Effect of Preferential Solvation on the Thermodynamic Properties of Antidepressant Drug Trazodone in Aqueous Ethanol: Linear Free-Energy Relationships

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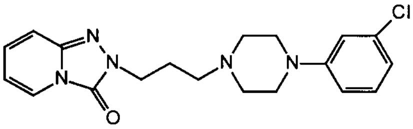
Dissociation constants (pK_a) of trazodone hydrochloride (TZD · HCl) in EtOH/H_2O media containing 0, 10, 20, 30, 40, 50, 60, 70, and 80% (*v*/*v*) EtOH at 288.15, 298.15, 308.15, and 318.15 K were determined by potentiometric techniques. At any temperature, pK_a decreased as the solvent was enriched with EtOH. The dissociation and transfer thermodynamic parameters were calculated, and the results showed that a non-spontaneous free-energy change ($\Delta_{diss}G^o > 0$) and unfavorable enthalpy ($\Delta_{diss}H^o > 0$) and entropy ($\Delta_{diss}S^o < 0$) changes occurred on dissociation of trazodone hydrochloride. The free-energy change or pK_a varied nonlinearly with the reciprocal dielectric constant, indicating the inadequacy of the electrostatic approach. The dissociation equilibria are discussed on the basis of the standard thermodynamics of transfer, solvent basicity, and solute-solvent interactions. The values of $\Delta_{trans}G^o$ and $\Delta_{trans}H^o$ increased negatively with increasing EtOH content, revealing a favorable transfer of trazodone hydrochloride from H_2O to EtOH/H_2O mixtures and preferential solvation of H^+ and trazodone (TZD). Also, $\Delta_{trans}S^o$ values were negative and reached a minimum, in the H_2O-rich zone that has frequently been related to the initial promotion and subsequent collapse of the lattice structure of water. The pK_a or $\Delta_{diss}G^o$ values correlated well with the *Dimroth-Reichardt* polarity parameter $E_T(30)$, indicating that the physicochemical properties of the solute in binary H_2O/organic solvent mixtures are better correlated with a microscopic parameter than the macroscopic one. Also, it is suggested that preferential solvation plays a significant role in influencing the solvent dependence of dissociation of trazodone hydrochloride. The solute-solvent interactions were clarified on the basis of the linear free-energy relationships of *Kamlet* and *Taft*. The best multiparametric fit to the *Kamlet-Taft* equation was evaluated for each thermodynamic parameter. Therefore, these parameters in any EtOH/H_2O mixture up to 80% were accurately derived by means of the obtained equations.

1. Introduction. – Trazodone (=2-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one = TZD) is a triazolopyridine-derivative antidepressant. Trazodone has an overall therapeutic efficacy in depressive illness comparable with that of imipramine and amitriptyline [1].



Trazodone (TZD)

The drugs pK_a values are physical properties that are applied to dispensing problems and dosage-form development, to decide to what pH the dosage form should

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be adjusted to provide optimum bioavailability, and to predict the drug solubility in aqueous solution at a given pH and drug concentration [2]. pK_a Values are of vital importance in various chemical and biochemical areas [3]. These are essential in understanding the distribution, transport behavior, binding to receptors, mechanism of action of certain pharmaceutical preparations, dissolution rates, rates of gastrointestinal absorption, incompatibilities, *etc.*, and to interpret structure–activity relationships.

Water/organic solvent mixtures are characterized by dramatic changes in properties such as dielectric constant, basicity, *etc.*, upon modification of their compositions that influence many solute properties of these mixtures. Furthermore, basic drugs (like trazodone) are lipid-soluble and water-insoluble, and their behavior in plasma samples is closer to that in alcohol than to that in H_2O [4] [5]. Thus, EtOH/H_2O mixtures offer a suitable medium for modelling biological interactions because they simultaneously exhibit low polarity and a partially aqueous content as is always present in biological systems.

Despite the importance of trazodone as a powerful antidepressant, little is known about its acid-base equilibrium and about temperature and solvent effects on this equilibrium. Previously, the solvent effect on the dissociation equilibrium was believed to be chiefly guided by electrostatic interactions (*Born* model). But recent studies [6–10] reveal that the change in the dielectric constant cannot be the sole factor, but that the chemical nature of the mixed solvent plays a vital role in dictating the overall solvent effect. Thus, it is desirable to develop other empirical functions to take into account the complete picture of all intermolecular forces acting between solute and solvent molecules. Thus, it is interesting to calculate the dissociation constants and the thermodynamic parameters in mixed-solvent systems and to correlate these parameters with the properties of the mixed solvent.

As a continuation of our extensive systematic study [6] [7] [11] [12] on the effect of solvent composition on the thermodynamic parameters, this paper reports the determination of the thermodynamic parameters of dissociation and transfer of trazodone from H_2O to EtOH/H_2O mixtures *via* calculation of the pK_a values from potentiometric measurements. Also, correlations of these functions were made with the *Dimroth–Reichardt* [13] polarity parameter $E_T(30)$, with the *Mayer–Gutmann* [14] acceptor number *AN*, with the *Kosower* [15] polarity value *Z*, and with the solvatochromic parameters (α, H-bond donor; β, H-bond acceptor; π^*, polarity-polarizability) of *Kamlet* and *Taft* [16–18].

2. Results and Discussion. – 2.1. *Preamble.* The dissociation constant for $TZDH^+$ was determined from the potentiometric titration of HCl in the absence and presence of the drug by different computational methods [19] [20]. In *Table 1*, the pK_a values at different temperatures in various EtOH/H_2O mixtures are given. The errors in the pK_a values are calculated from the uncertainties associated with experimental measurements. In all cases, the standard deviations ($\pm 0.01-0.04$) are very low, thus demonstrating the precision of the pK_a values and the excellent reproducibility of the automated titration procedure. Moreover, in aqueous solution, the pK_a is in good agreement with the literature value [1b]. The data given in *Table 1* show that there is a drastic increase in the acidity of $TZDH^+$ on increasing the mol fraction of EtOH in the

Table 1. pK_a *Values for Trazodone Hydrochloride in Various EtOH/H_2O Mixtures at Different Temperatures and Its Thermodynamic Parameters* [kJ/mol] *of Dissociation and Transfer from H_2O to EtOH/H_2O Mixtures at 298.15 K*[a])

	T [K]	EtOH (v/v) [%]								
		0	10	20	30	40	50	60	70	80
pK_a[a])	288.15	6.92	6.70	6.52	6.33	6.13	5.98	5.81	5.70	5.58
	298.15	6.74 6.72[c])	6.55	6.37	6.19	6.00	5.86	5.70	5.59	5.47
	308.15	6.60	6.41	6.24	6.07	5.89	5.76	5.60	5.50	5.38
	318.15	6.48	6.30	6.14	5.97	5.80	5.67	5.53	5.42	5.30
$\Delta_{diss}G^{o}$[b])	298.15	38.48	37.39	36.36	35.34	34.25	33.45	32.54	31.91	31.23
$\Delta_{diss}H^{o}$[b])	298.15	25.14	23.55	22.34	21.10	19.34	18.10	16.54	16.35	16.35
$-T\Delta_{diss}S^{o}$[b])	298.15	13.34	13.84	14.02	14.24	14.91	15.35	16.00	15.56	14.88
$-\Delta_{trans}G^{o}$	298.15	0	1.09	2.12	3.14	4.23	5.03	5.94	6.57	7.25
$-\Delta_{trans}G^{o}(H^+)$[d])	298.15	0	1.04	1.82	2.67	3.58	4.51	5.33	5.74	–
$-\Delta$[d])	298.15	0	0.05	0.30	0.47	0.65	0.52	0.61	0.83	–
$-\Delta_{trans}H^{o}$	298.15	0	1.59	2.80	4.04	5.80	7.04	8.60	8.79	8.79
$-T\Delta_{trans}S^{o}$	298.15	0	0.50	0.68	0.90	1.57	2.01	2.66	2.22	1.54

[a]) p$K_a \pm (0.01-0.04)$. [b]) $\Delta_{diss}G^{o} \pm (0.06-0.23)$, $\Delta_{diss}H^{o} \pm (0.25-0.91)$, $T\Delta_{diss}S^{o} \pm (0.32-1.03)$. [c]) [1b] [d]) From [21] after adaptation to the appropriate solvent composition. [e]) $\Delta = \Delta_{trans}G^{o} - \Delta_{trans}G^{o}(H^+) = \Delta_{trans}G^{o}(TZD) - \Delta_{trans}G^{o}(TZDH^+)$.

solvent. Acid-base equilibria in H_2O/organic solvents can be studied from the standpoint of two effects, dielectric and chemical. Also, as long as a proton transfer is involved in acid-base equilibria, the *Brønsted–Lowry* formulation is particularly useful for discussing these reactions.

In *Fig. 1*, the pK_a values of $TZDH^+$ are plotted against the reciprocal of the dielectric constant $1/\varepsilon$ of EtOH/H_2O mixtures, showing a nonlinear decrease of the pK_a with increasing EtOH concentrations. Thus, the macroscopic properties of the EtOH/H_2O mixtures are inadequate to explain the variation in pK_a values of $TZDH^+$. Accordingly, the connection of pK_a values with the dielectric constant of the medium cannot always be explained by simple electrostatic theory, and a purely electrostatic treatment is inadequate to account for the solvent effects on the dissociation of charged acids such as $TZDH^+$ because the dissociation equilibrium of $TZDH^+$ is isoelectric (involves no change in the number of charges). Thus, the effect of the dielectric constant on the action of various solvents in this reaction has no consequence, and the chemical effects on the acid-base equilibrium can be studied independently from electrostatic complications. Trazodone (TZD) will be solvated better by EtOH than its electrically charged conjugate acid $TZDH^+$ whose dissociation will, thus, be facilitated.

The equilibrium of a cationic acid like $TZDH^+$ in water or H_2O/organic solvent (S) is represented by *Eqn. 1*. Since the ion product of EtOH (*ca.* 10^{-17}) is lower than that of H_2O (10^{-14}) (*i.e.*, EtOH ionizes only slightly), one can conclude that solvents enriched with EtOH (low autoprotolysis constant) would have greater affinity for H^+ ions and would be more basic solvents than H_2O. This is in good agreement with the known value of the K_a of NH_4^+ in EtOH, which is *ca.* 6 times greater than in H_2O [22].

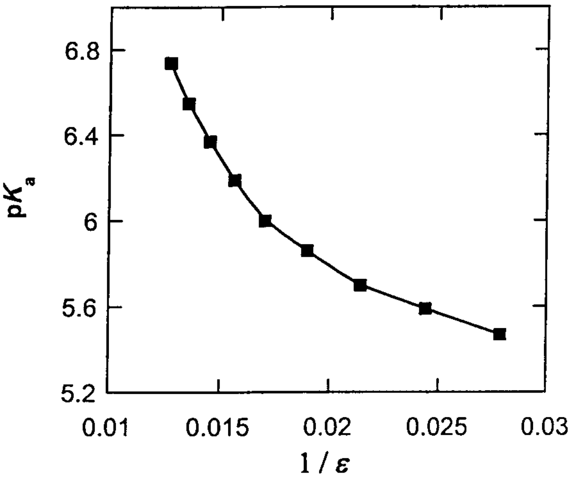

Fig. 1. *Variation of* pK_a *at 298.15 K for trazodone hydrochloride with the reciprocal of the dielectric constant of* $EtOH/H_2O$ *mixtures*

$$\mathrm{TZDH^+ + S \rightleftarrows SH^+ + TZD} \tag{1}$$

2.2. *Thermodynamics of Dissociation.* From the pK_a values of $TZDH^+$ obtained by potentiometric measurements at different temperatures in different $EtOH/H_2O$ mixtures (see above, *Table 1*), the standard free-energy changes of dissociation $\Delta_{diss}G^o$ were calculated by *Eqn. 2*. The plot of $\Delta_{diss}G^o$ *vs.* T for each solvent composition did not deviate from the most probable straight line by more than the experimental error (regression coefficients ≥ 0.99). Therefore, the standard enthalpy ($\Delta_{diss}H^o$) and entropy ($\Delta_{diss}S^o$) changes had constant values over the examined temperature range (288.15–318.15 K) and *Eqn. 3* holds providing the $-\Delta_{diss}S^o$ and $\Delta_{diss}H^o$ values from the $\Delta_{diss}G^o$ *vs.* T plots.

$$\Delta_{diss}G^o = 2.303\ RT\ \mathrm{p}K_a \tag{2}$$

$$\Delta_{diss}G^o = \Delta_{diss}H^o - T\Delta_{diss}S^o \tag{3}$$

Moreover, the *Van't Hoff* plot of pK_a *vs.* $1/T$ was linear between 288.15 and 318.15 K, a range over which the enthalpy was independent of T and could be easily calculated from the slope. The calculated thermodynamic parameters of dissociation are included in *Table 1*. Inspection of *Table 1* reveals that the pK_a values decrease with increasing temperature, indicating that the acidity of the drug increases independently of the solvent composition. The $\Delta_{diss}G^o$ values are positive, revealing that the dissociation process is nonspontaneous. These values decrease with increasing EtOH content in the solvent mixtures (*i.e.*, the nonspontaneity decreases), suggesting the preferential stabilization of H^+ and TZD by the mixed solvent. The positive $\Delta_{diss}H^o$ values indicate that the dissociation process is endothermic, thus made more favorable at higher temperature, while the negative $\Delta_{diss}S^o$ suggest a higher degree of order in the system in the dissociated state as a result of the solvation process, *i.e.*, the total sum of the solvent molecules bound around H^+ and TZD is more than that originally accompanying $TZDH^+$. Since the mixed solvents are less structured than pure H_2O, the species present after the dissociation will orient the solvent molecules to a greater extent in $EtOH/H_2O$ than in pure H_2O. Thus, one can expect that the $\Delta_{diss}S^o$ values increase negatively in $EtOH/H_2O$ mixtures with respect to those in pure H_2O.

2.3. *Thermodynamics of Transfer.* Knowledge of the free energy of transfer $\Delta_{trans}G^o$ of a solute from H_2O to H_2O/organic solvent mixtures is essential for the elucidation of the nature of solute-solvent interactions. Moreover, this parameter is an index for the preference of a solute for one environment over the other [23]. The $\Delta_{trans}G^o$ of $TZDH^+$ (*Table 1*) were calculated according to *Eqn. 4.* As *Fig. 2* shows, $\Delta_{trans}G^o$ values for $TZDH^+$ decrease with increasing mol fraction x of EtOH indicating preferential stabilization of H^+ and TZD by the mixed solvent.

$$\Delta_{trans}G^o = \Delta_{diss}G^o(\text{mixed solvent}) - \Delta_{diss}G^o(\text{water}) \qquad (4)$$

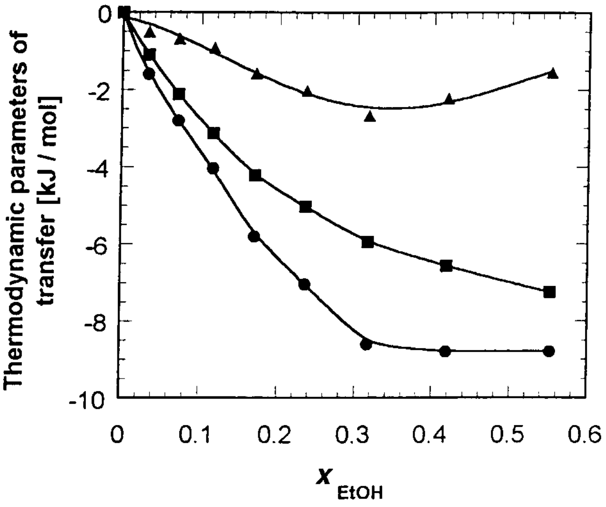

Fig. 2. *Variation of* $\Delta_{trans}G^o$ (■), $\Delta_{trans}H^o$ (●), *and* $T\Delta_{trans}S^o$ (▲) *at 298.15 K for trazodone hydrochloride with the mol fraction* x *of EtOH in* $EtOH/H_2O$ *mixtures*

For a better understanding of the solvent effect on the dissociation process, it is essential to elucidate the nature of ion-solvent interactions. This can be measured quantitatively by splitting $\Delta_{trans}G^o$ into individual components according to *Eqn. 5.* The $\Delta_{trans}G^o(H^+)$ values were taken from [21] after adaptation to the appropriate solvent composition, and, thus, the difference $\Delta = \Delta_{trans}G^o(TZD) - \Delta_{trans}G^o(TZDH^+)$ could be easily calculated (see *Table 1*).

$$\Delta_{trans}G^o = \Delta_{trans}G^o(H^+) + \Delta_{trans}G^o(TZD) - \Delta_{trans}G^o(TZDH^+) \qquad (5)$$

Since $EtOH/H_2O$ mixtures are more basic than H_2O, H^+ is better solvated in $EtOH/H_2O$ than in H_2O, *i.e.*, more $TZDH^+$ is dissociated in $EtOH/H_2O$. Also, the values of Δ

increase negatively with increasing EtOH content. This can be explained as described below. The aromatic moiety of TZD or $TZDH^+$ undergoes dispersion interactions with the alkyl group of EtOH. These interactions are expected to grow stronger as the EtOH content in the mixed solvent increases. Also, since such a hydrophobic interaction is more important with TZD than with $TZDH^+$, the $\Delta_{trans}G^o$(TZD) should be more negative than $\Delta_{trans}G^o(TZDH^+)$, leading to increased stabilization of the drug and increasingly negative $\Delta_{trans}G^o$ and Δ.

The enthalpy of transfer $\Delta_{trans}H^o$ and the entropy of transfer $\Delta_{trans}S^o$ were calculated in the usual way [6][7] (see *Table 1*). The $\Delta_{trans}H^o$ profile for $TZDH^+$ in EtOH/H_2O mixtures is depicted in *Fig. 2*. The $\Delta_{trans}H^o$ values are negative and monotonically increasing with increasing EtOH content up to 60% (*v*/*v*). This reveals a favorable transfer of $TZDH^+$ from H_2O to EtOH/H_2O mixtures, which can be attributed to the preferential solvation of H^+ and TZD by the mixed solvent. With increasing mol fraction x of EtOH, the basicity and the dispersion interaction increase gradually, causing increased stabilization of H^+ and TZD in the mixed solvent as compared with that in pure H_2O.

It is known that the entropies of transfer are usually better probes of solvent structure than enthalpy changes. The variation in $\Delta_{trans}S^o$ with the content of EtOH (*Fig. 2*) shows a noticeable minimum in the H_2O-rich region ($x_{EtOH} \approx 0.3$, corresponding to *ca.* 60% EtOH). This minimum appears to result from the effects of the initial enhancement and subsequent breakdown of the three-dimensional H_2O structure caused by the increasing addition of EtOH.

The $T\Delta_{trans}S^o$ values are negative and increase negatively with the addition of EtOH reaching a minimum at *ca.* 60% and then decrease negatively on further addition of EtOH. Similar behaviors have been reported for other solutes [6][24]. It is well-established that H_2O molecules surround a hydrophobic solute by the formation of a H-bonded network involving themselves [25], *i.e.*, the solute is enclosed in a highly ordered H-bonded solvent cage (skin phase). This order increases in the H_2O-rich zone by the addition of EtOH. An ordering effect is also produced by the formation of dispersion interactions between the uncharged part of the drug and the skin phase, which increases as the proportion of EtOH increases, thus increasing $T\Delta_{trans}S^o$ negatively. On the other hand, in the EtOH-rich zone, the order in the skin phase decreases with increasing EtOH content in the mixed solvent as a result of the breakdown of the tetrahedral lattice structure of H_2O. Consequently, the negative $T\Delta_{trans}S^o$ value can be ascribed to the predominance of the order resulting from the dispersion interactions over the disorder caused by the addition of EtOH to H_2O molecules. The increase in $T\Delta_{trans}S^o$ in this region, yielding a minimum at *ca.* 60% EtOH, is believed to be due to the dispersion interaction reaching a maximum constant value (saturation), whereas the disorder in the skin phase still increases with increasing EtOH.

2.4. *Linear Free-Energy Relationships.* 2.4.1. *Preamble.* The study of solvent-dependent physicochemical properties is much more complicated for binary solvents than for pure ones. Indeed, the solute can be preferentially solvated by each of the solvent components; moreover, such solute-solvent interactions can be strongly influenced by the intermolecular forces between the solvent components. The electrostatic approach based on single macroscopic solvent parameters such as dielectric constants, dipole moments, *etc.*, often fails to evaluate adequately medium effects. Currently, empirical equations, within the framework of linear free-energy relationships, are extensively used to understand solvent effects on chemical reactions in a more quantitative way [6–10]. Thus, for recording medium effects, various empirical solvent scales have been developed based on the spectral data of a single or more standard probe molecule (solvatochromic compounds). Indeed, UV/VIS/near-IR absorption spectra of chemical compounds may be influenced by the surrounding medium, and solvents can bring about a change in the position, intensity, and shape of absorption bands [8]. Also, the transition energy of the indicator depends on the solvation-sphere composition and solvent properties [26], and knowledge of some solvent properties [16–18] [26] (*e.g.*, polarity and H-bond capabilities) can be obtained by the solvatochromic-indicator approach. The so-called empirical parameters of solvent take into account all possible intermolecular forces (nonspecific and specific) between solute (ions or molecules) and solvent molecules. Also, such empirical functions should take into account the solute-solvent interactions derived from modifications in the solvation shell on varying solvent composition, as well as the effects derived from the destruction of the H_2O structure by influence of organic solvent.

2.4.2. *Correlation with the Acceptor Number and with the* Dimroth–Reichardt *Polarity Parameter*. The *Mayer–Gutmann* acceptor number *AN* and the *Dimroth–Reichardt* polarity scale $E_T(30)$ currently enjoy widespread use among the many polarity indices available.

The *AN* values of various H_2O/organic solvent mixtures were measured based on the ^{31}P-NMR chemical shifts of triethylphosphine oxide [14]. The plot of the $\Delta_{diss}G^o$ values of $TZDH^+$ *vs.* *AN* reveals two linear zones (*Fig. 3*). This is the case for many solvent mixtures for which two equations [27] are needed to cover the whole range of solvent composition. One equation is applied in the H_2O-rich zone and the other in the organic-solvent-rich one. The two lines in *Fig. 3* intersect at *ca.* 50–60% EtOH, which is consistent with published data [28]. The first zone (0–60% EtOH) implies that the H_2O structure is retained to an appreciable extent. Thus, the protons are accommodated in the interstices of the tetrahedral H_2O lattice. In the second zone ($\geq$60% EtOH), the H_2O solvation shell is dispersed by the interposition of the EtOH molecules. Therefore, the participation of EtOH in the solvation of H^+ cannot be ignored. It is well-known [29–31] that a small addition of alcohol leads to an enhancement of the structure of H_2O, producing an increase in excess polarity-polarizability π^* and H-bond-donor acidity α and a decrease in excess H-bond-acceptor basicity β. Moreover, the increase in the degree of order in the system must continue until it passes through a maximum. Above the corresponding solvent composition, the highly ordered solvent structure begins to collapse, *i.e.*, the tetrahedral lattice structure of H_2O is gradually broken down [32]. This is not surprising, since many of the thermodynamic and physical properties of EtOH/H_2O mixtures exhibit a maximum or minimum at low mol fraction of EtOH. This is because H_2O molecules organize themselves around the hydrophobic group to produce low-entropy structures of fairly regular and longer-living H-bonds [31], leading to a reinforcement of the H_2O structure.

The colinearity of the $\Delta_{diss}G^o$ *vs.* *AN* plot is in good agreement with the assumption that the first addition of EtOH enhances the H_2O structure, whereas at high proportions of EtOH, a breakdown of the H-bridged H_2O structure occurs, which results in the

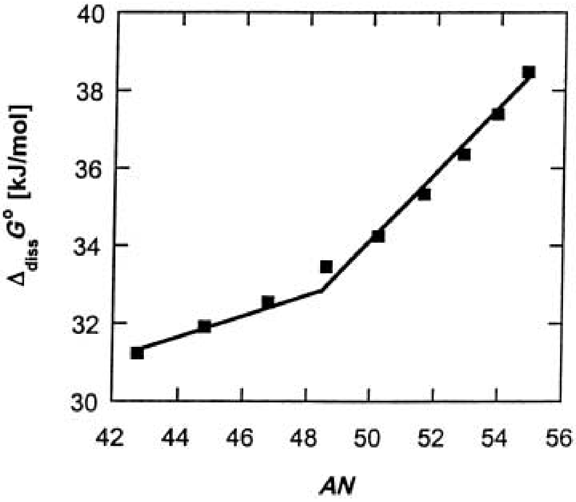

Fig. 3. *Variation of* $\Delta_{diss}G^o$ *at 298.15 K for trazodone hydrochloride with* AN *of EtOH/*H_2O *mixtures*

two linear zones (*Fig. 3*). Moreover, *AN* is a composite of polarity-polarizability π^* and the H-bond-donation ability α: $AN = 2.9 + 14.0\ \pi^* + 29.7\ \alpha$ [33]. Since α will change strongly on destruction of the H_2O structure (minimum of α [31] at $x_{EtOH} \approx 0.3$ corresponding to *ca.* 60% EtOH in the α *vs.* x_{EtOH} plot for EtOH/H_2O mixtures), it is not surprising to observe the two different behaviors of $TZDH^+$. Further evidence could come from the nonlinear dependence of *AN* on x_{EtOH} [14]. Such deviation from the ideal behavior is an index of preferential solvation as well as solvent structures. Linear regression of the data shown in *Fig. 3* furnished $\Delta_{diss}G^o = -5.978 + 0.805\ AN$ ($R = 0.9906$) for the H_2O-rich zone and $\Delta_{diss}G^o = 17.265 + 0.327\ AN$ ($R = 0.9999$), for the EtOH-rich zone, both at 298.15 K.

The *Dimroth-Reichardt* polarity scale $E_T(30)$ is considered to be one of the more comprehensive solvent scales. The $E_T(30)$ value measures the polarity of the solvation microsphere surrounding the solvatochromic indicator. The $E_T(30)$ values are defined as the molar electronic-transition energies of a dissolved negatively solvatochromic pyridinium *N*-phenolate betaine dye (*Eqn. 6*), where λ_{max} is the wavelength of the maximum of the longest-wavelength intermolecular charge-transfer $\pi \rightarrow \pi^*$ absorption band of the dye. Although preferential solvation derived on the basis of $E_T(30)$ is specific to betaine dyes, it is likely to show parallel behavior with other polar solutes and may be used as an aid in the interpretation of kinetic [34] and thermodynamic [35] parameters.

$$E_T(30)\ (\text{kcal mol}^{-1}) = 28591/\lambda_{max}(\text{nm}) \qquad (6)$$

In *Fig. 4*, the $\Delta_{diss}G^o$ values of $TZDH^+$ are plotted against the corresponding mixed-solvent $E_T(30)$ values, and it can be seen that there is excellent linear correlation over the whole composition range ($R = 0.9997$). Thus, the behavior of $TZDH^+$ with regard

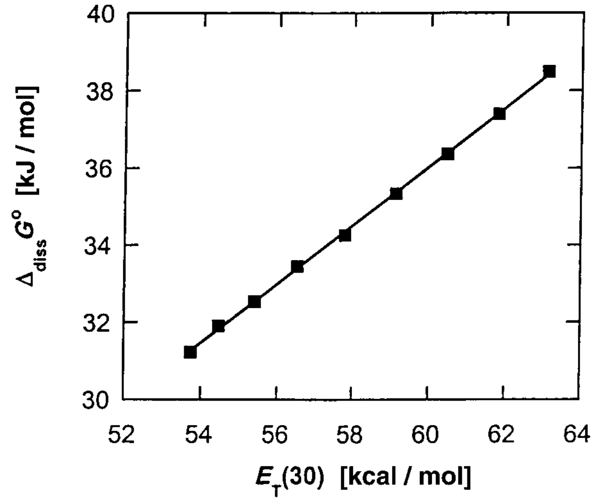

Fig. 4. *Variation of* $\Delta_{diss}G^o$ *at 298.15 K for trazodone hydrochloride with* $E_T(30)$ *of EtOH/*H_2O *mixtures*

to preferential solvation must be similar to that of the betaine dye used to measure the $E_T(30)$ values, namely preferential solvation by EtOH [34][35].

It is clear that the dissociation of $TZDH^+$ is related to the $E_T(30)$ values and that the correlation is much better than that obtained with only an electrostatic model. Thus, correlating the $\Delta_{diss}G^o$ (or pK_a) values of solutes with the microscopic parameters (the properties of their immediate environment) is valid. This motivated us to compare the microscopic parameters of EtOH/H_2O mixtures with macroscopic ones present in bulk solution. Although ε and $E_T(30)$ are both polarity parameters, a nonlinear $1/\varepsilon$ *vs.* $E_T(30)$ plot is obtained (*Fig. 5*), revealing that these parameters have different natures. This is not surprising, since the first represents the polarity in the bulk solution, whereas the second describes the polarity of the solvation microsphere. Also, *Roses et al.* [36] pointed out that the solvatochromic indicator can interact to different degrees with the two solvents of a binary mixture, and the solvation microsphere will reflect these interactions. In the solvation microsphere, the proportion of the solvent with the strongest interaction with the indicator will be larger than in the bulk solvent, and the indicator will be preferentially solvated by this solvent. The $1/\varepsilon$ *vs.* $E_T(30)$ plot shows two linear portions intersecting at *ca.* 60% EtOH. The first portion is assigned to the H_2O-rich zone ($\leq$60% EtOH) and the second one to the EtOH-rich zone ($\geq$60% EtOH). The different nature of the two polarity quantities $E_T(30)$ and $1/\varepsilon$ may be the reason why a purely electrostatic model is inadequate to account for solvent effects on the dissociation of $TZDH^+$.

Furthermore, it could be of great interest to apply a least-squares analysis to the thermodynamic parameters of dissociation (and transfer) and the usual macroscopic parameters (x or $1/\varepsilon$) or the microscopic properties ($E_T(30)$, *AN*, and *Kosower* polarity value Z) as the intercept variables. As shown in *Table 2* for the thermodynamic parameters of dissociation as a representative example, the correlations with the microscopic parameters are much better than those obtained with the macroscopic

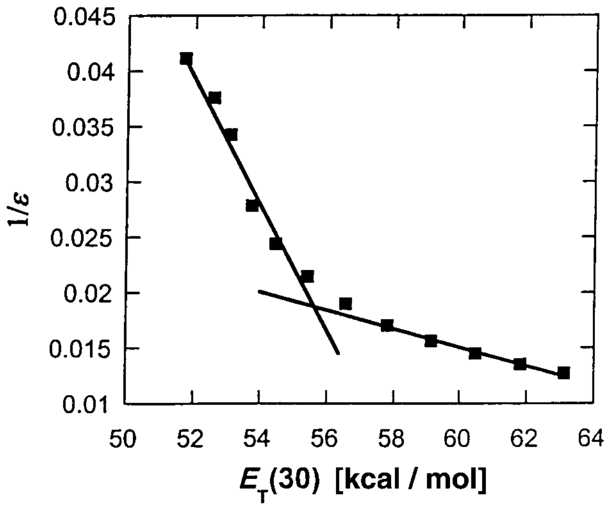

Fig. 5. *Variation of 1/ε* vs. E_T*(30) for EtOH/*H_2O *mixtures*

ones, thus establishing that the empirical scales of microscopic parameters are the best tools to explain solvent-dependent properties of a solute. Indeed, these parameters take into account all possible intermolecular forces between solute and surrounding solvent molecules. The $\Delta_{diss}G^o$ (or pK_a) and $\Delta_{trans}G^o$ of $TZDH^+$ transferred from H_2O to EtOH/H_2O mixtures correlate linearly with $E_T(30)$, revealing that the likelihood of preferential solvation plays a significant role in determining the solvent dependence of the dissociation and transfer of $TZDH^+$.

Table 2. *Comparison of the Linear Correlations of Various Thermodynamic Parameters Obtained with Macroscopic and Microscopic Parameters*

	Variable	Equation	R
$\Delta_{diss}G^o$	x_{EtOH}	$\Delta_{diss}G^o = 37.29(0.43) - 12.88(1.58)\ x_{EtOH}$	0.9513
	$1/\varepsilon$	$\Delta_{diss}G^o = 43.03(1.14) - 459.44(59.72)/\varepsilon$	0.9457
	$E_T(30)$[a])	$\Delta_{diss}G^o = -9.61(0.42) + 0.76(0.01)E_T(30)$	0.9997
	Z[b])	$\Delta_{diss}G^o = -41.10(8.22) + 0.85(0.09)Z$	0.9611
	AN[c])	$\Delta_{diss}G^o = 5.41(2.42) + 0.59(0.05)AN$	0.9768
$\Delta_{diss}H^o$	x_{EtOH}	$\Delta_{diss}H^o = 23.34(0.75) - 16.35(2.71)x_{EtOH}$	0.9161
	$1/\varepsilon$	$\Delta_{diss}H^o = 30.64(1.91) - 583.48(99.93)/\varepsilon$	0.9109
	$E_T(30)$[a])	$\Delta_{diss}H^o = -37.94(2.68) + 1.00(0.05)E_T(30)$	0.9926
	Z[b])	$\Delta_{diss}H^o = -77.12(13.97) + 1.09(0.16)Z$	0.9345
	AN[c])	$\Delta_{diss}H^o = -17.61(4.53) + 0.76(0.09)AN$	0.9528
$T\Delta_{diss}S^o$	x_{EtOH}	$-T\Delta_{diss}S^o = -13.94(0.33) - 3.47(1.21)x_{EtOH}$	0.7347
	$1/\varepsilon$	$-T\Delta_{diss}S^o = -12.39(0.84) - 124.04(43.76)/\varepsilon$	0.7310
	$E_T(30)$[a])	$-T\Delta_{diss}S^o = -28.33(2.72) + 0.24(0.05)E_T(30)$	0.8848
	Z[b])	$-T\Delta_{diss}S^o = -36.02(6.55) + 0.24(0.07)Z$	0.7761
	AN[c])	$-T\Delta_{diss}S^o = -23.02(2.37) + 0.17(0.05)AN$	0.8000

[a]) *Dimroth–Reichardt* polarity value. [b]) *Kosower* polarity value. [c]) *Mayer–Gutmann* acceptor number.

2.4.3. *Correlation with Solvatochromic Parameters of* Kamlet *and* Taft. To trace the influence of different EtOH/H_2O mixtures on the dissociation constant as well as on the thermodynamic parameters of dissociation and transfer of $TZDH^+$, the methodology of linear solvation-energy relationship (LSER) expressed by means of *Eqn. 7* was applied, where F is the solute property studied, F_o is the hypothetical value for this property in a solvent where $\alpha = \beta = \pi^*$, and a, b, and s are solvent-independent coefficients characteristic of the process under study and indicative of its susceptibility to the solvent properties α, β, and π^*.

$$F = F_o + a\alpha + b\beta + s\pi^* \tag{7}$$

The LSER developed by *Kamlet* and *Taft* is one of the most ambitious, and successful, quantitative treatments of solvent effects by means of a multiparameter equation. It has been used to unravel, identify, and evaluate the individual solute-solvent interactions that determine the solvent effects of numerous systems [6][7][9][37]. The procedure used in this approach involves a rigorous statistical treatment. This was applied to find out which multiparametric equation is the best description of the behavior of each thermodynamic parameter in the full composition range of the EtOH/H_2O mixtures (0–80%). Then, a stepwise procedure and least-squares analysis were applied to select the significant solvent properties to be included in the model and to obtain the final expression for each thermodynamic parameter. The computer program used yielded the correlation coefficients, the values of a, b, and s (including their standard errors), and the residual output. Moreover, it was checked by t-testing the significant constants. The expression of the *Kamlet* and *Taft* equations thus obtained for each property are shown in *Table 3*. These linear solvation-energy relationships allow to calculate the pK_a and the thermodynamic parameters of dissociation and transfer of $TZDH^+$ in any EtOH/H_2O mixture up to 80% EtOH. Depending on the cases, *Kamlet–Taft* general equation was reduced to only two or three terms to describe the modification of the studied properties in EtOH/H_2O mixtures.

Table 3. *Linear Solvation-Energy Relationships for Various Thermodynamic Parameters of Trazodone Hydrochloride at 298.15 K*. Values in parentheses are the standard errors for the coefficients a, b, and s.

Equation	R
$pK_a = 8.04\ (0.22) - 4.97\ (0.22)\ \beta + 0.93\ (0.11)\ \pi^*$	0.9977
$\Delta_{diss}G^o = 45.90\ (1.26) - 28.41\ (1.26)\ \beta + 5.30\ (0.62)\ \pi^*$	0.9977
$\Delta_{diss}H^o = 38.87\ (1.59) - 40.70\ (1.61)\ \beta + 4.95\ (0.78)\ \pi^*$	0.9978
$-T\Delta_{diss}S^o = -7.66\ (0.98) - 11.86\ (1.64)\ \beta$	0.9392
$-\Delta_{trans}G^o = 7.42\ (1.26) - 28.41\ (1.26)\ \beta + 5.30\ (0.62)\ \pi^*$	0.9977
$-\Delta$[a]$) = 1.86\ (0.32) - 3.90\ (0.54)\ \beta$	0.9473
$-\Delta_{trans}G^o(H^+) = -7.46\ (1.00) - 25.25\ (0.86)\ \beta + 3.96\ (0.58)\ \pi^*$	0.9986
$-\Delta_{trans}H^o = 13.73\ (1.59) - 40.70\ (1.61)\ \beta + 4.95\ (0.78)\ \pi^*$	0.9978
$-T\Delta_{trans}S^o = 5.68(0.98) - 11.86\ (1.64)\ \beta$	0.9392

[a]) $\Delta = \Delta_{trans}G^o(TZD) - \Delta_{trans}G^o(TZDH^+)$.

Careful inspection of the equations listed in *Table 3* suggests the following:

1) The coefficients of β terms are higher than those of the π^* terms indicating that the dependence of the thermodynamics of dissociation and transfer on the H-bond-accepting basicity of the solvent for the whole range of composition studied is determining. Also, the coefficients of β are negative suggesting that an increase in the basicity of the solvent mixture decreases the pK_a, $\Delta_{diss}G^o$, $\Delta_{diss}H^o$, $-\Delta_{trans}G^o$, $-\Delta_{trans}H^o$, $-\Delta_{trans}G^o(H^+)$, and $-\Delta$ values. Thus, an increase in basicity increases the solvation (stabilization) of H^+ and TZD, and concomitantly dissociation as well as a spontaneous transfer of $TZDH^+$ from H_2O to EtOH/H_2O mixtures. The presence of the positive charge of the $TZDH^+$ ions enhances their interactions with the H-bond acceptor groups of the solvent mixture, and, thus, dissociation is facilitated.

2) The small coefficient of the π^* terms confirms the aforementioned discussion that for isoelectric reactions, the polarity has little effect on the dissociation process. Furthermore, the positive π^* coefficients imply that increases in the polarity of the mixed solvent decrease the dissociation of $TZDH^+$. Thus, a decrease in the polarity promotes the solvation of H^+ and $TZDH^+$, and, therefore, dissociation.

Experimental Part

Materials. Trazodone hydrochloride (TZD · HCl) was obtained from Egyptian international pharmaceutical industries company as salt in crystalline form and was used without further purification. The drug was stored in the refrigerator and placed in an air-tight container protected from light. Freshly prepared drug solns. were prepared under protection from light, the latter causing decomposition of the drug [1]. Deionized H_2O was distilled from alkaline $KMnO_4$ and redistilled before use. Stock solns. of strong acid (HCl) and strong base (NaOH) were prepared from anal. reagent-grade materials. Solns. of NaOH were prepared in 0, 10, 20, 30, 40, 50, 60, 70, and 80% (*v*/*v*) EtOH/H_2O mixtures and standardized by titration against standard potassium hydrogen phthalate. The TZD · HCl was dissolved in H_2O, and chemically pure NaCl was used to maintain a constant ionic strength (0.05M). EtOH (*BDH*, *AnalaR* ≥ 99.7%) was used without further purification. The solvent mixtures were prepared by mixing EtOH and H_2O in the required proportions by volume.

Apparatus. Potentiometric measurements were performed with a *Metrohm 686* titroprocessor equipped with a *665-Dosimat* (*Metrohm*, Herisau, Switzerland). All titrations were carried out under N_2 and at constant temp. (±0.05°), which was maintained by circulating water from a constant-temp. ultrathermostat (*Thermomix 1420*, *K. Kolb*, Germany) through the double-wall *Pyrex* titration cell of 50-ml capacity. The titration cell was equipped with a combined electrode, N_2 inlet and outlet tubes, a magnetic stirrer, and a titrant inlet. Before flushing into the titration cell, the pure N_2 gas was first saturated with the particular solvent used in the reaction cell. The combined glass electrode was standardized before and checked after each titration with prepared buffer solns. from *Orion* (Boston).

Procedure. The following soln. mixtures were prepared and titrated potentiometrically with CO_2-free standard NaOH soln.: 1) 2.5 ml of 10^{-2} M HCl + 2.5 ml of 1M NaCl; 2) 2.5 ml of 10^{-2} M TZD · HCl + 2.5 ml of 1M NaCl. These soln. mixtures were made up to 50 ml with appropriate volumes of EtOH and H_2O to keep on the desired composition. The pH-meter readings in various EtOH/H_2O mixtures were corrected according to the *Van Uitert* and *Hass* method [38]. All measurements were made in triplicate and averaged. The methods of pK_a calculation are described in detail elsewhere [19][20].

Sources of the Characteristic Properties of EtOH/H_2O Mixtures. Values of dielectric constants ε of EtOH/H_2O mixtures were taken from *Akerlof* and *Short* [39], whereas the solvatochromic parameters α, β, π^*, *Z*, and $E_T(30)$] were obtained from *Marcus* [40]. The values of *AN* were taken from *Mayer et al.* [14]. All of these values were used after adaptation to the appropriate solvent composition.

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