Effects of Solvent Medium on Solubility IV: Comparison of the Hydrophilic–Lipophilic Character Exhibited by Functional Groups in Ethanol–Water and Ethanol–Cyclohexane Mixtures

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Abstract □ Solvent effects on the solubility of a set of structurally related solid compounds (A_x, A_y, *etc.*) in ethanol-water (system 1) and ethanol-cyclohexane (system 2) are compared by the equation, $\log S_y = P_y \log S_x + C$. For a given structural change, $A_x \rightarrow A_y$, it yields the respective medium-effects parameters, P_{y1} and P_{y2}. They are used to compare the sensitivity of both solvent systems with the structural changes in the substrates by the equation, $\Delta_{12} = (P_{y1} - 1) - (1 - P_{y2})$. Structural changes involving the full replacement of the hydrogen atoms bonded to either O or N afford $\Delta_{12} < 0$, while those involving solely an increase in the alkyl chain of the substrates yield $\Delta_{12} > 0$. A structural change where the donor-acceptor capacity of hydrogen bonding is maintained yields a Δ_{12} approaching zero.

Keyphrases □ Solubility—effects of solvent medium, hydrophilic-lipophilic character, ethanol-water, ethanol-cyclohexane □ Hydrophilic-lipophilic character—effects of solvent medium, ethanol-water, ethanol-cyclohexane, solubility

In previous papers of this series (1-3) Eq. 1 has been used successfully to correlate solvent effects with solubility equilibria:

$$\log S_y = P_y \log S_x + C \qquad \text{(Eq. 1)}$$

S_y and S_x are, respectively, two sets of solubility data of a pair of structurally related compounds, A_y and A_x, which arise from measurements in the same set of adequately selected solvent conditions. This linear free energy relationship (LFER) affords the medium effect parameter P_y, which in a given system of solvents measures the difference in hydrophilicity (or lipophilicity) between A_y and A_x. Equation 1 has been used to measure the hydrophilic-lipophilic character exhibited by a variety of functional groups in ethanol-water mixtures (3).

A theoretical model to rationalize solvent effects on solubility was developed (1). In two-solvent systems, each consisting of binary mixtures of increasing lipophilicity, one (system 1) in which the solubility of both substrates (A_x and A_y) increases, and the other (system 2) in which the solubilities decrease as the lipophilicity of the mixtures is raised, the model predicts the following: in system 1, P_y will be higher than unity when A_y is more lipophilic than A_x and *vice versa;* in system 2, P_y will be lower than unity when A_y is more lipophilic than A_x and higher than unity in the reverse situation.

This paper deals with the comparison of the sensitivity of two-solvent systems with a variety of structural changes in the substrates. Thus, if the sensitivities of systems 1 and 2 to a given structural change ($A_x \rightarrow A_y$) are the same, the following relation between P_{y1} and P_{y2} would be expected to hold (1):

$$(P_{y1} - 1) = (1 - P_{y2}) \qquad \text{(Eq. 2)}$$

which is conveniently expressed as:

$$(P_{y1} - 1) - (1 - P_{y2}) = \Delta_{12} = 0 \qquad \text{(Eq. 3)}$$

However, when the solvent systems have different sensitivities to the structural change, Δ_{12} becomes different from zero, having a positive value when system 1 is more sensitive than system 2, and a negative value in the reverse situation.

In this paper, the former measurements of solvent effects in ethanol-water mixtures (2,3), now system 1, were extended to a nonaqueous medium consisting of ethanol-cyclohexane mixtures which were selected as system 2. System 2 forms a less structured environment of lower dielectric constant than system 1 and the hydroxyl groups are less disponible and freer to interact with the substrates through hydrogen bonding.

EXPERIMENTAL SECTION

The compounds of the basic structure p-X_1—C_6H_4—X_2 were used for the solubility measurements. The numbers assigned to each compound in a previous paper (3) were maintained. The corresponding X_1 and X_2 are, respectively: H_2N—, —$COOCH_3$ (I); H—, —$NHCOCH_3$ (III); HO—, —$NHCOCH_3$ (IV); $(CH_3)_2N$—, —$COOCH_3$ (VII); CH_3O—, —$NHCOCH_3$ (X); C_2H_5O—, —$NHCOCH_3$ (XI); CH_3COO—, —$NHCOCH_3$ (XII); H—, —$N(CH_3)COCH_3$ (XIII); H_2N—, —$COOC_2H_5$ (XIV); H_2N—, —$COO(CH_2)_2CH_3$ (XV); HO—, —$COO(CH_2)_2CH_3$ (XVI).

Preparation and physical constants of I, III, IV, VI, VII, XV, and XVI were reported (2, 3); X and XII were prepared through acetylation, X from *p*-anisidine (4), and XII from IV (5). The following were commercially available: XI[1], XIV[1], and XIII[2]. The melting points for these compounds were: X, mp 127.0-127.5°C (water) [lit. (6) mp 129-131°C]; XI, mp 134-135°C (ethanol-water, 50:50) [lit. (6) mp 134-135°C]; XII, mp 153.0-154.5°C (water) [lit. (5) mp 152-156°C]; XIII, mp 99.0-99.5°C (water) [lit. (6) mp 101-102°C]; XIV, mp 88-89°C (ethanol-water, 15:85) [lit. (6) mp 88-90°C]. 5,5′-Diethylbarbituric acid (barbital) (XVII)[1], mp 189-191°C (water), and 5-ethyl-5-isoamylbarbituric acid (amobarbital) (XVIII), mp 155.5-156.5°C (ethanol-water, 20:80), were also used. Compound XVIII was extracted with chloroform from commercial tablets[3].

Solvent mixture preparations and solubility determinations have been reported (2, 3). Solubility data of XVII and XVIII in ethanol-water mixtures (0-70% ethanol) were taken from Breon and Paruta (7).

RESULTS AND DISCUSSION

Solubility data of the structurally related derivatives p-X_1—C_6H_4—X_2 in systems 1 and 2 are reported in Table I with data of a pair of barbituric acid derivatives (XVII and XVIII). The data of p-X_1—C_6H_4—X_2 derivatives complement previously reported results (2, 3, 7). The solubility of all compounds of the set is raised with increasing amounts of ethanol in system 1 and lowered by the increase of the cyclohexane content in system 2.

To incorporate low solubility values into the data set of system 2, measurements were performed in mixtures having cyclohexane content as high as 94 and 96%. P_{y1} and P_{y2} were obtained from the correlation of the solubility data according to Eq. 1, and are reported in Table II. These values can be used to compare the sensitivity of both solvent systems with a variety of structural changes in the substrates.

[1] Sigma Chemical Co.
[2] BDH.
[3] Quait N; Química Ariston S.A.

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Table I—Solubility in Systems 1 and 2 at 25°C

Solvent Composition		Solubility, mg/g_{soln}									
		III	IV	VI	X	XI	XII	XIII	XIV	XVII	XVIII
					System 2 (Ethanol-Cyclohexane)						
4	96	16.6	0.529	27.6	2.36	0.717			11.0	2.44	16.6
6	94	26.8	1.57		3.67	3.13	1.38	91.4	16.8	5.84	31.9
8	92	35.4	2.65	35.1	6.11	5.01	2.16		24.2		
10	90	47.7	4.50	39.5	8.35	6.55	3.10	131	34.2	10.7	53.5
15	85	90.3	9.45	47.5	15.2	12.7	5.66	168	49.6	15.9	86.4
20	80	96.5	18.4	58.3	20.4	16.1	9.80	190	73.4	24.3	111
25	75	140	26.1	60.6	27.1	23.4	11.1	222	110		
30	70	195	39.0	69.6	34.1	26.6	15.3	260	132	39.3	185
40	60	214	64.7	78.9	47.9	32.6	19.4	296	191	57.6	236
50	50	241	92.3	82.7	72.6	46.9		423	362	70.9	
60	40	246	117							78.6	
					System 1 (Ethanol-Water)						
0	100				2.24	0.502	2.20	26.5	1.37		
10	90				3.29	0.824	3.06	46.4	1.63		
20	80				3.37	1.15	3.51	78.3	3.08		
30	70				8.99	2.31	5.28	196	8.06		
40	60				11.3	5.08	12.6	295	23.8		
50	50				28.6	12.7	26.6	423	56.5		
60	40				42.6	19.1	31.6		110		
70	30				64.2	34.1	50.7		176		

Table II—Correlation of Solubility Data According to Eq. 1 [a]

Compounds Correlated	n	Range	P_y	Intercept	r
System 2		CH, %			
XII/IV	8	94-60	0.717	−0.698	0.995
XII/III	8	94-60	1.11	−1.34	0.997
VI/I	6	96-50	0.393	−0.144	0.994
XI/III	8	94-50	1.06	−0.981	0.992
XI/IV	9	94-50	0.638	−0.454	0.993
XIII/III	7	94-60	0.592	0.242	0.990
IV/III	12	96-30	1.71	−0.836	0.995
XI/X	10	96-50	0.922	−0.221	0.997
X/IV	10	96-50	0.664	−0.274	0.997
X/III	10	96-50	1.11	−0.841	0.993
XIV/I	7	96-50	1.10	0.690	0.996
XV/XIV	8	96-50	0.908	0.281	0.994
XVIII/XVII	6	94-60	0.926	0.576	0.997
System 1		Water, %			
XII/IV	8	100-30	0.971	−1.07	0.985
XII/III	7	100-30	0.827	−0.860	0.992
XI/III	8	100-30	1.66	−1.05	0.990
XI/IV	8	100-30	1.36	−1.31	0.992
XIII/III	6	100-50	1.26	0.942	0.998
XI/X	6	90-30	1.17	−0.226	0.997
X/IV	7	100-30	1.13	−0.847	0.992
X/III	8	100-30	0.957	−0.667	0.988
XIV/I	8	100-30	1.22	0.297	0.999
XV/XIV	8	100-30	1.25	0.126	0.998
XVIII/XVII	8	100-30	2.19	−2.15	0.998

[a] Solubility data in molality units were used in all cases except those of the correlation XVIII/XVII in system 1, which were taken from Ref. 7 and are expressed in mg/mL. However, as previously discussed (1), P_y obtained by using different units to express solubility, remains essentially unchanged. It should be emphasized that all the solubility data of barbituric derivatives reported in Ref. 7 can be correlated according to Eq. 1.

Table III contains Δ_{12} values of some relevant structural changes. They were grouped under the headings of the structural change involved after clearly defined patterns were recognized.

$\Delta_{12} < 0$—Inspection of Table III reveals that a structural change ($A_x \rightarrow A_y$) involving the full replacement of the hydrogen atoms bonded to either O or N affords a negative value of Δ_{12} (correlations 1-4). Therefore, the sensitivity of system 2 to such structural modification is greater than that of system 1. One reason for this behavior might be that an aqueous medium, such as system 1, has a number of ways to interact with both A_x and A_y structures due to its high donor-acceptor capacity toward hydrogen bonding. System 2, having a lower ability to produce specific interactions, has an enhanced sensitivity toward a structural change involving the full replacement of the hydrogen atoms and thus the number of potential interactions are limited.

$\Delta_{12} > 0$—A structural change which solely involves the increase of the alkyl chain yields a positive value of Δ_{12}. This behavior was observed with chain extensions of ether, ester, and barbituric acid derivatives (correlations 5-8). Consequently, in this situation system 1 appears to be more sensitive than system 2. This could be explained by considering that an increase in the size of the hydrocarbon moiety of a substrate is better accepted by a less rigid system such as 2 than by a highly structured system such as 1.

Δ_{12} Approaching Zero—For a structural change like —OH→ —NH_2, where the donor-acceptor capacity toward hydrogen bonding is maintained, a similar sensitivity in both systems is expected. From the values reported previously (2), a random value of Δ_{12} approaching zero (−0.04) is calculated for such a structural change.

On the other hand, the direct comparison of the structural difference —OH → —OC_2H_5 between two pharmacologically related drugs, IV (acetaminophen) and XI (phenacetin), affords a Δ_{12} of zero. This result can be seen as a consequence of two opposite effects: the hydrogen atom replacement generates a negative Δ_{12} for —OH→—OCH_3, as occurs in IV→X (correlation

Table III—Sensitivity of Systems 1 and 2 to Structural Changes

Structural Change, $A_x \rightarrow A_y$	Compounds	Δ_{12}
$\Delta_{12} \neq 0$		
Full Replacement of H		
$-OH \rightarrow -OCH_3$	X/IV	−0.21
$-OH \rightarrow -OOCCH_3$	VIII/VII	−0.69
	XII/IV	−0.31
$-NH_2 \rightarrow -N(CH_3)_2$	VI/I	−0.28
$-NH-OCCH_3 \rightarrow -N(CH_3)-OCCH_3$	XIII/III	−0.15
Chain Extension		
$-OCH_3 \rightarrow -OC_2H_5$	XI/X	+0.11
$-COOCH_3 \rightarrow -COOC_2H_5$	XIV/I	+0.32
$-COOC_2H_5 \rightarrow -COO(CH_2)_2CH_3$	XV/XIV	+0.16
$-C_2H_5 \rightarrow -(CH_2)_2CH(CH_3)_2$	XVIII/XVII	+1.12
$\Delta_{12} \cong 0$		
Changes Which Preserve H		
$-NH_2 \rightarrow -OH$	VII/I	−0.09
	XVI/XV	+0.05
Hydrogen Replacement Plus Chain Extension		
$-OH \rightarrow -OC_2H_5$	XI/IV	0.00

1); the chain extension $-OCH_3 \rightarrow -OC_2H_5$ (X→XI) generates a positive Δ_{12} (correlation 5). Obviously, the extent of the affinity of a functional group for a given medium is the result of a number of well-defined molecular interactions usually described as specific, nonspecific, solvophobic, *etc.* (8).

Because of the importance of the hydrophilic-lipophilic concept, considerable effort has been made to measure such properties from partition coefficient or solubility measurements (9, 10) and more recently from solvent effects on solubility (2, 3).

The results discussed here show that functional groups may exhibit different hydrophilic-lipophilic properties in different environments, *i.e.*, XVIII appears to be 16-fold more lipophilic than XVII in ethanol-water, but only ~1.2-fold more lipophilic in ethanol-cyclohexane. Thus, it is now clear that the order of hydrophilic strength of different functional groups in ethanol-water reported previously (3) should be quite different from the order of the same groups in ethanol-cyclohexane.

Just as Hammett pointed out the ambiguity of the concepts of acidity and basicity (11), the inherent ambiguity of the hydrophilic-lipophilic concept should be emphasized. However, Eq. 1 appears to be a useful tool to obtain information about the hydrophilic-lipophilic properties of different solvent media.

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Synthesis and Evaluation of Novel *N*-Substituted *N'*-(3-Hydroxy-17-oxoestra-1,3,5(10)-trien-2- and -4-yl)thiourea Derivatives for Binding to the Estrogen Receptor and Cytotoxic Activity on MCF-7 Cells

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Received October 25, 1982, from the **Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Alexandria, Alexandria Egypt* and the ‡*Laboratoire de Cancérologie Mammaire, Service de Médecine, Institut Jules Bordet, 1000 Brussels, Belgium.* Accepted for publication October 26, 1983.

Abstract □ A novel series of estrone derivatives having a free 3-phenolic group with the 2- or 4-position substituted with a thiourea function was synthesized. None of the products showed significant binding to the estrogen receptor, and the cytotoxic activity on MCF-7 cells for VII and X was weak.

Keyphrases □ Estrone 2- and 4-thiourea derivatives—free phenolic group, synthesis, binding to the estrogen receptor, cytotoxic activity □ Steroidal thiourea derivatives—2- or 4-position of estrone, synthesis binding to the estrogen receptor, cytotoxic activity

Several types of compounds containing structural modifications of steroidal and nonsteroidal estrogens were synthesized during past years, in the hope of developing agents with a high binding affinity to the estrogen receptor (1, 2) and reduced estrogenic properties. These, in accordance with their capabilities in antagonizing the action of estradiol at the estrogen receptor (3), can be used as antiestrogens (4–9) or as cytotoxic agents with selective activity against the hormone-dependent tumor cells (10–13). In connection with an extensive program studying the effect of structural modifications on the biological activity of hormones, a variety of modified steroids were synthesized and tested for antiestrogenic (14), endocrinological (15–17), and anticancer (15, 17, 18) properties. As a supplemental investigation, a novel series of estrone thiourea derivatives (V–XI) were synthesized to check their binding to