Fluorescence and Reactivity of *p*-Aminosalicylic Acid: an Example of Proton Transfer in the Solid State

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The emission spectrum of *p*-aminosalicylic acid in ethanol solutions exhibits maxima in the visible (445 nm) and u.v. (*ca.* 350 nm) spectral regions. These maxima are attributed to the protonated and unprotonated forms of this molecule. Protonation occurs in the excited state as a result of intramolecular transfer of the phenolic proton to the oxygen of the carbonyl group and involves an ordered transition state. A similar process is identified in the solid state. By following the fluorescence emission attributed to this protonated species as a function of time and temperature we have evaluated the activation parameters for the deprotonation occurring in the excited state. Decarboxylation of *p*-aminosalicylic acid together with the dehydration and decarboxylation of the sodium salt have also been investigated. The mechanism of the solid state decomposition of these materials involves the initial step of intramolecular proton transfer from the phenolic hydroxy to the carbonyl oxygen with the creation of a disordered transition state leading to the final products.

p-AMINOSALICYLIC ACID (PAS) has pharmaceutical applications as an anti-tuberculosis drug. It has been reported that PAS undergoes decarboxylation to *m*-aminophenol both in solution and in the solid state.[1-3] Recently, several studies have been conducted on the kinetics of decomposition in the solid state and on its structure–reactivity relationship.[4,5] The kinetic studies have yielded inconsistent activation energies.

The mechanism of the proton catalysed decarboxylation in solution [1] has been explained in terms of a proton transfer to the ring carbon atom. This is preferred to one-step simultaneous proton transfer and

[1] A. V. Willi, *Trans. Faraday Soc.*, 1959, **55**, 433.
[2] S. S. Kornblum and B. J. Sciarrone, *J. Pharmaceutical Sci.*, 1964, **53**, 935.
[3] J. R. Cartensen and P. Pothisiri, *J. Pharmaceutical Sci.*, 1975, **64**, 37.
[4] S. R. Byrn, *J. Pharmaceutical Sci.*, 1976, **65**, 1.
[5] C. T. Lin, P. Y. Siew, and S. R. Byrn, *J.C.S. Perkin II*, 1978, 957.

decarboxylation in view of the comparison with other aromatic substitutions occurring by a proton transfer mechanism, *e.g.* nitration [6] and azo-coupling [7] where intermediates have been identified. It has been concluded that the solid state decomposition occurs by a similar mechanism and that it propagates through the crystal by the addition of a carboxylate proton to either ArCOOH or $ArCOO^-$. In all the earlier studies except for the suggestion by Willi [1] the role of the phenolic proton in the reaction has been disregarded.

In this paper, following an examination of changes in the fluorescence emission of PAS with temperature and its decomposition in the crystalline and molten states, and a study of its sodium salt (NaPAS), we demonstrate that the phenolic proton plays a role in the decarboxylation of PAS to yield *m*-aminophenol.

EXPERIMENTAL

NaPAS dihydrate supplied by B.D.H. was used without further purification.* Free PAS was prepared by mixing equimolar quantities of the aqueous sodium salt and dilute hydrochloric acid followed by successive frequent washing with water, m.p. 425 K (lit.,[4] 493 K), in accord with the literature value.[8] Fluorescence measurements in reflection off crystalline material were performed using a Reichert optical microscope with fluorescence attachment. Excitation was by a mercury arc and filters (λ_{exc} 365 ± 10 nm), and the spectra were photoelectrically recorded *via* a monochromator and photon counter (Ortec Brookdeal 5Cl). This allowed the investigation of selected crystalline areas *ca.* ⩽100 μm in diameter. Changes in fluorescence

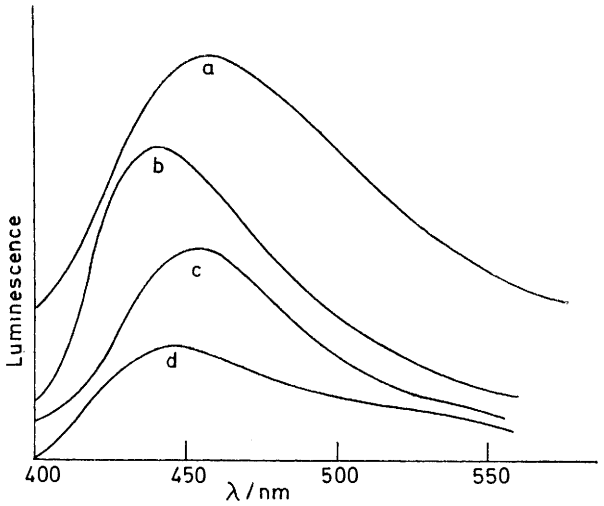


FIGURE 1 Emission spectra of crystalline samples of: a, SA; b, PAS; c, salicylamide; and d, NaPAS,$2H_2O$

intensity were followed with the sample mounted on a hot stage and temperature measurement employed a thermocouple very close to the crystal. Solution fluorescence spectra were recorded in a commercial spectrophotometer (Aminco–Keins).

* Byrn [5] reports that the sodium salt of PAS is prepared by adding PAS to the equivalent amount of aqueous NaOH. Upon cooling, needles separated which gave, on elemental analysis, values consistent with an anhydrous form. However, one would expect that such a recrystallisation yields the dihydrate as supplied by B.D.H. and other drug suppliers (see ref. 1).

The decomposition studies were conducted on a differential scanning calorimeter (Perkin-Elmer DSC 1B) operating in the dynamic and isothermal modes. For dynamic

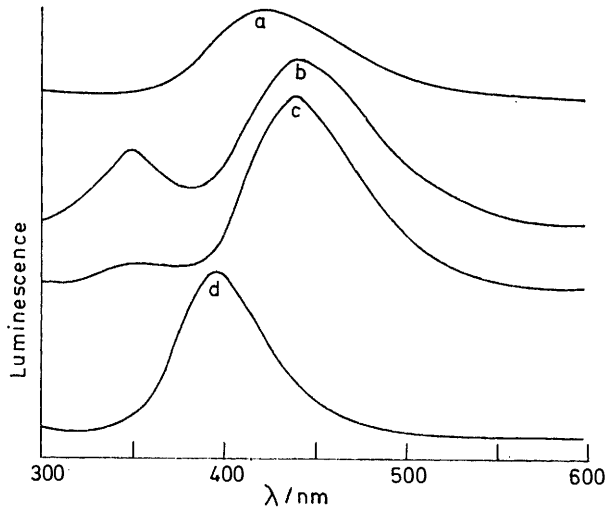


FIGURE 2 Emission spectra in ethanol solution of: a, SA; b, PAS; c, salicylamide; and d, NaPAS,$2H_2O$ (λ_{exc} 300 nm)

measurements the temperature was programmed at different linear rates up to 64° min^{-1}.

RESULTS

Fluorescence of Salicylic Acid (SA), PAS, and NaPAS.—The fluorescence spectra of crystalline SA, PAS, and NaPAS are shown in Figure 1. The three materials yield broad emission maxima at 440 for NaPAS, 445 for PAS, and 460 nm for SA. (Under similar conditions benzoic acid and its derivatives do not fluoresce.) The fluorescence spectra of the same three compounds in ethanol solutions (λ_{exc} 300 nm) are shown in Figure 2. SA shows one emission maximum at 440, NaPAS one band at 395, and PAS shows one maximum at 440 and another at 348 nm.

Fluorescence Changes of PAS.—The PAS fluorescence intensity decreases with increasing time at constant temperature. The change in fluorescence at different temperatures between 313 and 382 K allowed the determination of fractional fluorescence decays $\alpha_F = (F_0 - F_t)/F_0$ where F_0 and F_t are the fluorescence intensities at times 0 and t respectively. Such curves obey a unimolecular decay law (see Figure 3) with a value for the activation energy evaluated from Arrhenius plots and the values of the enthalpy and entropy of activation from the Eyring

A summary of the activation parameters for the reactions of PAS

	E_a/ kJ mol^{-1}	ΔH^*/ kJ mol^{-1}	ΔS^*/ J mol^{-1} K^{-1}
Fluorescence decay (proton transfer process)	35.0	33.0	−178
Decarboxylation	169.0	165	+168

H^* and S^* were calculated from the equation $\ln k/T = \ln k'/h + \Delta S^*/R - \Delta H^*/RT$.

equation (see Table). Similar fluorescence behaviour is observed with repeated heating and cooling indicating the

[6] See ref. 17 of ref. 1.
[7] Hch. Zollinger, *Helv. Chim. Acta*, 1955, **38**, 1597.
[8] 'Handbook of Physics and Chemistry,' Chemical Rubber Co., Cleveland, 1976—1977.

reversibility of the proton transfer and the absence of decomposition over the time and temperature ranges employed.

Decomposition of PAS.—With a slow temperature scanning rate the calorimetric profiles of PAS display one endothermic peak which embraces both the melting and decomposition ranges. However, with faster scanning

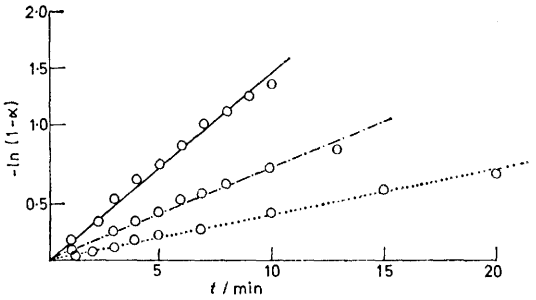


FIGURE 3 Unimolecular decay plots for the fluorescence of PAS at —— 382 K, —·—·— 368.5 K, and ···· 354.5 K [$\alpha_F = (F_0 - F_t)/F_0$]

rates the melting and decomposition processes may be separated with melting preceding decomposition upon heating.

For the study of the decomposition of PAS calorimetric scans were run at a fixed temperature (*ca.* 373 K) with the energy change recorded with time. Melting accompanied decomposition above 376 K. The fractional decomposition–time curves were calculated from such isothermal scans by dividing the energy change at time t by the total energy change during the reaction. Such curves are acceleratory in nature and typical of an autocatalytic reaction. Furthermore, the long induction periods followed by an exponentially increasing rate until termination of the reaction are typical of a chain branching reaction. Since the time for commencement of the reaction τ is constant and characteristic of the reaction, at constant temperatures plots of $1/\tau$ *versus* $1/T$ yield activation energies and enthalpies. The determined parameters are shown in the Table.

NaPAS,$2H_2O$ is dehydrated at *ca.* 365 K and commences decomposition at *ca.* 493 K (see Figure 4).

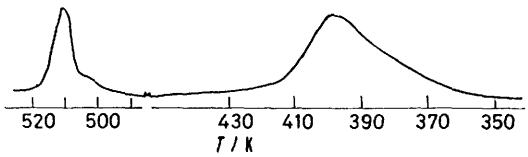
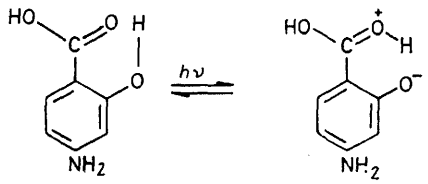


FIGURE 4 Typical differential scanning calorimeter profiles for NaPAS,$2H_2O$ showing dehydration at the lower temperature and decarboxylation at the higher temperature

DISCUSSION

SA and its derivatives contain a phenolic OH group which forms an intramolecular hydrogen bond to the carbonyl group of the acid. The long wavelength absorption band of all these compounds in ethanol occurs at *ca.* 300 nm so that we should not expect fluorescence from these materials in the visible region of the spectrum.[9] However, Weller [10,11] has observed that methyl salicylate (MeS) in non-polar solvents has an emission in the visible region with a large Stokes shift (10 000 cm^{-1}) and a shoulder in the u.v. Upon lowering the temperature the intensity of the long wavelength emission band increases. The activation enthalpy for the excited state proton transfer was found to be *ca.* 42 ± 2.0 kJ mol^{-1} whilst for the ground state proton transfer values of *ca.* 56.4 kJ mol^{-1} have been reported. The proton transfer reaction also occurs at 4 K with even smaller activation, *ca.* <0.4 kJ mol^{-1}, suggesting proton tunnelling as the transfer mechanism.[9]

The spectra shown in Figure 1 demonstrate that all the crystalline compounds studied emit visible fluorescence and this may be rationalized as due to proton transfer occurring in the solid state since excitonic emission cannot account for such high Stokes shifts. The spectra in ethanol (Figure 2) confirm that for PAS the two bands occurring in the u.v. and visible regions may be assigned to the non-protonated and protonated species (I) and (II). The one emission band for NaPAS may be explained in terms of rapid proton transfer in the excited state so that the emission from a species similar to (I) is not observed. The blue shift of the NaPAS emission relative to that for PAS may be due to complete



(I) (II)

ionization of the salt resulting in delocalization of the negative charge on the oxygen before excited state proton transfer occurs. The decrease in fluorescence intensity of the protonated species (II) indicates that with increasing temperature the deprotonation occurs thermally leading to species (I) in either its ground or excited state. In this respect the behaviour is similar to that reported for MeS where the relative intensity of the fluorescence due to the visible and u.v. emitting species was found to increase with decreasing temperature.[12]

Since in this case the decrease in fluorescence intensity is a molecular process which is not controlled by the usual geometric factors controlling nucleus formation and growth in solids,[13] a unimolecular decay law applies. In this respect the system behaves kinetically like other luminescence decay processes (involving only deactivation) with a factor of *ca.* 10^{10} decrease in velocity and the activation energy measured is in accord with the strength of hydrogen bonding in such systems. Negative values for the entropy of activation indicate that the reaction occurs *via* an ordered activated state.

The rate of the initial decomposition of small (a few mg) samples of PAS in the solid state yields an activation

[9] See *e.g.* W. Klopffer, *Adv. Photochem.*, 1977, **10**, 311.
[10] A. Weller, *Naturwiss.*, 1955, **42**, 175.
[11] A. Weller, *Progr. Reaction Kinetics*, 1961, **1**, 188.
[12] A. Weller, *Z. Electrochem.*, 1956, **60**, 1144.
[13] See *e.g.* D. A. Young, ' Decomposition of Solids,' Pergamon, London, 1966.

energy of 169.3 kJ mol^{-1} in accordance with the previously reported value [2] of 171.0 kJ mol^{-1} for bulk samples decomposed at much lower temperatures over longer periods of time (*ca.* a few days). Positive values of the activation entropy indicate the activated state to be disordered.

The mechanism of the solid state decomposition of PAS and its sodium salt may thus be pictured as follows. A proton is transferred from the phenolic group to the carbonyl of the carboxy group followed by a polar rearrangement of this intermediate to give the product. Positive values of the activation entropy for decomposition confirm the disordered nature of the intermediate. The decomposition of NaPAS dispenses with the requirement [1,4] that the carboxylic proton is responsible for the decomposition of PAS.

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