Asian Journal of Chemistry Vol. 1, No. 3 (1989) 219-223

Thermodynamics and Mechanism of Molecular Association of Butyrophenones and Related Molecules with Iodine—Part II

ARADHANA AND A. R. SAKSENA*

Department of Chemistry, C. M. P. Degree College, Allahabad-211 002, India

Dielectric constant measurements have been made for the various compositions of butyrophenones-iodine system in benzene at a radio frequency of 1 MHz at 30°C and 40°C. Precise density determination of donor-acceptor solutions has been made by a calibrated double stem pyknometer. Kinetic and thermodynamic parameters have been evaluated to interpret 1 : 1 molecular association. UV spectra has been used to support the mechanism. A correlation has been discussed in the light of above studies.

INTRODUCTION

Pharmacological action of drugs has been searched by several workers[1,2] and has been interpreted in terms of physical interactions e.g. molecular complex or collisional complex, charge transfer complex or H-bonding in the receptor biophase. The neuroleptic drugs probably out in the brain neurons without any degradation during the passage in the human body[3].

Recently Saucin and Van de Vorst[4] have studied the interaction of neuroleptic drugs with chloranil in 50% acetone-ethanol mixture. Their results show total absence of charge transfer interaction at the activity site and have suggested to reinvestigate the drugs with some other electron acceptors.

Iodine is present in the biophase and can interact easily with the drugs during their progression in the human body. It is a good acceptor and has been selected to study interaction with the butyrophenones and related compounds. Such drugs are usually insoluble in water but are sparingly soluble in benzene. Further, the cell of dipole meter has 2–3 pf capacity and therefore studies in acetone-ethanol solutions are not possible. Fairly dilute solutions having higher concentration of drug comparatively exclude the possibility of I_3^-, I^-, $Bz-I_2$ and ion pair formation. The iodine reacts differently in a non polar solvent than in a polar solvent. Ultrasonic studies are in progress at 5 MHz and will be presented separately. The scope of this paper has been limited to the solution chemistry specially the kinetic and mechanism of donor-acceptor complexes by a precise technique.

EXPERIMENTAL

Materials and Methods

Benzene, A. R. (B.D.H.) has been distilled in a quick fit vertical column? Fraction distilling between 79-80°C has been collected and kept overnight in a desiccator. M/s. Janseen Pharmaceutica Ltd., Belgium has supplied free samples of the drugs fluspirilene, penfluridol, haloperidol and pimozide. These drugs have been used without further purification. However, mpt.'s have been checked and found in good agreement with the confidential reports supplied by M/s. Janseen Pharmaceutica Ltd., Belgium. Iodine, G. R. (Merck) has been used as such in the present studies.

A Toshniwal RL09 dipole-meter operating on Heterodyne Beat principle[5] has been used to determine dielectric constant of solvent and solutions at radio frequency of 1 MHz. Ultrathermostat NBE type has been used to circulate water at ± 0.1°C precision in the cell jacket. Procedure of calibration of dipole-meter and pyknometer has been described elsewhere[6]. Double stem-stem perkin-sterling type pyknometer, has been used to determine densities. The error in ϵ and d is of the order of 0.1% approximately.

Initial solution of donor (10^{-3} to 10^{-4} M) and acceptor (10^{-3} M) have been prepared in benzene. Various compositions have been made in a 25 ml volumetric keeping the concentration of donor constant and varying acceptor concentration. Dielectric constant and density measurements have been carried out at 30° and 40°C simultaneously on donor-acceptor and initial solutions. Ultraviolet spectra between 200–700 nm on Beckmann-DU for various compositions have been recorded on separate sheets at different scales using 1 cm cell. Various peaks and bands have been studied qualitatively and support the mechanism proposed. Reproduction of spectra on a simple graph is useless hence only analysis is being reported in the discussion part.

Calculation

The polarisation of donor-acceptor solution, P can be related to the dielectric constant by the Clausius-Mosotti's equation :

$$\frac{M}{d}\cdot\frac{\epsilon-1}{\epsilon+2} = P = P_x(W_x - \Delta W) + P_y(W_y - \Delta W) + P_2\Delta W + P_1W_1 \qquad \ldots(1.0)$$

where,

$$M = \frac{W_1M_1 + W_xM_x + W_yM_y}{1 - \Delta W} \qquad \ldots(1.1)$$

$$1 - \Delta W = W_x - W_y + W_1 \qquad \ldots(1.2)$$

Subscripts 1, 2. x and y refer to solvent, complex, donor and acceptor

respectively. Terms e.g. M, d, P, W & ΔW refer to molecular weight, density, polarisation, weight fraction & weight fraction of complex respectively. Foster[7] has pointed out that association constant K_c^{xy} can be evaluated from the following equation :

$$\frac{\Delta P}{(P_x^* - P_x)} = 1 + \frac{M_y}{K_c^{xy} \cdot W_y \cdot d} \qquad \ldots(1.3)$$

where

$$\Delta P = P_2 - P_x - P_y$$

and

$$P_x^* = \frac{P - P_y W_y - P_1 W_1}{W_x} \qquad \ldots(1.4)$$

Here, P_x^* is the apparent polarisation constant assuming no complex formation. Also P_x^* and P_x are the values extrapolated to infinite dilution and ΔP is for 1 mole of complex formed. A plot of $(P_x^* - P_x)^{-1}$ vs. $W_y^{-1} \cdot d^{-1}$ is straight line with a intercept of ΔP^{-1} and a gradient of $M_y/K_c^{xy} \cdot \Delta P$, gives the value of K_c^{xy}. In our calculations, points falling far away of the straight line have been rejected. The intercept C and slope m have been evaluated by the graphical method.

The linearity of the plot suggests that (1 : 1) molecular association and the Bensi-Hildebrand[8] equation is applicable to represent molecular association. The association coefficient is actually a quotient because the activity coefficient have not been considered. The possibility of (2 : 1) complex have been excluded due to fairly dilute solutions.

The enthalpy of dissociation, $\Delta H°$ is the most commonly used parameter and is obtained from the variation of K_c^{xy} with absolute temperature from the Van't-Hoff reaction isochore. Thus,

$$\frac{\ln K_c^{xy}(T_1)}{\ln K_c^{xy}(T_2)} = \frac{-\Delta H°}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad \ldots(1.5)$$

where R is gas constant, K_c^{xy} is in inverse mole (M^{-1}) and $\Delta H°$ is in kcal. T_1 and T_2 are 303° & 313°K respectively.

Other parameters which can be obtained are the standard free energy, $\Delta F°$ (kcal. M^{-1}) given by,

$$\Delta F° = -RT \ln K_c^{xy} \qquad \ldots(1.6)$$

and the standard entropy, $\Delta S°$ (e.u.) given by,

$$\Delta F° = \Delta H° - T\Delta S° \qquad \ldots 1.7)$$

All the kinetic and thermodynamic parameters have been presented in the Table 1.

DISCUSSION

In the calculation of association constant, it has been predicted that all the iodine molecules in the solution are complexed with the donor

TABLE 1
KINETIC & THERMODYNAMIC PARAMETERS FOR THE MOLECULAR ASSOCIATION (1 : 1) OF BUTYROPHENONES WITH IODINE

Drug	ΔF^{o}_{303} kcal. M^{-1}	ΔF^{o}_{313} kcal. M^{-1}	ΔS^{o}_{303} e.u.	ΔS^{o}_{313} e.u.	ΔH^{o} kcal. M^{-1}	$K^{xy}_{c_{303}}$ (M^{-1})	$K^{xy}_{c_{313}}$ (M^{-1})
Fluspirilene	−4.01	−4.12	−48.9	−47.0	−18.8	793.75	762.76
Penfluridol	−3.77	−4.87	−49.7	−47.8	−18.8	529.16	508.00
Haloperidol	−4.03	−4.15	−49.01	−47.5	−18.9	808.18	793.75
Pimozide	−4.06	−4.17	−48.8	−46.5	−18.9	846.66	815.05

Uncertainity in K^{xy}_{c} 1% approximately.

molecules and that the concentration of free iodine, the iodide ion I^-, tri-iodide ion I_3^-, the iodine complex with benzene, CTS and the ion pairs of the type $D^+ A^-$, is negligibly small. Amino acids with iodine in water exhibit spectral changes in two stages[9]. In the first stage, iodine I_2 band reduces in intensity with the gradual increase in tri-iodide ion I_3^- absorption band. In the second stage there is gradual loss of I_2 and I_3^- absorption and the appearance of the absorption spectrum of the iodide ion I^-. The second stage leads to the formation of amino acid iodide.

The present workers decided to study butyrophenones and related drugs with iodine in benzene and correlate the association constant and thermodynamic parameters with the drug action. However, the state of affair of drug action in aqueous medium would be somewhat different than benzene.

The K_c^{xy} represents the association constant for the (1 : 1) molecular association between donor-acceptor molecules,

$$D + A - D : A \qquad \ldots(1.8)$$

$$K_c^{xy} = \frac{[D : A]}{[D][A]} \qquad \ldots(1.9)$$

Activity coefficients have not been considered in equation (1.9), therefore K_c^{xy} is actually association quotient and would be nearly equal to the association constant K_x (concentration taken is in mole fraction). It is clear that the values of K_c^{xy} at 30° & 40°C are nearly equal for the donor–I_2 system in benzene. The enthalpy of formation $\Delta H°$, is of the order of 18.9 kcal. M^{-1}.

The $\Delta F°$ and $\Delta S°$ values at two temperatures suggest that the complex is more stabilised at 30°C and this tendency shall increase on lowering the temperature.

As a regular feature band I^- has shifted to 245 nm, I_3^- to 345 nm and CTS to 495 nm respectively. The intensities of I_3^- and CTS gradually decrease on increasing donor concentration. A maxima in fluspirilene appears at 294 ± 2 nm and in penfluridol —I_2 at 292 ± 2 nm in haloperidol

$-I_2$ and pimozide $-I_2$ spectra, a broad and flat band appears at 294 ± 2 nm due to the perturbation of ground state structure of donor with the excited state of iodine. Spectra does not show absorption bands for I_2, I_3^- and 2 : 1 molecular complex supporting our predictions. A NO-BOND CTC structure predominates over other unstable structures. The values of $\Delta H°$ are practically constant due to maximum absorption in the same region of 292–294 nm. Hence, the drug response can not entirely depend on $\Delta H°$ values, it also depends on the stabilization energy for the CTC structure. The drug activity possibly arises due to a hydrogen bond acceptor features on the acceptor molecules[10] and does not completely depend on $\Delta H°$ values in the above systems. However, $\Delta H°$ values in aqueous medium will dominate to give rise activity as has been suggested by Van De Vorst in his paper. The charge transfer mechanism[11] lies between depolarisation excitation and hyperpolarisation inhibition depending upon the donor molecule electron donating power at the cell surface from outside or inside respectively. Model of association[12], thermodynamics of association of related drugs[13] and solvation[14] of butyrophenones by ultrasonics and viscometric measurements have already been reported earlier. Such studies support the present finding.

ACKNOWLEDGEMENTS

The authors are thankful to CST (Lucknow, India), for the support of this research and to the staff of the college for providing facilities. Thanks to M/s. Janseen Pharmaceutica Ltd. Belgium for providing free samples and confidential file to the Chief Investigator, Dr. A. R. Saksena.

REFERENCES

1. A. Szent-Gyorgi, Introduction to a Sub-molecular Biology, Academic Press, New York, N. Y. (1960).
2. A. Cier and G. Cuisinaud, *Ann. Pharm. Franck*, **26**, 615 (1968).
3. A. Dresse, "Contribution experimentale a lé tude du mécanisme d'action der neuroleptiques", Thesis, Liege, Belgium (1967).
4. M. Saucin and A. Van De Vorst, *Biochem. Phormacol.*, **21**, 2673 (1972).
5. J. W. Smith, Electric Dipole moments, Butterworths Scientific Publications, London, p. 34 (1955).
6. Aradhana and A. R. Saksena, *J. Mol. Liq.*, **26**, 197 (1983).
7. R. Foster, Organic Charge-Transfer Complexes, Academic Press, New York, N. Y. (1969).
8. H. A. Bensi and J. H. Hildebrand, *J. Amer, Chem. Soc.*, **71**, 2703 (1949).
9. M. A. Slifkin, *Spectrochim. Acta*, **20** 1543 (1964).
10. T. Nash and A. C. Allison, *Biochem. Pharmacol.*, **12**, 601 (1963).
11. G. Karremann, I. Isenberg and A. Szent-Gyorgi, *Science*: **130**, 1191 (1959).
12. Aradhana and A. R. Saksena, *Indian, J. Pure & Appl. Phys.*, **22**, 342 (1984).
13. ———, *J. Phys. Chem*, **89**, 363 (1985).
14. Aradhana, J. D. Pandey and A. R. Saksena, *Acoustica*, **65** 254 (1988).

[*Received*: 16 September 1988; *Accepted*: 5 March 1989] AJC-37