serum albumin. In Fig. 3B the rate data of Fig. 3A are plotted according to Eqn. 2. From the slope and intercept of the plot the following values of k′, k″ and K were obtained:

$k' = 8.6 \times 10^{-2}\ min^{-1}$

$k'' = 4.0 \times 10^{-3}\ min^{-1}$

$K = 3.4\%^{-1}$ or $2.3 \times 10^{4}\ M^{-1}$

According to these results, the protein-bound compound is hydrolyzed much more slowly (by a factor of about 20) than the unbound compound. In considering the

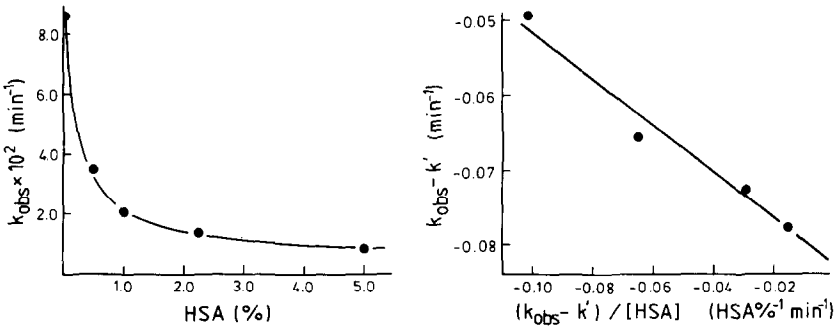


Fig. 3. A: the effect of human serum albumin (HSA) on the rate of hydrolysis of compound IV in 0.05 M phosphate buffer solution of pH 7.40 (37°C). B: plot of the rate data in Fig. 3A according to Eqn. 2.

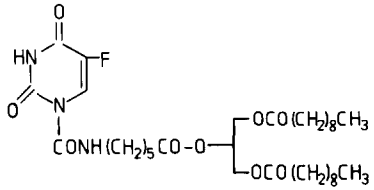
observed inhibition of serum albumin of the spontaneous hydrolysis of the carbamoyl 5-fluorouracil derivative it is of interest to note that binding of acetylsalicylic acid to albumin has similarly been reported to decrease the rate of spontaneous hydrolysis of the ester (Aarons et al., 1980).

The observed inhibition of the rate of hydrolysis by human plasma or serum albumin in vitro may explain the relatively low efficiency of various 1-alkylcarbamoyl-5-fluorouracil derivatives such as the hexylcarbamoyl derivative to be converted to the parent drug in vivo (Kobari et al., 1978, 1981; Iigo et al., 1980a and b; Kono et al., 1980). If the rates of conversion in vivo were similar to those in aqueous buffer solutions at pH 7.4 the half-lives for the derivatives would be only about 10 min, which is much lower than that appearing from the pharmacokinetic and metabolic studies cited. An apparent exception to this is a recently described 1-carbamoyl derivative, 1,3-didecanoyl-2-[6-[(5-fluorouracil-1-yl)carbonylamino]hexanoyl]glyceride (VII). The half-life of hydrolysis of this compound in rat plasma in vitro was found to be 4 min and about 3 h in buffer solution of pH 7.4 (Takada et al., 1983). There may possibly be a species difference in enzymatic activity.

Several 1-carbamoyl derivatives have been tested for antitumor activity and shown to be active against various murine tumors such as L-1210 leukemia, Lewis lung carcinoma and ascites sarcoma 1980 (Hoshi et al., 1975, 1978; Iigo et al., 1979). In these studies the great lability of the derivatives at physiological conditions of pH and temperature does not appear to have been noted. Thus, the 1-phenylcarbamoyl derivative V was found to possess the same antitumor activity as 5-fluorouracil upon oral administration in mice (Hoshi et al., 1975, 1978). At pH 6–8 the half-life of hydrolysis of this compound is only about 5 s and hence, the compound will most likely be degraded to 5-fluorouracil already in the gastrointestinal tract.

Lipophilicity and aqueous solubility of the carbamoyl derivatives

Apparent partition coefficients as determined using an octanol–aqueous buffer system (pH 4.0) are listed in Table 3 along with melting points and solubilities in water at pH 4.0. As can be seen from the data the derivatives are all more lipophilic than the parent 5-fluorouracil. The difference in the log P values for the derivatives II–V is as expected on the basis of the π substituent values for a methylene and phenyl group (Hansch and Leo, 1979) except for the dimethylcarbamoyl derivative VI. The log P value for this compound should be expected to be about 0.5 unit greater than that for the methylcarbamoyl derivative but it is in fact even lower. This



VII

TABLE 3

MELTING POINTS, PARTITION COEFFICIENTS (P) AND AQUEOUS SOLUBILITIES (S) OF 5-FLUOROURACIL AND VARIOUS N_1-CARBAMOYL DERIVATIVES [a]

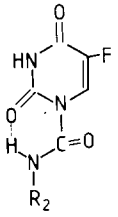
Compound	m.p. (°C)	log P	S ($mg \cdot ml^{-1}$)
5-Fluorouracil [b]	280-284	−0.83	11.1
1-Methylcarbamoyl-5-fluorouracil (II)	225-228	−0.20	0.62
1-Ethylcarbamoyl-5-fluorouracil (III)	190-196	0.35	1.5
1-Butylcarbamoyl-5-fluorouracil (IV)	136	1.44	0.82
1-Phenylcarbamoyl-5-fluorouracil (V)	221-24	1.5 [c]	n.d. [d]
1-Dimethylcarbamoyl-5-fluorouracil (VI)	226-27	−0.37	6.0

[a] P and S values were determined at 22°C in octanol–acetate buffer of pH 4.0 and in acetate buffer of pH 4.0, respectively.

[b] Data from Buur and Bundgaard (1984a).

[c] Determined on the basis of a linear relationship between the logarithm of chromatographic capacity factors for II–V and log P values for II–IV, cf. Buur and Bundgaard (1984a).

[d] Not determined due to stability reasons.



VIII

behaviour can most likely be ascribed to the occurrence of intramolecular hydrogen bonding (VIII) in the monoalkyl substituted carbamoyl derivatives as suggested by Ozaki et al. (1977) based on NMR measurements. X-Ray diffraction measurements have revealed the presence of such an internal hydrogen bonded structure for the related 1-methylcarbamoyluracil (Parthasarathy et al., 1973). This phenomenon which results in a more lipophilic molecule cannot occur in the dimethylcarbamoyl derivative.

The increased lipophilicity of the derivatives as compared with 5-fluorouracil is accompanied by a decreased water solubility. As discussed in the previous paper on N-acyl derivatives (Buur and Bundgaard, 1984a) derivatization of 5-fluorouracil may lead to compounds possessing both higher lipophilicity and aqueous solubility due to a decreased intermolecular hydrogen bonding in the crystal lattice. Apparently, the decreased intermolecular hydrogen bonding achieved by blocking the 1-NH group in 5-fluorouracil by carbamoylation and manifested in the melting point decrease is too small to compensate for the increased lipophilicity introduced by the substituents per se.

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