0.05% Na_2EDTA and 0.1% $Na_2S_2O_5$, with a motor-driven Teflon pestle and Eppendorf 1.5-mL centrifuge tubes. An internal standard of 100 ng/mL of 3-(3,4-dihydroxyphenyl)propionic acid (DHPPA) was used. The samples were centrifuged at 14000*g* for 4 min with a tabletop centrifuge. The supernatant was assayed for catecholamines, 5-HT, and their metabolites by injection of 50 μL onto a Brownlee C18 analytical column (Anspec, Ann Arbor, MI). The HPLC-EC system consisted of a refrigerated autosample (TosoHaas, Philadelphia, PA) and a Model 400 EG&G Princeton electrochemical detector (Princeton, NJ) with a dual electrode potential set at E_1 = -200 mV and E_2 = 850 mV versus the Ag/AgCl reference electrode. The mobile phase containing 0.05 M NaH_2PO_4, 0.03 M citric acid, 0.1 mM Na_2EDTA, 0.034% sodium octyl sulfate, and 25% methanol was delivered at a flow rate of 1.0 mL/min. The concentrations of NE, DA, HVA, DOPAC, 5-HT, and 5-HIAA were determined with the Dynamax Method Manager software (Rainin, Woburn, MA) implemented on an Apple Macintosh SE computer.

Statistical Analysis. In drug-discrimination experiments a compound was defined as fully substituting for the training drug if at one or more doses 80% of the animals responded on the drug lever. The ED_{50} and 95% confidence intervals values were determined from quantal dose-response curves according to the procedure of Litchfield and Wilcoxon.[42] Drugs were said to partially substitute if at the highest dose at least 60-79% of the animals responded on the drug lever; no substitution was said to occur if 59% or less of the animals responded at the highest dose. Percent uptake inhibition was defined as the difference between specific [^{3}H]-5-HT uptake in control and drug tubes divided by control × 100%. The IC_{50} values for uptake inhibition were determined from graded dose-response curves according to the procedure of Tallarida and Murray.[43] All comparisons utilized an analysis of variance followed by a post hoc comparison as embodied in the computer program EPISTAT (EPISTAT Services, Richardson, TX).

Materials. Pargyline hydrochloride and the HPLC standards were purchased from Sigma Chemical Co. (St. Louis, MO). [^{3}H]Paroxetine and [^{3}H]-5-HT were obtained at a specific activity of 28.8 and 15.1 Ci/mmol from New England Nuclear (Boston, MA). LSD tartrate was obtained from the National Institute on Drug Abuse. Fluoxetine hydrochloride was graciously provided by Eli Lilly Laboratories (Indianapolis, IN). MDMA·HCl, 2·HCl and (*S*)-amphetamine sulfate were synthesized in our laboratory by using standard procedures.

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Using Theoretical Descriptors in Quantitative Structure-Activity Relationships: Some Toxicological Indices

Leland Y. Wilson*

Department of Chemistry, Loma Linda University Riverside, Riverside, California 92515

George R. Famini

U.S. Army Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, Maryland 21010.
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The application of computational techniques to medicinal chemistry is growing at a tremendous rate. Quantitative structure-activity relationships (QSAR), which relate biological and toxicological activities to structural features, have been employed widely to correlate structure to activity. A difficulty of this approach has been nonuniformity of parameter sets and the inability to examine contributions across properties and data sets. Linear solvation energy relationships (LSER) developed by Kamlet and Taft circumvent many of the difficulties and successfully utilize a single set of parameters for a wide range of physical, chemical, and biological properties. We have replaced the LSER solvato-chromatic parameters with theoretically determined parameters to permit better a priori prediction of properties. Comparison of the two parameter sets for five biological activities is presented, showing the excellent fit of the theoretically determined parameters.

1. Introduction

Quantitative structure-activity relationships (QSAR) have been used extensively in correlating molecular structural features of compounds to their biological, chemical, and physical properties. The basic tenet of QSAR is that there is a quantitative connection between the microscopic (molecular structure) and the macroscopic (empirical) properties (particularly biological activity) of a compound. Furthermore, this connection can be used to predict empirical properties of a compound given its molecular structure. One such connection is the *Linear free energy relationship* (LFER). In 1935 Burkhardt[1] and Hammet[2] reviewed the existence of LFER's and in 1937 Hammet[3] proposed the equation that bears his name.

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2. Linear Solvation Energy Relationships

Based on solvent effect LFER's proposed by earlier workers,[4] Kamlet and Taft[5-10] developed a method for writing linear free energy relationships involving solute/

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solvent interactions. Equation 1 shows the form of this general *Linear Solvation Energy Relationship* (LSER).

$$\log \text{property} = \text{bulk} + \text{polarizability} + \text{hydrogen bonding} \quad (1)$$

A given property of a compound can be described as a linear expression with terms for a bulk effect, a polarizability effect, and hydrogen-bonding effects. For solubility-related properties of multiple solutes in single solvents or distribution between two solvents, the specific terms (with their corresponding descriptors, the Kamlet–Taft solvato-chromatic parameters) are as follows: bulk, molar volume (V_m or V_I); polarizability, spectroscopically determined dipolarity–polarizability (π^*), and hydrogen bonding, spectroscopically determined hydrogen-bonding acidity and basicity (α and β). The terms are chosen to provide an "orthogonality of effects" in that each describes a separate phenomenon; there is minimal covariance.

The bulk (or cavity) term is a measure of the energy needed (endoergic) to overcome the cohesive solvent–solvent molecule interactions in order to form a cavity for the solute molecule. The dipolarity–polarizability term measures the energies of the solute–solvent dipole and induced dipole interactions (exoergic) which contribute to the solution formation. Hydrogen-bonding terms measure the energy of interaction (again exoergic) when a solute–solvent complex is formed. Hydrogen-bonding basicity (HBB) refers to hydrogen bonding acceptor basicity; it involves the acceptance of a proton from a neighboring molecule. Similarly, hydrogen-bonding acidity (HBA) refers to hydrogen bonding donor acidity; it involves the donation of a proton to a neighboring molecule. This terminology is consistent with Brönsted–Lowry acid–base definitions. These descriptors have been described in terms of the energy contributions to the solvent–solute interactions. These can be related to the enthalpy terms in the free energy expression; entropy contributions have not been directly accounted for.

However, the LSER derived equation describing a given property may not require all four of these terms. The importance of each descriptor may be separately evaluated by examining its coefficient and associated statistical parameters. In this way the LSER can be used to offer insight into solute–solvent interactions. One major difficulty of the LSER approach is that the descriptors are empirically determined and so are of limited use for making a priori predictions. Kamlet, Taft, and co-workers[11] have replaced V_m with a computer-generated volume parameter, V_I. Some attempts to correlate more fundamental structural and electronic descriptors with the Kamlet–Taft solvato-chromatic parameters have been made and have met with moderate degrees of success.[12]

3. Theoretical Linear Solvation Energy Relationship

Theoretical chemistry has been used in the past to supply structural and electronic descriptors for QSAR relations.[13-15] In order to extend the LSER idea to permit a priori prediction, a theoretical approach has been applied. The theoretical linear solvation energy relationship (TLSER) is such a derivation and uses the LSER philosophy and general structure but replaces the empirically derived descriptors with computationally derived descriptors.

The TLSER descriptors have been developed with three main goals. First, the TLSER descriptors should correlate optimally with the LSER descriptors. Second, the correlation equations should give correlation coefficients and standard deviations as accurate as those from LSER. Third, the TLSER descriptors should be as generally applicable to solute/solvent interactions as are the LSER descriptors.

The bulk term for TLSER is the molecular van der Waals volume, V_{mc},[16] in cubic angstroms. The dipolarity–polarizability related term for TLSER is the polarizability index, π_I, and is obtained by dividing the polarizability volume by the volume V_{mc} in order to get a size-independent parameter. This term defines the ease with which the electron cloud may be moved or polarized. Aromatics rank high and alkanes low on the scale.

As in LSER the hydrogen bonding term is separated into acidic (HBA) and basic (HBB) terms.[17,18] Since any bond can be considered to have covalent and electrostatic parts,[13] TLSER requires individual descriptors for these two bonding contributions. The covalent contribution to the HBB is taken as the energy, ϵ_b, of the highest occupied molecular orbital (HOMO). This orbital has the electrons to form a complex with a proton on a neighboring molecule. For aesthetic reasons, the difference between the HOMO of the compound and LUMO (lowest unoccupied molecular orbital) of water is used and the result divided by 100 to give values on the order of those for the polarizability index and results in energy units of hecto(100)-electron volts (heV). A lower value for ϵ_b indicates a greater tendency to form a hydrogen bond with water. The electrostatic contribution to the basicity is taken as the magnitude of the most negative formal charge, q_-, in the molecule and has units of atomic charge units (acu). Again, this follows the LSER philosophy in that the most negatively charged atom would have the greatest interaction with a proton on a neighbor molecule.

The covalent contribution to the HBA is taken as the energy, ϵ_a, of the lowest unoccupied molecular orbital (LUMO). Again, for aesthetic reasons, the difference between the LUMO of the compound and the HOMO of water is used and that result divided by 100 to give values on the order of the other descriptors and hectoelectron volts for energy units. As in the case for the basicity, a lower value for ϵ_a indicates a greater tendency to form a hydrogen bond with water. Here, too, the LSER concept of the hydrogen-bonding acidity is applied with this orbital being available to accept electrons from the HOMO of another molecule. In analogy to the basicity, the electro-

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Table I. Toxicity Parameters Used in This Study

parameter	symbol	units	refs LSER	refs data
microtox test toxicity (inhibition of luminescence in *Photobacterium phosphoreum*)	EC_{50}	μmol/L	27	28–30
golden orfe fish (*Leuciscus idus melanotus*) toxicity	$LC_{50}(G)$	μmol/L	31	33
tadpole narcosis	C	(unclear)	11	32
Könemann's industrial pollutants on *Poecilia reticulata*	$LC_{50}(K)$	μmol/L	34	20
frog (*Rana pipiens*) muscle activity inhibition	MBC	mmol/L	11	35

static contribution to the acidity is taken as the most positive formal charge, q_+ (acu), on a hydrogen atom in the molecule; this is the portion of the molecule most attracted to a negative portion on a neighbor.

4. Nonspecific Toxicity

An organic nonelectrolyte is said to exhibit *nonspecific toxicity* (including narcosis) behavior if present in sufficient concentration and if the rate-controlling step in the mechanism apparently involves the transport and partitioning of the compound into the hydrophobic phase (membrane of the organism) from the aqueous phase. Partitioning of the molecule into the hydrophobic phase (membrane) permits it to interfere with the organism in some way. Indeed, studies have shown that aqueous solubility, S_w, has a good (inverse) correlation and octanol/water partition coefficient, K_{ow}, has a good (direct) correlation with pharmacological and toxicological properties of solutes.[19,20]

No QSAR technique can directly determine a mechanism for the activity of a compound. However, some inferences can be made by examining compounds that display large deviations from what would be calculated from a correlation equation generated by a large set of compounds and by examining the significant descriptors. For example, toxicity values calculated for aldehydes with the correlation equation are often significantly smaller than experimental values; this is considered to involve *specific toxicity* with one explanation being Schiff base formation between the aldehyde group on the solute and an amine group on the membranes.

5. Procedure

The toxicity parameter data and the toxicant sample sets were chosen from the references listed in Table I. Molecular geometries were optimized with the MNDO algorithm of Thiel and Dewar[21] within MOPAC;[22,23] this also produced the orbital energies and formal charges. The polarizability was determined from the method of Stewart and Dewar[24] also incorporated in MOPAC. Volumes are calculated by using the method of Hopfinger[25] as incorporated in the U.S. Army developed molecular modeling package MMADS.[26] Multilinear correlation analysis was used to obtain the regression equations relating the toxicity parameter to the descriptors.

6. Results

Table I lists the five toxicological parameters used in this study. Table II shows the TLSER results based on the same sets that produced the optimum LSER correlations contained in Table III; this was done for purposes of comparison. Table IV shows the TLSER results obtained from the same starting sets used in the LSER work with outliers deleted according to the TLSER analysis. LSER descriptors gave more outliers than did those for TLSER. Table V contains a list of all the toxicants in this study along with their descriptors. The experimental and calculated values of the toxicological parameters for the TLSER toxicant sets used in Table IV are contained in Tables VI–X. Table XI contains a correlation matrix for the TLSER descriptors that are significant in describing each toxicity parameter.

The TLSER results were chosen on the basis of the correlation coefficient, R, the t statistic for the term coefficient, the F statistic (which increases when R increases), and the presence of compounds with large deviations. Values of the F statistic were not given in the LSER references, so they are not included here. Terms with coefficients significant at the 95% confidence level or higher, as determined by their t statistic, were retained in the correlation equation. Compounds with residuals of three or more standard deviations (SD) were dropped from the data set and classified as outliers.

7. Discussion

The TLSER results listed in Tables II and IV show that the TLSER descriptors correlate well with the toxicity parameters. However, comparing R and SD in Table III with those in Tables II and IV indicates that the LSER descriptors give better correlations than the TLSER descriptors except for Könemann's toxicity. This exception may be partly explained by the selection of LSER descriptors from various LSER references; the values chosen and estimated may not be as consistent as more recently obtained parameters. The TLSER results still can be classified as quite good. One advantage of using the

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Table II. TLSER Correlations for Direct Comparison with LSER Results Based on Optimal LSER Sample Sets Used in Table III

$$\log P = \log P_0 + AV_{mc}/100 + B\pi_1 + C\epsilon_b + Dq_- + E\epsilon_a + Fq_+$$

property symbol	$\log P_0$ (t statistic)	A	B	C	D	E	F	N	R	SD	F
				Microtox Test							
EC_{50}	11.4	-3.63	-45.8	n/s[f]	3.71	n/s	-2.92	38[a]	0.977	0.37	176
	(13.6)	-18.6	(-6.51)	n/s	(4.88)	n/s	(-3.13)				
				Golden Orfe							
LC_{50}(G)	7.42	-2.57	-46.3	n/s	3.52	n/s	-1.81	32[b]	0.960	0.30	78
	(12.1)	(-10.5)	(-8.86)	n/s	(-4.89)	n/s	(-2.24)				
				Tadpole Narcosis							
C	7.40	-2.15	-41.1	-25.5	4.18	n/s	n/s	39[c]	0.969	0.30	129
	(4.29)	(-10.5)	(-4.86)	(-3.72)	(5.91)	n/s	n/s				
				Könemann's Industrial Pollutants							
LC_{50}(K)	22.2	-1.78	-97.9	-39.6	n/s	n/s	n/s	28[d]	0.992	0.21	477
	(21.3)	(-6.79)	(-16.0)	(-9.27)							
				Frog Muscle Inhibition							
MBC	5.76	-2.58	-17.4	n/s	n/s	n/s	n/s	20[e]	0.979	0.23	195
	(16.7)	(-14.8)	(-5.10)	n/s	n/s	n/s	n/s				

[a] Cyclohexanone excluded as outlier; cyclohexanol, 2-decanone, 5-methyl-2-hexanone dropped to match LSER. [b] Benzonitrile an outlier but included to match LSER. [c] Acetonitrile an outlier; acetophenone and nitromethane dropped to match LSER. [d] Tetrachloromethane and 1,3-bis(chloromethyl)benzene excluded as outliers. [e] (Hydroxymethyl)benzene dropped to match LSER. Outliers are more than three standard deviations out. [f] n/s, not significant at the 0.95 level (or higher) by Student's t test.

Table III. LSER Correlations Based on Optimal Sample Sets (LSER Outliers Excluded)

$$\log P = \log P_0 + AV_m/100 + B\pi^* + C\beta + D\alpha$$

property symbol	$\log P_0$	A	B	C	D	N	R	SD
				Microtox Test				
EC_{50}	7.61	-4.22	-1.54	3.94	-1.51	38[a]	0.987	0.28
				Golden Orfe				
LC_{50}(G)	2.90	-5.71	-0.92	4.36	-1.27	32[b]	0.972	0.25
				Tadpole Narcosis				
C	-0.67	-4.87	-0.48	4.57	-0.65	39[c]	0.990	0.17
				Könemann's Industrial Pollutants				
LC_{50}(K)	5.33	-3.19	n/s	4.29	n/s[e]	28[d]	0.950	0.50
				Frog Muscle Inhibition				
MBC	3.93	-5.16	-0.46	1.38	n/s	20[c]	0.989	0.17

[a] Reference 27. [b] Reference 31. [c] Reference 11. [d] Reference 34. [e] n/s, not significant at the 0.95 level by Student's t test.

TLSER descriptors is that they are obtained by computation; traditional chemical experimentation was not needed to obtain the descriptors as is the case for the LSER parameters. In addition, corrections are used for the LSER descriptors that produce better correlations than the original values. A similar analysis of TLSER descriptors for classes of toxicants would likely improve correlations; this idea has not been pursued beyond preliminary work because it went against the basic philosophy of developing readily obtained parameters.

Further confidence in the correlation equations comes from comparing the SD values, 0.21–0.37 in the TLSER case, with the estimated experimental error in the logarithm, 0.04–0.1. The SD is significantly larger than the error, suggesting that the equations are *not* artifacts. The error had to be estimated because it was not readily available in the references. The measured properties were concentrations in the range of moles/liter with typical values in the range 0.1–0.000 01; this provided negative

Table IV. TLSER Correlations Based on Sample Sets with Only TLSER Outliers Excluded

$$\log P = \log P_0 + AV_{mc}/100 + B\pi_1 + C\epsilon_b + Dq_- + E\epsilon_a + Fq_+$$

property symbol	$\log P_0$ (t-statistic)	A	B	C	D	E	F	N	R	SD	F
				Microtox Test							
EC_{50}	11.7	-3.41	-49.3	n/s[e]	3.72	n/s	-4.28	41[a]	0.970	0.41	141
	(12.5)	(17.1)	(-6.34)	n/s	(4.38)	n/s	(-4.45)				
				Golden Orfe							
LC_{50}(G)	7.63	-2.63	-49.4	n/s	4.18	n/s	-1.90	31[b]	0.975	0.24	124
	(15.5)	(-13.4)	(-11.6)	n/s	(6.96)	n/s	(-2.93)				
				Tadpole Narcosis							
C	7.46	-2.16	-42.0	-25.2	4.11	n/s	n/s	41[c]	0.970	0.29	141
	(4.65)	(-12.0)	(-5.76)	(-4.36)	(6.27)	n/s	n/s				
				Könemann's Industrial Pollutants							
LC_{50}(K)	22.2	-1.78	-97.9	-39.6	n/s	n/s	n/s	28[d]	0.992	0.21	477
	(21.3)	(-6.79)	(-16.0)	(-9.27)	n/s	n/s	n/s				
				Frog Muscle Inhibition							
MBC	5.68	-2.58	-11.5	n/s	n/s	n/s	n/s	21	0.975	0.24	171
	(15.6)	(-14.0)	(-4.59)	n/s	n/s	n/s	n/s				

[a] Cyclohexanone excluded as outlier. [b] Benzonitrile excluded as outlier. [c] Acetonitrile excluded as outlier. [d] Tetrachloromethane and 1,3-bis(chloromethyl)benzene excluded as outliers. Outliers are more than three standard deviations out. [e] n/s, not significant at the 0.95 level (or higher) by Student's t test.

Table V. Toxicants with TLSER Descriptors

	$V/100$	π_1	ϵ_b	q_-	ϵ_a	q_+
(1) pentane	1.004	0.100	0.163	0.081	0.156	0.045
(2) 1-pentene	0.914	0.106	0.154	0.116	0.133	0.050
(3) bromomethane	0.685	0.109	0.169	0.141	0.127	0.032
(4) nitromethane	0.471	0.110	0.170	0.335	0.118	0.050
(5) dichloromethane	0.603	0.104	0.179	0.161	0.123	0.056
(6) trichloromethane	0.753	0.113	0.184	0.112	0.115	0.088
(7) tetrachloromethane	0.916	0.116	0.187	0.070	0.109	0.000
(8) chloroethane	0.619	0.101	0.176	0.215	0.131	0.030
(9) 1,1-dichloroethane	0.792	0.105	0.178	0.163	0.123	0.063
(10) 1,2-dichloroethane	0.773	0.106	0.179	0.185	0.121	0.049
(11) 1,1,1-trichloroethane	0.941	0.111	0.182	0.117	0.116	0.036
(12) 1,1,2-trichloroethane	0.942	0.108	0.180	0.153	0.119	0.068
(13) 1,1,2,2-tetrachloroethane	1.085	0.113	0.182	0.122	0.121	0.092
(14) 1,2-dichloropropane	0.967	0.105	0.177	0.188	0.126	0.058
(15) 1-chlorobutane	0.930	0.108	0.175	0.216	0.131	0.031
(16) trichloroethene	0.862	0.116	0.161	0.072	0.117	0.109
(17) methanol	0.365	0.086	0.169	0.329	0.162	0.193
(18) ethanol	0.542	0.093	0.167	0.324	0.157	0.180
(19) 1-propanol	0.713	0.097	0.167	0.325	0.156	0.180
(20) 2-propanol	0.721	0.096	0.166	0.320	0.155	0.178
(21) 2-methyl-1-propanol	0.894	0.098	0.167	0.324	0.154	0.181
(22) 2-methyl-2-propanol	0.891	0.098	0.166	0.318	0.156	0.177
(23) 1-butanol	0.898	0.098	0.167	0.325	0.155	0.180
(24) 2-butanol	0.897	0.098	0.166	0.322	0.154	0.178
(25) 2-methyl-2-butanol	1.065	0.100	0.166	0.322	0.154	0.177
(26) 1-pentanol	1.074	0.100	0.167	0.325	0.154	0.180
(27) 2-pentanol	1.068	0.100	0.166	0.322	0.153	0.179
(28) 3-pentanol	1.068	0.100	0.166	0.323	0.153	0.179
(29) cyclopentanol	0.946	0.104	0.165	0.315	0.154	0.179
(30) 1-hexanol	1.211	0.104	0.167	0.325	0.154	0.180
(31) 2-hexanol	1.242	0.101	0.166	0.321	0.153	0.179
(32) 3-hexanol	1.239	0.101	0.165	0.322	0.152	0.180
(33) cyclohexanol	1.122	0.107	0.164	0.322	0.152	0.180
(34) 1-heptanol	1.394	0.104	0.167	0.325	0.154	0.180
(35) 1-octanol	1.591	0.103	0.167	0.325	0.153	0.160
(36) 2-decanol	1.950	0.103	0.166	0.320	0.153	0.179
(37) propanone	0.639	0.098	0.162	0.287	0.129	0.023
(38) 2-butanone	0.810	0.101	0.161	0.287	0.129	0.022
(39) 2-pentanone	1.001	0.100	0.161	0.284	0.129	0.023
(40) 3-pentanone	0.972	0.104	0.161	0.285	0.129	0.021
(41) cyclopentanone	0.944	0.099	0.160	0.276	0.129	0.036
(42) 4-methyl-2-pentanone	1.174	0.101	0.161	0.286	0.129	0.029
(43) cyclohexanone	1.056	0.106	0.160	0.280	0.129	0.033
(44) 5-methyl-2-hexanone	1.356	0.102	0.161	0.285	0.129	0.023
(45) 6-methyl-5-hepten-2-one	1.455	0.108	0.152	0.285	0.129	0.044
(46) 2-octanone	1.541	0.102	0.161	0.284	0.129	0.023
(47) 2-decanone	1.888	0.104	0.161	0.284	0.129	0.023
(48) ethoxyethane	0.897	0.100	0.163	0.342	0.154	0.007
(49) butoxybutane	1.614	0.103	0.163	0.345	0.152	0.018
(50) tetrahydrofuran	0.786	0.103	0.162	0.327	0.153	0.022
(51) ethyl methanoate	0.702	0.102	0.170	0.362	0.132	0.102
(52) methyl ethanoate	0.708	0.101	0.169	0.357	0.131	0.027
(53) ethyl ethanoate	0.889	0.102	0.169	0.357	0.131	0.026
(54) propyl ethanoate	1.061	0.104	0.168	0.357	0.131	0.026
(55) butyl ethanoate	1.210	0.106	0.168	0.357	0.131	0.026
(56) isobutyl ethanoate	1.230	0.104	0.168	0.357	0.131	0.027
(57) pentyl ethanoate	1.415	0.104	0.168	0.357	0.131	0.026
(58) ethyl propanoate	1.073	0.102	0.168	0.357	0.132	0.035
(59) ethyl butanoate	1.211	0.106	0.168	0.357	0.132	0.034
(60) ethyl 2-methylpropanoate	1.229	0.104	0.167	0.358	0.132	0.042
(61) ethyl pentanoate	1.420	0.104	0.168	0.357	0.132	0.034
(62) butyl pentanoate	1.768	0.105	0.168	0.357	0.132	0.034
(63) dimethylformamide	0.765	0.105	0.156	0.472	0.135	0.057
(64) acetonitrile	0.451	0.094	0.182	0.115	0.138	0.021
(65) benzene	0.846	0.120	0.148	0.059	0.159	0.059
(66) chlorobenzene	0.994	0.124	0.151	0.112	0.121	0.078
(67) 1,2-dichlorobenzene	1.143	0.127	0.153	0.082	0.117	0.083
(68) 1,3-dichlorobenzene	1.148	0.127	0.153	0.099	0.117	0.092
(69) 1,2,3-trichlorobenzene	1.295	0.129	0.156	0.071	0.114	0.087
(70) 1,2,4-trichlorobenzene	1.295	0.130	0.155	0.088	0.113	0.099
(71) 1,3,5-trichlorobenzene	1.304	0.129	0.156	0.086	0.113	0.099
(72) 1,2,3,4-tetrachlorobenzene	1.446	0.131	0.157	0.622	0.110	0.092
(73) 1,2,3,5-tetrachlorobenzene	1.451	0.131	0.157	0.077	0.110	0.102
(74) 1,2,4,5-tetrachlorobenzene	1.448	0.132	0.157	0.060	0.109	0.103
(75) pentachlorobenzene	1.593	0.134	0.158	0.053	0.107	0.106
(76) toluene	1.000	0.123	0.147	0.101	0.124	0.081
(77) 3,4-dichlorotoluene	1.327	0.126	0.152	0.086	0.116	0.083
(78) 2,4,5-trichlorotoluene	1.487	0.128	0.154	0.093	0.112	0.086
(79) 2-methyltoluene (*o*-xylene)	1.189	0.121	0.147	0.106	0.124	0.081
(80) 3-methyltoluene (*m*-xylene)	1.232	0.117	0.147	0.106	0.124	0.081
(81) 1,3-dichloromethylbenzene	1.498	0.125	0.153	0.216	0.116	0.070
(82) (hydroxymethyl)benzene	1.067	0.123	0.148	0.325	0.124	0.183
(83) phenol	0.892	0.126	0.143	0.248	0.124	0.193
(84) 2-methylphenol	1.090	0.122	0.143	0.249	0.137	0.195
(85) 3-methylphenol	1.060	0.126	0.143	0.249	0.124	0.192
(86) 4-nitrophenol	1.092	0.132	0.153	0.334	0.113	0.204
(87) 2,4-dimethylphenol	1.294	0.120	0.142	0.250	0.124	0.194
(88) 2-isopropyl-5-methylphenol	1.614	0.120	0.143	0.252	0.123	0.194
(89) 4-*tert*-butylphenol	1.532	0.125	0.143	0.247	0.124	0.193
(90) acetophenone	1.191	0.120	0.151	0.259	0.121	0.065
(91) methoxybenzene	1.090	0.124	0.143	0.286	0.125	0.075
(92) aniline	0.945	0.128	0.142	0.228	0.125	0.113
(93) nitrobenzene	1.017	0.131	0.158	0.342	0.110	0.095
(94) 2-nitrotoluene	1.158	0.132	0.156	0.330	0.114	0.084
(95) benzonitrile	0.997	0.128	0.153	0.087	0.117	0.070
(96) pyridine	0.780	0.122	0.151	0.230	0.122	0.084
(97) naphthalene	1.363	0.130	0.140	0.058	0.119	0.060
(98) 2-hydroxynaphthalene	1.325	0.143	0.139	0.247	0.118	0.194
(99) phenanthrene	1.697	0.151	0.139	0.058	0.117	0.061
(100) quinoline	1.233	0.145	0.139	0.147	0.119	0.112

Table VI. Microtox Test Toxicity, EC_{50}

	log EC_{50}				log EC_{50}				log EC_{50}		
no.[a]	calc	exp	resid	no.[a]	calc	exp	resid	no.[a]	calc	exp	resid
10	4.050	3.853	−0.197	35	1.620	2.041	0.421	65	3.310	2.913	−0.397
11	2.900	3.328	0.428	36	0.870	0.535	−0.335	66	2.120	2.329	0.209
13	1.700	2.553	0.853	37	5.570	5.676	0.106	68	1.350	1.587	0.237
16	3.160	2.932	−0.228	38	4.850	4.948	0.098	69	1.140	0.896	−0.244
17	6.360	6.775	0.415	42	2.900	3.683	0.783	76	2.290	2.322	0.032
18	5.980	5.853	−0.127	44	3.930	3.030	−0.900	77	0.940	1.006	0.066
19	5.160	5.076	−0.084	45	2.140	2.332	0.192	79	1.940	1.784	−0.156
20	5.760	5.086	−0.674	46	2.140	2.384	0.244	83	2.630	2.704	0.074
21	4.350	4.394	0.044	47	1.700	1.136	−0.564	84	2.280	2.222	−0.058
23	4.540	4.396	−0.144	48	4.880	4.957	0.077	86	1.970	2.016	0.046
28	4.230	3.884	−0.346	49	2.680	2.341	−0.339	87	1.550	1.658	0.108
30	2.710	3.044	0.334	53	4.840	4.877	0.037	89	0.150	0.580	0.430
33	3.600	3.166	−0.434	58	3.840	4.219	0.379	96	4.510	3.591	−0.919
34	1.930	2.416	0.486	63	5.432	5.479	0.047				

[a] See Table V for toxicant names.

logarithms from 1 to 5. Very small concentrations are difficult to measure. Taking the smallest relative error as 0.10–0.25 (10–25%) provides an error for the logarithm in the range of 0.04–0.1 (0.10/2.3). The smallest SD (TLSER) value is 0.21, which is 2–5 times larger than the estimated error.

Qualitatively the LSER and TLSER results are quite similar. The coefficients for the volume (V_m and V_{mc}),

Table VII. Golden Orfe Fish Toxicity, LC_{50}

	log LC_{50}(G)				log LC_{50}(G)				log LC_{50}(G)		
no.[a]	calc	exp	resid	no.[a]	calc	exp	resid	no.[a]	calc	exp	resid
7	−0.210	−0.220	−0.010	29	1.240	0.970	−0.270	48	1.580	1.722	0.142
10	0.560	1.012	0.452	30	0.100	0.315	0.215	49	−0.260	−0.303	−0.043
11	−0.040	0.087	0.127	31	0.450	0.359	−0.091	50	1.590	1.815	0.225
16	0.010	−0.293	−0.303	32	0.540	0.363	−0.177	64	2.150	2.227	0.077
19	1.880	1.972	0.092	34	−0.450	−0.163	0.287	65	−0.370	−0.417	−0.047
20	2.170	2.005	−0.165	35	−0.810	−0.594	0.216	83	−0.580	−0.256	0.324
21	1.310	1.430	0.120	37	2.290	2.259	−0.031	85	−0.750	−0.694	0.056
23	1.210	1.432	0.222	38	1.800	1.663	−0.137	91	0.050	−0.305	−0.355
24	1.670	1.447	−0.223	41	1.580	1.359	−0.221	93	−0.310	−0.263	0.047
25	1.440	0.907	−0.533	43	0.740	0.660	−0.080	94	−0.670	−0.741	−0.071
26	0.740	0.894	0.154								

[a] See Table V for toxicant names.

Table VIII. Tadpole Narcosis, C

	log C				log C				log C		
no.[a]	calc	exp	resid	no.[a]	calc	exp	resid	no.[a]	calc	exp	resid
1	−2.550	−2.649	−0.099	25	−1.240	−1.859	−0.619	57	−2.720	−2.727	−0.007
2	−2.640	−2.364	0.276	27	−1.640	−1.861	−0.221	58	−1.960	−1.898	0.062
3	−2.570	−2.263	0.307	35	−3.400	−3.148	0.252	59	−2.370	−2.367	0.003
4	−1.090	−1.080	0.010	37	−0.540	−0.924	−0.384	60	−2.240	−2.300	−0.060
6	−2.850	−3.065	−0.215	38	−1.040	−1.401	−0.361	61	−2.720	−2.716	0.004
8	−2.350	−1.655	0.695	39	−1.720	−1.785	−0.065	62	−3.600	−3.504	0.096
10	−2.640	−2.374	0.266	40	−1.540	−1.861	−0.321	65	−2.680	−2.905	−0.225
17	−0.240	0.170	0.410	48	−1.570	−1.389	−0.181	79	−3.420	−3.440	−0.020
18	−0.540	−0.484	0.056	51	−1.150	−1.111	0.039	88	−4.260	−3.574	0.686
19	−0.960	−1.021	−0.061	52	−1.100	−1.075	0.025	90	−3.030	−2.891	0.139
20	−0.890	−0.977	−0.087	53	−1.520	−1.502	0.018	91	−2.820	−2.493	0.327
22	−0.890	−1.429	−0.539	54	−1.960	−1.969	−0.009	97	−4.190	−4.225	−0.035
23	−1.420	−1.463	−0.043	55	−2.300	−2.374	−0.074	99	−5.430	−5.791	−0.361
24	−1.350	−1.433	−0.083	56	−2.370	−2.332	0.038				

[a] See Table V for toxicant names.

Table IX. Könemann's Industrial Pollutants Toxicity, LC_{50}(K)

	log LC_{50}(K)				log LC_{50}(K)				log LC_{50}(K)		
no.[a]	calc	exp	resid	no.[a]	calc	exp	resid	no.[a]	calc	exp	resid
5	3.851	3.540	−0.311	22	4.479	4.680	0.201	71	1.052	1.260	0.208
6	2.518	2.930	0.412	28	3.976	4.050	0.074	72	0.566	0.570	0.004
9	3.462	3.310	−0.152	37	5.052	5.040	−0.012	73	0.538	0.570	0.032
10	3.322	3.030	−0.292	48	4.314	4.460	0.146	74	0.508	0.150	−0.358
12	2.826	2.850	0.024	65	3.019	2.910	−0.109	75	0.003	−0.150	−0.153
13	1.965	2.340	0.375	66	2.280	2.230	−0.050	76	2.525	2.870	0.345
14	3.246	3.010	−0.236	67	1.664	1.600	−0.064	78	0.945	0.940	−0.005
15	3.079	3.020	−0.059	69	1.113	1.110	−0.003	79	2.409	2.520	0.111
18	5.516	5.380	−0.136	70	1.049	1.120	0.071	80	2.724	2.550	−0.174
20	4.959	5.070	0.111								

[a] See Table V for toxicant names.

Table X. Frog Muscle Activity Inhibition, MBC

	log MBC				log MBC				log MBC		
no.[a]	calc	exp	resid	no.[a]	calc	exp	resid	no.[a]	calc	exp	resid
6	1.872	1.500	−0.372	30	0.840	0.560	−0.280	83	1.306	1.000	−0.306
17	3.320	3.090	−0.230	34	0.370	0.200	−0.170	88	−0.457	−0.520	−0.063
18	2.751	2.750	−0.001	35	−0.123	−0.016	0.107	92	1.134	1.300	0.166
19	2.241	2.400	0.159	37	2.415	2.600	0.185	93	0.898	0.470	−0.428
20	2.243	2.550	0.307	48	1.709	1.930	0.221	96	1.651	1.770	0.119
23	1.745	1.780	0.035	76	1.069	1.000	−0.069	98	−0.094	0.000	0.094
26	1.266	1.200	−0.066	82	0.895	1.300	0.405	100	0.112	0.300	0.188

[a] See Table V for toxicant names.

polarizability (π and π_I), and hydrogen bonding (β and q_-, α and q_+) are all negative. The volume and polarizability terms are significant for each toxicity parameter with the exception of Könemann's toxicity in the LSER case; this latter result might change with a more accurate set of descriptors as mentioned earlier. Another qualitative agreement is the lack of significance for the HBA as indicated by its appearing the least number of times for each set. This illustrates the observation that not all descriptors are needed for a given property for either set of descriptors.

The importance of the TLSER descriptors in each correlation is indicated by the sign and magnitude of the coefficient and from the value of the t statistic. Negative terms in the logarithms imply a decrease in the concentration that produces the toxic effect and, consequently, a greater toxicity. The molecular volume and polarizability index terms are most important since they are most statistically significant in each of the five toxicity parameters.

Table XI. Correlation Matrixes for Significant TLSER Descriptors

Microtox Test (n = 42)				
	$v_{mc/100}$	π_1	q_-	q_+
$v_{m/100}$	1.000			
π_1	0.203	1.000		
q_-	0.018	−0.632	1.000	
q_+	−0.106	0.066	0.174	1.000
Golden Orfe (n = 32)				
	$v_{mc/100}$	π_1	q_-	q_+
$v_{mc/100}$	1.000			
π_1	0.146	1.000		
q_-	0.371	−0.361	1.000	
p_+	0.256	−0.108	0.409	1.000
Tadpole Narcosis (n = 42)				
	$v_{mc/100}$	π_1	ϵ_b	q_+
$v_{mc/100}$	1.000			
π_1	0.542	1.000		
ϵ_b	−0.470	−0.721	1.000	
q_-	0.020	−0.551	0.380	1.000
Könemann's Industrial Pollutants (n = 23)				
	$v_{mc/100}$	π_1	ϵ_b	
$v_{mc/100}$	1.000			
π_1	0.849	1.000		
ϵ_b	−0.533	−0.595	1.000	
Frog Muscle Inhibition (n = 21)				
	$v_{mc/100}$	π_1		
$v_{mc/100}$	1.000			
π_1	0.447	1.000		

These each have a negative sign, indicating that increased values increase the toxicity. In light of the nonspecific toxicity mechanism, one might expect that a larger polarizability index would make a compound more soluble in water, resulting, possibly, in a lesser tendency be partitioned into the membrane of the organism. However, that does not preclude an interaction of the solute with polar portions of a membrane.

The covalent HBB is used in only two cases and has the same sign and numerical importance as do the volume and polarizability index with a statistical significance low in one case and high in the other. The covalent HBA is not significant since it is not used in any of the five parameters. The electrostatic contribution to the HBB occurs in three cases, has a positive sign, is statistically significant, and contributes less numerically. The positive sign indicates that increased basicity decreases the toxicity. The electrostatic term for the HBA is used in only two cases, and in those cases, they have the least numerical importance and statistical significance. Furthermore, the signs on the electrostatic HBA terms are negative, indicating that increased acidity increases the toxicity.

The fact that each of these toxicity properties has a different correlation equation suggests different modes of action for each organism. An interpretation is that the membranes in contact with the water phase interact differently; perhaps they differ in permeability. More particularly, if the hydrogen-bonding basicity is significant, then the toxicant could interact with acidic sites (proton donors or cations) in the organism. This interpretation could apply for the first four toxicity parameters in the TLSER tables (II and IV). A corresponding interpretation would apply to the hydrogen-bonding acidity which is significant in only the first two cases in those tables. Frog muscle activity inhibition apparently does not involve hydrogen-bonding interactions.

Outlying compounds can be explained in several ways. The experimental value may be in error. Then, too, the toxicant might undergo a more specific toxicity mechanism in which the rate controlling step may involve a specific reaction with a functional group or receptor site in a membrane. Furthermore, the TLSER descriptors may be inadequate on two counts. The conformation involved in the reaction may not be well represented by the gas-phase parameters calculated here; the initial molecular model is chosen intuitively to produce a conformation corresponding to a global minimum. Another possibility is that there may be other molecular parameters which should be included; the theory is incomplete.

It should be noted that the discussion is based on terms being significant at the 0.95 level. The applicability of LSER and TLSER to the five toxicity parameters in Tables I is readily apparent from the correlation equations given in Tables II–IV. In addition, the TLSER descriptors, based solely on theoretically derived and determined parameters, result in correlations of almost the same quality as those for the LSER descriptors. Using these equations, then, toxicity (narcosis included) related parameters involving solute/solvent interactions can be related to fundamental descriptors (structural and electronic) of the molecule. Furthermore, these correlation equations and the computational nature of these TLSER descriptors make possible the a priori prediction of these toxicity parameters for compounds expected to follow a generic nonreactive toxicity mechanism.

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Registry No. **1**, 109-66-0; **2**, 109-67-1; **3**, 74-83-9; **4**, 75-52-5; **5**, 75-09-2; **6**, 67-66-3; **7**, 56-23-5; **8**, 75-00-3; **9**, 75-34-3; **-10**, 107-06-2; **11**, 71-55-6; **12**, 79-00-5; **13**, 79-34-5; **14**, 78-87-5; **15**, 109-69-3; **16**, 79-01-6; **17**, 67-56-1; **18**, 64-17-5; **19**, 71-23-8; **20**, 67-63-0; **21**, 78-83-1; **22**, 75-65-0; **23**, 71-36-3; **24**, 78-92-2; **25**, 75-85-4; **26**, 71-41-0; **27**, 6032-29-7; **28**, 584-02-1; **29**, 96-41-3; **30**, 111-27-3; **31**, 626-93-7; **32**, 623-37-0; **33**, 108-93-0; **34**, 111-70-6; **35**, 111-87-5; **36**, 1120-06-5; **37**, 67-64-1; **38**, 78-93-3; **39**, 107-87-9; **40**, 96-22-0; **41**, 120-92-3; **42**, 108-10-1; **43**, 108-94-1; **44**, 110-12-3; **45**, 110-93-0; **46**, 111-13-7; **47**, 693-54-9; **48**, 60-29-7; **49**, 142-96-1; **50**, 109-99-9; **51**, 109-94-4; **52**, 79-20-9; **53**, 141-78-6; **54**, 109-60-4; **55**, 123-86-4; **56**, 111-19-0; **57**, 628-63-7; **58**, 105-37-3; **59**, 105-54-4; **60**, 97-62-1; **61**, 539-82-2; **62**, 591-68-4; **63**, 68-12-2; **64**, 75-05-8; **65**, 71-43-2; **66**, 108-90-7; **67**, 95-50-1; **68**, 541-73-1; **69**, 87-61-6; **70**, 120-82-1; **71**, 108-70-3; **72**, 634-66-2; **73**, 634-90-2; **74**, 95-94-3; **75**, 608-93-5; **76**, 108-88-3; **77**, 95-75-0; **78**, 6639-30-1; **79**, 95-47-6; **80**, 108-38-3; **81**, 94060-74-9; **82**, 100-51-6; **83**, 108-95-2; **84**, 95-48-7; **85**, 108-39-4; **86**, 100-02-7; **87**, 105-67-9; **88**, 89-83-8; **89**, 98-54-4; **90**, 98-86-2; **91**, 100-66-3; **92**, 62-53-3; **93**, 98-95-3; **94**, 88-72-2; **95**, 100-47-0; **96**, 110-86-1; **97**, 91-20-3; **98**, 135-19-3; **99**, 85-01-8; **100**, 91-22-5.