N-Substituted Granatanine-3-spiro-5′-hydantoins as Zwitterions. Potentiometric Determination of the pK_1 and pK_2 Values for the Conjugate Acids

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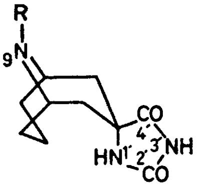
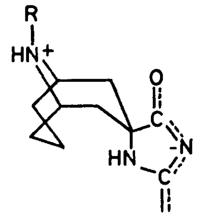
Remarkable pK_1 and pK_2 values for *N*-substituted granataninespirohydantoins which have the zwitterion structure (II) have been found by potentiometry. Previously proposed conformations for the conjugate acids (H_2Z^+) and the zwitterion forms (HZ^{+-}) may explain these values.

HYDANTOINS are weak acids which owe their acidic character to dissociation of the proton bonded to the 3-nitrogen atom in the imide (CONHCO) function of the heterocyclic nucleus.[1] Previously reported pK_a values [2-4] have covered a relatively narrow range of acid strengths for hydantoins and 5,5-disubstituted hydantoins (pK_a 8.33—9.19). The present work is concerned with the determination of the pK_a values (pK_1 and pK_2), related to the first and second ionizations of the conjugate acid, of a series of eight *N*-substituted granatanine-3-spiro-5′-hydantoins (Ia—h).



(I)



(II)

a; R = H
b; R = CH_3
c; R = C_2H_5
d; R = n-C_3H_7
e; R = i-C_3H_7
f; R = C_4H_9
g; R = CH_2CH_2OH
h; R = $CH_2CH_2CH_2OH$

In a previous ^{1}H n.m.r. study,[5] results in D_2O solution showed that these compounds had the zwitterion structure (II) formed by proton transfer from the acid 3′-NH group to the basic piperidine nitrogen atom at the solution pH (*ca.* 9). I.r. spectra in D_2O solution of compounds (Ia, b, g, and h) also showed the same zwitterion structure (II).[6] Although in the solid state, i.r. and *X*-ray diffraction data showed the existence of strong hydrogen bonds 3′-N-H · · · 9-N in most compounds,[7] for compound (Ia) and the hydrates of (Ig and h) the same techniques showed zwitterion forms in the solid state.[6]

Since zwitterions are molecules which have an acidic pK_a numerically lower than the basic pK_a, the pK_a values of compounds (Ia—h), which would support the zwitterion structures, were determined. The results are summarized in the Table.

The pK_2 values follow the pattern described for some *N*-substituted norpseudopelletierines.[8] The basicity increases with the degree of α-branching [see pK_2 of compounds (Ib—e)]. The pK_1 values on the other hand do not follow this pattern. This provides independent confirmation of the zwitterion structures of these compounds since the pK_2 value is the dissociation constant for the protonated amino-group instead of the dissociation constant of the hydantoin.

By comparing the data with the pK_a values of singly charged analogous compounds (6.9 for the conjugate acid of pseudopelletierine in 36 : 64 v/v EtOH-H_2O [8] and 9.12 for hydantoin in water [2]), Δ pK_1 and Δ pK_2 are remarkably high. The difference between pK_1 of compound (Ia) and hydantoin gives Δ pK_1 −1.6 while the effect of a γ-amino group calculated as the difference between pK_1 of γ-aminobutyric acid and pK_a of butyric acid [9] gives Δ pK_1 −0.79.

pK_1 and pK_2 values of compounds (Ia—h)

Compound	pK_1	pK_2
(Ia)	7.52 ± 0.04	11.37 ± 0.04
(Ib)	7.23 ± 0.03	10.76 ± 0.05
(Ic)	7.05 ± 0.05	11.11 ± 0.05
(Id)	7.03 ± 0.04	11.47 ± 0.04
(Ie)	7.04 ± 0.03	11.52 ± 0.05
(If)	7.02 ± 0.04	11.54 ± 0.03
(Ig)	7.16 ± 0.04	10.81 ± 0.04
(Ih)	7.00 ± 0.04	10.74 ± 0.05

Several theories have been developed to account for the effect of dipolar or charged substituents on the strengths of carboxylic acids (Δ pK_1) and ammonium groups (Δ pK_2) in amino-acids but this is the first report to show the same effects in hydantoins including basic centres. In the above mentioned ^{1}H n.m.r. study of these compounds [5] we assigned boat conformations to the spiropiperidine ring in D_2O solution and at pH *ca.* 1. The boat conformation could be stabilized by hydrogen bonding between the quaternary 9-N group and the C-4′ carbonyl group in H_2Z^+ (pH *ca.* 1) and the $(O \overset{...}{-} C \overset{...}{-} N \overset{...}{-} C \overset{...}{-} O)^-$ in HZ^{+-} (zwitterion structure). The stability of H_2Z^+ and HZ^{+-} may explain the high pK_2 and low pK_1 values, respectively.

EXPERIMENTAL

Materials.—Syntheses and purification of compounds (Ia—h) have been previously described.[5,10]

Physical Measurements.—Boiled-out distilled water protected from carbon dioxide was always used. Calibrated volumetric flasks and pipettes were used as were a 25 ml burette (0.1 ml graduations) and a 2 ml burette (0.1 ml graduations). Carbonate-free potassium hydroxide solution[11] was used in titrations, and was standardized against AnalaR potassium hydrogen phthalate with phenolphthalein as indicator. In replicate titrations, end-points were obtained for matched colours. The potassium hydroxide solution was restandardized on completion of the work and no significant change in molarity was found. Hydrochloric acid solutions were standardized against AnalaR potassium carbonate by using Methyl Red as indicator. Commercial buffer solutions of pH 4.01 and 7.00 were employed to standardize the pH meter at 30 °C.

pH Value Determinations.—pH Values were determined with a Radiometer pH meter model 22 fitted with glass (G202C) and saturated calomel (K401) electrodes. On stabilization of the instrument and after calibration and standardization, the pH meter and electrodes were considered ready for further pH measurements.

Potentiometric Titrations.—The titrations were carried out in a 300 ml water-jacketted vessel maintained at 30 °C. A known volume of water was added to the vessel from a calibrated burette. The hydantoin derivative, accurately weighed to give a concentration of 0.01M, was added and dissolved. When dissolution was complete, glass and calomel electrodes and the burette containing the standard potassium hydroxide or hydrochloric acid solutions were inserted through a glass cap covering the thermostatted vessel. The vessel contents were stirred by a slow stream of nitrogen bubbles during all operations. pH Values found after each addition of titrant were rechecked until no change was evident between successive measurements.

p*K Equations*.—From the dissociation reactions the pK_1 and pK_2 values are derived from relationships (1)—(4).

$$H_2Z^+ \rightleftharpoons HZ^{+-} + H^+ \qquad (1)$$

$$HZ^{+-} + OH^- \rightleftharpoons Z^- + H_2O \qquad (2)$$

$$pK_1 = pH + \log([H_2Z^+]/[HZ^{+-}]) \qquad (3)$$

$$pK_2 = pH + \log([HZ^{+-}]/[Z^-]) \qquad (4)$$

For pH values above 10, corrections for hydroxide ion concentrations are introduced [equation (5)]. The hydroxide ion activity $\{OH^-\}$ is calculated from the pH: $\{OH^-\} = \text{antilog}\,(pH - pK_w)$ and pK_w = ionic product of water at 30 °C expressed as its negative logarithm.

$$pK_2 = pH + \log\frac{[HZ^{+-}] + \{OH^-\}}{[Z^-] - \{OH^-\}} \qquad (5)$$

Accuracy and Precision.—A p*K* value is calculated for each volume increment of standard titrant added in the titration. The p*K* is calculated as the logarithm of the average of the antilogarithms of each p*K* value in a set. The scatter is the largest deviation between this value and any value in the set.

[1/877 *Received*, 1*st June*, 1981]

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