

Studies on the Dissociation Constants of Indan Acids and their Hypoglycemic Activities

A. K. CHATTOPADHYAY and S. C. LAHIRI

Department of Chemistry, Kalyani University, Kalyani, Nadia, West Bengal
and
SAMIR CH. LAHIRI and JAYANTA K. GUPTA

Department of Pharmacy, Jadavpur University, Jadavpur, Calcutta-700032

Manuscript received 1 June 1976, accepted 24 December 1976

The dissociation constants of some indan acids, structurally related to hypoglycemic indole acids, were determined spectrophotometrically. Efforts have been made to correlate the dissociation constants with their hypoglycemic activities without much success. The observed activities of these carboxylic acids may be due to decrease in free acids in blood plasma. The results indicate that the highest activity is observed in compounds containing one methoxy substituent in the benzenoid part of the indan moiety.

THE biological properties of indane derivatives are wellknown. The indane nucleus has the molecular frame work which can fix the relative position of the biologically active moieties in a stereospecific manner making them pharmacologically active molecules¹. The peculiar property prompted Lahiri and co-workers²⁻⁴ to synthesize a number of indan acids and to utilise them as potent oral hypoglycemic agents. Since the potentialities of the drug molecules can be well-correlated by the various physico-chemical properties particularly by their dissociation constants, it was thought worthwhile to undertake the studies of the dissociation constants of the molecules by spectrophotometry. The results are described in this communication.

Experimental

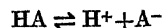
The indan acids were prepared and purified in the same way as described elsewhere⁵. The solutions were prepared by direct weighing the acids and dissolving in water. KH_2PO_4 and Na_2HPO_4 (B.D.H.) were purified by crystallisation from water and dried. Perchloric acid and caustic soda were of E. Merck's reagent grade. The solutions were prepared using double distilled water.

For the determination of the dissociation constants of the acids, optical densities of various solutions of the acids were measured in the U.V. region. These were found to absorb strongly in this region. The reduced acids generally have absorption maxima around 265 nm whereas those of the keto acids lie around 250 nm and 285 nm (very weak). The positions of the absorption maxima (due to the $^1\text{L}^0$ transition of the benzene nucleus present in the compound) do not change appreciably with the changes in pH values. The changes in o.d. values in keto acids with changes in alkali concentrations (N/1000 to N/10) are not appreciable. The U.V.

absorption curves of the acids in the molecular and ionic forms were obtained by measuring in excess acid (HClO_4) and in excess alkali (NaOH) solutions respectively. To have the accurate values of the dissociation constants, suitable wavelengths were chosen where the o.d. value of the two forms differ to the maximum extent but do not change appreciably with wavelength. First the approximate pK values of the acids were determined by suitable titration of the acids with alkali and measuring the pH of the solutions. The pHs at the half neutralization gave these values. For accurate determination of pH, the o.d. values of the acids ($\approx 3 \times 10^{-5} M$) in $\text{KH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4$ buffers (with appropriate addition of KCl to keep the ionic strength at 0.1M) of pH values ranging between 6.0 to 7.4 and in N/10 HClO_4 and N/10 NaOH were taken at the analytical wavelengths. The blank solutions were of the same composition except the acids. The pHs of the buffers were measured with a cambridge bench type battery operated pH meter. All optical density measurements were taken with a Beckman DU2 spectrophotometer kept at 25°.

Results and Discussion

The thermodynamic dissociation constants K_T for the equilibrium



is represented by

$$K_T = \frac{(\text{H}^+)(\text{A}^-)}{(\text{HA})} \times f_{\pm}^2 \text{ (since HA is uncharged)}$$

or

$$\begin{aligned} \text{p}K_T &= \text{pH} + \log \frac{C_{\text{HA}}}{C_{\text{A}^-}} - \log f_{\pm} \\ &= \text{pH} + \log \frac{d_1 - d}{d - d_M} - \log f_{\pm} \end{aligned}$$

where d_i = optical density of the ionic form
 d_M = optical density of the molecular form
 d = optical density at an intermediate pH.

The activity coefficient value at 0.1M was calculated using Davies⁶ equation

$$-\log f_{\pm} = AZ_+Z_- \left[\frac{\mu^{\frac{1}{2}}}{1+\mu^{\frac{1}{2}}} - 0.2\mu \right].$$

The results are given in Table 1. The acids may be considered to arise from the replacement of H-atoms of formic and acetic acids by indan nucleus, a drastic reduction of pK-values is but expected. The keto-acids invariably have higher melting points than the corresponding reduced acids and as expected the keto acids are stronger than the reduced acids.

All these compounds show hypoglycemic activity to an appreciable extent. Though no correlation of the hypoglycemic activity with pK values can be made or no reason for hypoglycemic activity can be adduced, however, it may be said that hypoglycemic activity of all these carboxylic acids may be due to lowering of free fatty acid (FFA) level in blood plasma due to inhibited fatty acid synthesis. This is similar to the observations in case of salicylic acid, nicotinic acids etc. where it is amply demonstrated that a free carboxylic group or the facility with which the derivatives of pyrazole, isoxazoles etc. are converted to acids is necessary for hypoglycemic activity. Hypoglycemia is probably the result of increased glucose utilization when FFA becomes unavailable⁷.

The structures of all these compounds are essentially of similar nature and it can be assumed that all these compounds act at the same site at the molecular level to lipid mobilization.

The pK values of the compounds lie between 6 to 7, a region of profound biological activity. It is not known that whether the dissociated molecule or undissociated molecule are responsible for effective drug action. The ionic form, if effective, would be present approximately 60-70 percent in the physiological pH region (pH of blood 7.4). It is admitted that the unionized molecules possess higher lipid solubility and pass most membrane barriers more readily than the ionized molecules. The prolonged action of some of these drugs (compared to tolbutamide) may be due to absorption of the non-ionized forms in the various lipids and slow release of these drugs when the ionized form are used up in course of time. It is to be noted that all these compounds showed peak hypoglycemic response between 6-12 hours and the activity was maintained upto 24 hrs or more.

It has been found that compounds with one methoxy compounds are more effective as hypoglycemic agents. We are not sure but probably hydroxylation of methoxy group (an effective process of drug metabolism) takes place during biotransformation which may be more effective as hypoglycemic agent.

One feature which deserve mention is that some of these compounds may be utilised as good buffers

TABLE I

Sl. No.	Type	Compound	mcp	pK (+0.03) $\mu = 0.10$	pK _T (+0.03) (using Davies equation)	AV/Fall of Blood Sugar	
						In normal intact rabbits	In alloxan diabetic rabbits
1.	A	X = Y = H, n = 0	120(H ₂ O)	6.23	6.34	12.5(±1.0)	
2.	B		55-56(H ₂ O)	6.50	6.61	17.4(±3.1)	
3.	A	X = OCH ₃ ; Y = H, n = 0	187-188.5(H ₂ O)	6.30	6.41	20.0(±2.1)	28.2(±3.0)
4.	B		121-123	6.58	6.67	22.4(±1.4)	28.8(±3.0)
5.	A	X = Y = OCH ₃ , n = 0	190-191(H ₂ O)	6.38	6.49	15.7(±1.1)	
6.	B		114-115(C ₆ H ₆)	6.66	6.77	14.1(±1.2)	
7.	A	X = Y = H, n = 1	153-154(H ₂ O)	6.37	6.48	9.8(±2.4)	
8.	B		55-56	6.60	6.71	16.3(±3.1)	
9.	A	X = OCH ₃ , Y = H, n = 1	151-153(alc+H ₂ O)	6.43	6.54	21.9(±2.1)	32.3(±4.3)
10.	B		97-98 (C ₆ H ₆)	6.66	6.77	22.8(±1.3)	31.7(±3.4)
11.	A	X = Y = OCH ₃ , n = 1	175-177(H ₂ O)	6.48	6.59	17.2(±3.1)	
12.	B		159.5-161(50% alc)	6.74	6.85	19.2(±1.4)	25.4(±3.2)

A = Blood Sugar was determined by following the procedure of Jensen and Hagedorn⁸

B = Data on eight rabbits.

in the biological regions due to close proximity of pK values to the pH of the blood.

Acknowledgement

The authors (J.K.G. and A.K.C.) are thankful to C.S.I.R., India for awarding scholarships.

References

1. C. R. GANELLIN, *Advan. Drug. Res.*, 1967, **4**, 61-249.
2. S. C. LAHIRI and B. PATHAK, *J. Med. Chem.*, 1967, **8**, 131; 1971, **14**, 888; *J. Pharm. Sci.*, 1968, **67**, 1013.
3. S. C. LAHIRI and N. C. DE, *J. Med. Chem.*, 1968, **11**, 900.
4. S. C. LAHIRI, J. K. GUPTA, and A. MONDAL, *J. Pharm. Sci.*, 1975, **64**, 172.
5. S. C. LAHIRI and J. K. GUPTA, *J. Indian Chem. Soc.*, 1976, **53**, 1041.
6. C. W. DAVIES, *J. Chem. Soc.*, 1938, 2093.
7. F. F. KUPIECKI in *Progress in Biochemical Pharmacology*, Eds. W. L. Holmes and W. M. Bortz, Karger, Basel 1971. 1971, **6**, 274.
8. H. C. HAGEDORN and B. N. JENSEN, *Biochem. Z.*, 1923, **135**, 46; 1923, **137**, 92.