

Valence Topological Charge-Transfer Indices for Dipole Moments: Percutaneous Enhancers

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Abstract: Valence topological charge-transfer (CT) indices are applied to the calculation of dipole moments. The *algebraic* and *vector semisum CT indices* are defined. The combination of CT indices allows the estimation of the dipole moments. The model is generalized for molecules with heteroatoms. The ability of the indices for the description of the molecular charge distribution is established by comparing them with the dipole moments of homologous series of percutaneous enhancers (phenyl alcohols and 4-alkylanilines). Linear and quadratic correlation models are obtained. CT indices improve the multivariable quadratic regression equations for the dipole moment. The variance decreases 97% (4-alkylanilines). No superposition of the corresponding G_k-J_k and $G_k^V-J_k^V$ pairs is observed in the fits, which diminishes the risk of co-linearity. The inclusion of the heteroatom in the π -electron system is beneficial for the description of the dipole moment, owing to either the role of the additional p orbitals provided by the heteroatom or the role of *steric* factors in the π -electron conjugation. Inclusion of a conjugated double bond in the alkyl chain leads to more rigid structures with dipole moment variations <1%.

Keywords: Transdermal drug delivery, percutaneous enhancer, charge distribution, dipole moment, valence topological charge-transfer index.

Introduction

Passive drug penetration across absorbent membranes involves both the intrinsic resistance of the lipidic barriers themselves and that of the adjacent aqueous boundary layers, which can provide

substantial additional strength against the passage of penetrants [1,2]. When adjacent to the lipoidal membrane and its luminal side, aqueous boundary layer thickness can be modified by agitation and, for *in vitro* experiments, the importance of suitable stirring conditions to obtain reproducible results was recognized [3]. In comparative studies, the existence of the aqueous boundary layers, although acknowledged, was sometimes virtually ignored because of its uniformity throughout a strictly designed and controlled steady-state experimentation work [4–7].

Díez-Sales *et al.* performed *in vitro* permeability studies using a series of weakly basic xenobiotics of long-term toxicological interest across a homogeneous lipoidal artificial membrane under several working conditions, including the presence and the partial or total absence of aqueous boundary layers [8]. Synthetic surfactants, at either the critical micelle or supramicellar concentration, were reported to disrupt the *in vivo* aqueous stagnant diffusion layers adjacent to the membrane at its luminal side, as well as to increase the intrinsic membrane polarity through a direct penetration effect [9–12], and it was thought to evaluate these properties on *in vitro* artificial membranes. To achieve this, Díez-Sales *et al.* established permeability–lipophilicity correlations, and compared them for each condition according to previously reported discriminative equations [13–17].

Percutaneous penetration depends essentially on the lipophilicity of the tested substances [18]. The use of homologous series of compounds made it possible to establish behaviour models, which allow predicting the percutaneous absorption capacity of chemically related substances [19,20]. Much of the theoretical background information on percutaneous absorption was developed from studies of non-electrolytic permeating species [21,22], and only a little is available on the effect of *pH* and *pK_a* on permeation of ionizable drugs through the skin. The vehicle's *pH* may have a profound influence upon the percutaneous delivery from topical products [23]. Depending on the *pK_a* of the compound and on the *pH* of the vehicle, an equilibrium mixture of ionized and unionized species would be present in the immediate vicinity of the skin [24]. According to the *pH-partition simple hypothesis*, only the non-ionized forms of drugs are able to pass through lipoidal membranes in significant amounts. However, the permeation of ionized drugs through the skin is possible and therefore must be taken into account, although ionization reduces topical availability [25]. The mechanism by which percutaneous penetration enhancers operate is not fully understood, but the structured lipids within the intercellular channels play an important role in controlling absorption. Penetration enhancers may act by either interacting with the highly ordered lipid structure, or modifying the partitioning of the drug into the tissue [26,27].

In earlier publications, topological charge-transfer (CT) indices were applied to the calculation of the molecular dipole moment of hydrocarbons [28], valence-isoelectronic series of benzene, styrene [29,30] and cyclopentadiene [31], and phenyl alcohols [32]. An index inspired by biological plastic evolution [33,34] and fractal dimension analysis [35,36] improved the results. In the present study, the valence CT indices have been applied to the calculation of the dipole moment of phenyl alcohols, 4-alkylanilines and aliphatic amines. The next section presents the CT indices. Following that, the indices are generalized for heteroatoms. Next, the calculation results are discussed. The last section summarizes the conclusions.

Materials and methods

The most important matrices that delineate the labelled chemical graph are the *adjacency* (**A**) [37] and the *distance* (**D**) matrices, wherein $D_{ij} = \square_{ij}$ if $i = j$, “0” otherwise; \square_{ij} is the shortest edge count between vertices i and j [38]. In **A**, $A_{ij} = 1$ if vertices i and j are adjacent, “0” otherwise. The $\mathbf{D}^{[-2]}$ matrix is that whose elements are the squares of the reciprocal distances D_{ij}^{-2} . The intermediate matrix **M** is defined as the matrix product of **A** by $\mathbf{D}^{[-2]}$:

$$\mathbf{M} = \mathbf{A}\mathbf{D}^{[-2]}$$

The *CT matrix* **C** is defined as $\mathbf{C} = \mathbf{M} - \mathbf{M}^T$, where \mathbf{M}^T is the transpose of **M** [39]. By agreement $C_{ii} = M_{ii}$. For $i \neq j$, the C_{ij} terms represent a measure of the intramolecular *net charge* transferred from atom j to i . The *topological CT indices* G_k are described as the sum of absolute values of the C_{ij} terms defined for the vertices i, j placed at a topological distance D_{ij} equal to k :

$$G_k = \sum_{i=1}^{N-1} \sum_{j=i+1}^N |C_{ij}| \delta(k, D_{ij}) \quad (1)$$

where N is the number of vertices in the graph, D_{ij} are the entries of the **D** matrix, and δ is the Kronecker δ function, being $\delta = 1$ for $i = j$ and $\delta = 0$ for $i \neq j$. G_k represents the sum of all the C_{ij} terms, for every pair of vertices i and j at topological distance k . Other topological CT index, J_k , is defined as:

$$J_k = \frac{G_k}{N-1} \quad (2)$$

This index represents the mean value of CT for each edge, since the number of edges for acyclic compounds is $N - 1$.

The *algebraic semisum CT index* μ_{alg} is defined as

$$\mu_{\text{alg}} = \frac{1}{2} \sum_{i=1}^{N-1} \sum_{j=i+1}^N A_{ij} |C_{ij}| = \frac{1}{2} \sum_{e=1}^m |C^e| \quad (3)$$

where C^e is C_{ij} index for vertices i and j connected by edge e [28]. The sum extends for all pairs of adjacent vertices in the molecular graph and μ_{alg} is a graph invariant. An edge analysis suggests that each dipole moment μ^e , of edge e connecting vertices i and j can be evaluated from its edge C^e index as:

$$\mu^e = \frac{1}{2} C^e$$

Each edge dipole can be associated with a vector $\boldsymbol{\mu}^e$ in space. $\boldsymbol{\mu}^e$ has magnitude $|\boldsymbol{\mu}^e|$, lies in the edge e connecting vertices i and j , and its direction is $j \rightarrow i$. The molecular dipole vector $\boldsymbol{\mu}$ results as the vector sum of the edge dipoles as:

$$\boldsymbol{\mu} = \sum_{e=1}^m \boldsymbol{\mu}^e = \frac{1}{2} \sum_{e=1}^m C^e$$

summed for all the m edges in the molecular graph. The *vector semisum CT index* μ_{vec} is defined as the module of $\boldsymbol{\mu}$:

$$\mu_{\text{vec}} = N(\boldsymbol{\mu}) = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2} \quad (4)$$

Therefore, μ_{vec} is a graph invariant.

Valence charge-transfer indices for heteroatoms

When heteroatoms are present, some way of discriminating atoms of different kinds needs to be considered [40]. In valence CT indices terms, the presence of each heteroatom is taken into account by introducing its electronegativity value in the corresponding entry of the main diagonal of the adjacency matrix **A**. For each heteroatom *X*, its entry A_{ii} is redefined as:

$$A_{ii}^V = 2.2(\chi_X - \chi_C) \quad (5)$$

to give the *valence adjacency A^V matrix*, where χ_X and χ_C are the electronegativities of heteroatom *X* and carbon, respectively, in Pauling units. The subtractive term keeps $A_{ii}^V = 0$ for the C atom, and the factor gives $A_{ii}^V = 2.2$ for O, which was taken as standard. From **A^V**, **M^V** and **C^V**, G_k^V , J_k^V , μ_{alg}^V and μ_{vec}^V are calculated following the former procedure with **A^V**. C_{ii}^V , G_k^V , J_k^V , μ_{alg}^V and μ_{vec}^V are graph invariants. μ_{vec} is sensitive only to the *steric* effect of heteroatoms, while μ_{vec}^V is sensitive to both electronic and steric effects.

Calculation Results and Discussion

The molecular CT indices G_k , J_k , G_k^V and J_k^V (with $k < 6$) are reported in Table 1 for a series of 13 phenyl alcohols (eight form a homologous series and five are congeneric) and 14 amines (seven homologous 4-alkylanilines and seven congeneric). In particular, for the homologous phenyl alcohols, G_1 and G_2 are sensitive to the presence of the alkyl chain, and G_3 , G_4 and G_5 indicate, respectively, the occurrence of at least 2, 3 and 4 C atoms in this chain. For the 4-alkylanilines, G_1 is a sign of the incidence of the alkyl chain, and G_2 – G_5 signify the existence of at least 2–5 C atoms in this chain. For both series, G_1^V denotes the presence of the alkyl chain, and G_2^V – G_5^V imply the occurrence of at least 2–5 C atoms in this chain.

Table 1. Values of the G_k and J_k charge-transfer indices up to fifth order for phenyl alcohols or amines

Molecule	<i>N</i>	G_1	G_2	G_3	G_4	G_5
phenol	7	2.0000	0.8889	0.3750	0.2222	0.0000
benzyl alcohol	8	1.2500	6.7778	0.8125	0.4133	0.1250
2-phenyl-1-ethanol	9	1.2500	6.7778	0.8750	0.5644	0.2431
3-phenyl-1-propanol	10	1.2500	6.7778	0.8750	0.6044	0.3333
4-phenyl-1-butanol	11	1.2500	6.7778	0.8750	0.6044	0.3611
5-phenyl-1-pentanol	12	1.2500	6.7778	0.8750	0.6044	0.3611
6-phenyl-1-hexanol	13	1.2500	6.7778	0.8750	0.6044	0.3611
7-phenyl-1-heptanol	14	1.2500	6.7778	0.8750	0.6044	0.3611
1-phenyl-2-propanol	10	2.2500	6.7778	0.9375	0.7156	0.3611
2-phenyl-2-propanol	10	2.7500	7.2222	1.5625	0.7956	0.3750
3-phenyl-2-propen-1-ol	10	1.2500	8.2222	0.8750	0.4844	0.2708
1-phenyl-1-pentanol	12	1.7500	7.1111	1.3125	0.8756	0.4861
1-phenyl-2-pentanol	12	2.2500	7.0000	1.0625	0.7556	0.4792
aniline	7	1.2500	6.6667	0.5000	0.2222	0.0000
4-methylaniline	8	2.5000	8.0000	0.8750	0.5244	0.0000
4-ethylaniline	9	2.5000	8.1111	1.1875	0.7156	0.1806
4-propylaniline	10	2.5000	8.1111	1.2500	0.8667	0.2986

Table 1. Cont.

Molecule	N	G_1	G_2	G_3	G_4	G_5
4-butylaniline	11	2.5000	8.1111	1.2500	0.9067	0.3889
4-pentylaniline	12	2.5000	8.1111	1.2500	0.9067	0.4167
4-hexylaniline	13	2.5000	8.1111	1.2500	0.9067	0.4167
2-methylaniline	8	2.0000	8.2222	1.0000	0.4444	0.0000
4-isopropylaniline	10	3.0000	8.2222	1.5000	0.9067	0.3611
4-(1'-propenyl)aniline	10	2.5000	9.4444	1.0000	0.7467	0.2639
1-aminonaphthalene	11	1.7500	12.2222	1.6875	0.9822	0.1250
2-aminonaphthalene	11	2.2500	12.0000	1.5000	0.9911	0.1736
4-cyclohexylaniline	13	2.5000	8.2222	1.5625	1.0578	0.5208
4-aminobiphenyl	13	2.2500	13.7778	1.2500	0.7911	0.4167

Molecule	J_1	J_2	J_3	J_4	J_5
phenol	0.3333	0.1481	0.0625	0.0370	0.0000
benzyl alcohol	0.1786	0.9683	0.1161	0.0590	0.0179
2-phenyl-1-ethanol	0.1563	0.8472	0.1094	0.0706	0.0304
3-phenyl-1-propanol	0.1389	0.7531	0.0972	0.0672	0.0370
4-phenyl-1-butanol	0.1250	0.6778	0.0875	0.0604	0.0361
5-phenyl-1-pentanol	0.1136	0.6162	0.0795	0.0549	0.0328
6-phenyl-1-hexanol	0.1042	0.5648	0.0729	0.0504	0.0301
7-phenyl-1-heptanol	0.0962	0.5214	0.0673	0.0465	0.0278
1-phenyl-2-propanol	0.2500	0.7531	0.1042	0.0795	0.0401
2-phenyl-2-propanol	0.3056	0.8025	0.1736	0.0884	0.0417
3-phenyl-2-propen-1-ol	0.1389	0.9136	0.0972	0.0538	0.0301
1-phenyl-1-pentanol	0.1591	0.6465	0.1193	0.0796	0.0442
1-phenyl-2-pentanol	0.2045	0.6364	0.0966	0.0687	0.0436
aniline	0.2083	1.1111	0.0833	0.0370	0.0000
4-methylaniline	0.3571	1.1429	0.1250	0.0749	0.0000
4-ethylaniline	0.3125	1.0139	0.1484	0.0894	0.0226
4-propylaniline	0.2778	0.9012	0.1389	0.0963	0.0332
4-butylaniline	0.2500	0.8111	0.1250	0.0907	0.0389
4-pentylaniline	0.2273	0.7374	0.1136	0.0824	0.0379
4-hexylaniline	0.2083	0.6759	0.1042	0.0756	0.0347
2-methylaniline	0.2857	1.1746	0.1429	0.0635	0.0000
4-isopropylaniline	0.3333	0.9136	0.1667	0.1007	0.0401
4-(1'-propenyl)aniline	0.2778	1.0494	0.1111	0.0830	0.0293
1-aminonaphthalene	0.1750	1.2222	0.1688	0.0982	0.0125
2-aminonaphthalene	0.2250	1.2000	0.1500	0.0991	0.0174
4-cyclohexylaniline	0.2083	0.6852	0.1302	0.0881	0.0434
4-aminobiphenyl	0.1875	1.1481	0.1042	0.0659	0.0347

Table 1. Cont.

Molecule	G_1^V	G_2^V	G_3^V	G_4^V	G_5^V
phenol	2.2000	1.1000	0.3639	0.0847	0.0000
benzyl alcohol	2.9500	6.6611	0.5625	0.2533	0.0370
2-phenyl-1-ethanol	2.9500	7.1056	0.7444	0.4044	0.1319
3-phenyl-1-propanol	2.9500	7.1056	0.9944	0.5019	0.2222
4-phenyl-1-butanol	2.9500	7.1056	0.9944	0.6619	0.2824
5-phenyl-1-pentanol	2.9500	7.1056	0.9944	0.6619	0.3936
6-phenyl-1-hexanol	2.9500	7.1056	0.9944	0.6619	0.3936
7-phenyl-1-heptanol	2.9500	7.1056	0.9944	0.6619	0.3936
1-phenyl-2-propanol	3.4500	7.6556	0.8069	0.5556	0.2500
2-phenyl-2-propanol	3.4500	8.2056	1.3125	0.6356	0.2870
3-phenyl-2-propen-1-ol	2.9500	8.3278	0.6306	0.3819	0.1597
1-phenyl-1-pentanol	2.9500	7.3222	1.1819	0.7731	0.4861
1-phenyl-2-pentanol	3.4500	7.6556	1.0514	0.7331	0.3681
aniline	0.8500	6.2222	0.2556	0.1535	0.0000
4-methylaniline	2.1000	7.5556	0.6306	0.4557	0.0440
4-ethylaniline	2.1000	7.6667	0.9431	0.6468	0.1690
4-propylaniline	2.1000	7.6667	1.0056	0.7979	0.2871
4-butylaniline	2.1000	7.6667	1.0056	0.8379	0.3773
4-pentylaniline	2.1000	7.6667	1.0056	0.8379	0.4051
4-hexylaniline	2.1000	7.6667	1.0056	0.8379	0.4051
2-methylaniline	1.6000	7.7778	0.8778	0.3757	0.0000
4-isopropylaniline	2.6000	7.7778	1.2556	0.8379	0.3171
4-(1'-propenyl)aniline	2.1000	9.0000	0.7556	0.6779	0.2199
1-aminonaphthalene	1.3500	11.6722	1.3208	0.7760	0.0810
2-aminonaphthalene	1.8500	11.5556	1.2556	0.8536	0.0856
4-cyclohexylaniline	2.1000	7.7778	1.3181	0.9890	0.4768
4-aminobiphenyl	1.8500	13.3333	1.0056	0.7224	0.3727

Molecule	J_1^V	J_2^V	J_3^V	J_4^V	J_5^V
phenol	0.3637	0.1833	0.0606	0.0141	0.0000
benzyl alcohol	0.4214	0.9516	0.0804	0.0362	0.0053
2-phenyl-1-ethanol	0.3688	0.8882	0.0931	0.0506	0.0165
3-phenyl-1-propanol	0.3278	0.7895	0.1105	0.0558	0.0247
4-phenyl-1-butanol	0.2950	0.7106	0.0994	0.0662	0.0282
5-phenyl-1-pentanol	0.2682	0.6460	0.0904	0.0602	0.0358
6-phenyl-1-hexanol	0.2458	0.5921	0.0829	0.0552	0.0328
7-phenyl-1-heptanol	0.2269	0.5466	0.0765	0.0509	0.0303
1-phenyl-2-propanol	0.3833	0.8506	0.0897	0.0617	0.0278
2-phenyl-2-propanol	0.3833	0.9117	0.1458	0.0706	0.0319
3-phenyl-2-propen-1-ol	0.3278	0.9253	0.0701	0.0424	0.0177

Table 1. Cont.

Molecule	J_1^V	J_2^V	J_3^V	J_4^V	J_5^V
1-phenyl-1-pentanol	0.2682	0.6657	0.1074	0.0703	0.0442
1-phenyl-2-pentanol	0.3136	0.6960	0.0956	0.0666	0.0335
aniline	0.1417	1.0370	0.0426	0.0256	0.0000
4-methylaniline	0.3000	1.0794	0.0901	0.0651	0.0063
4-ethylaniline	0.2625	0.9583	0.1179	0.0809	0.0211
4-propylaniline	0.2333	0.8519	0.1117	0.0887	0.0319
4-butylaniline	0.2100	0.7667	0.1006	0.0838	0.0377
4-pentylaniline	0.1909	0.6970	0.0914	0.0762	0.0368
4-hexylaniline	0.1750	0.6389	0.0838	0.0698	0.0338
2-methylaniline	0.2286	1.1111	0.1254	0.0537	0.0000
4-isopropylaniline	0.2889	0.8642	0.1395	0.0931	0.0352
4-(1'-propenyl)aniline	0.2333	1.0000	0.0840	0.0753	0.0244
1-aminonaphthalene	0.1350	1.1672	0.1321	0.0776	0.0081
2-aminonaphthalene	0.1850	1.1556	0.1256	0.0854	0.0086
4-cyclohexylaniline	0.1750	0.6481	0.1098	0.0824	0.0397
4-aminobiphenyl	0.1542	1.1111	0.0838	0.0602	0.0311

The molecular dipole moments μ (experimental, and calculated as vector semisums of C_{ij} and C_{ij}^V) are listed in Table 2. As experimental values were not available for any whole series, some reference values were computed with program MOPAC-AM1. The reliability of AM1 results was tested with all the entries in Table 2 for which experimental data were available. AM1 calculations adequately reproduced the oscillatory behaviour of the experimental data, mimicking four minima (phenol, 2-phenyl-1-ethanol, aniline and 4-ethylaniline) and four maxima (benzyl alcohol, 3-phenyl-1-propanol, 4-methylaniline and 4-propylaniline). This test suggested that AM1 allows a good approximation, at least for the general performance of both homologous series, and that the error is sufficiently constant throughout the series. The number of compounds in both series was not increased because longer molecules are not percutaneous enhancers owing to their low transdermal penetration.

Table 2. Molecular dipole moment values, μ (D), for alcohols and amines calculated with charge-transfer indices.

Molecule	Number of carbon atoms in alkyl chain	Vector semisum	Valence vector semisum	Experimental ^a
phenol	0	0.737	2.431	1.400 (1.233 ^b)
benzyl alcohol	1	0.589	2.487	1.700 (1.568 ^b)
2-phenyl-1-ethanol	2	0.700	2.257	1.590 (1.497 ^b)
3-phenyl-1-propanol	3	0.573	2.519	1.640 (1.597 ^b)
4-phenyl-1-butanol	4	0.702	2.249	1.345 ^b
5-phenyl-1-pentanol	5	0.573	2.519	1.626 ^b

Table 2. Cont.

Molecule	Number of carbon atoms in alkyl chain	Vector semisum	Valence vector semisum	Experimental ^a
6-phenyl-1-hexanol	6	0.702	2.250	1.346 ^b
7-phenyl-1-heptanol	7	0.573	2.518	1.634 ^b
1-phenyl-2-propanol	3	0.923	2.347	1.564 ^b
2-phenyl-2-propanol	3	0.780	2.821	1.463 ^b
3-phenyl-2-propen-1-ol	3	0.561	2.495	1.591 ^b
1-phenyl-1-pentanol	5	0.426	2.794	1.746 ^b
1-phenyl-2-pentanol	5	0.895	2.367	1.496 ^b
aniline	0	0.655	0.792	1.560 (1.584 ^b)
4-methylaniline	1	0.079	1.526	1.640 (1.423 ^b)
4-ethylaniline	2	0.385	1.339	1.492 ^b
4-propylaniline	3	0.087	1.533	1.502 ^b
4-butylniline	4	0.398	1.333	1.511 ^b
4-pentylniline	5	0.093	1.533	1.489 ^b
4-hexylaniline	6	0.395	1.332	1.496 ^b
2-methylaniline	1	1.187	0.779	1.590 (1.560 ^b)
4-isopropylaniline	3	0.625	1.490	1.450 ^b
4-(1'-propenyl)aniline	3	0.108	1.512	1.512 ^b
1-aminonaphthalene	4	0.645	0.802	1.490 (1.690 ^b)
2-aminonaphthalene	4	0.655	0.792	1.820 (1.868 ^b)
4-cyclohexylaniline	6	0.480	1.126	1.760 (1.447 ^b)
4-aminobiphenyl	6	0.651	0.795	1.447 ^b

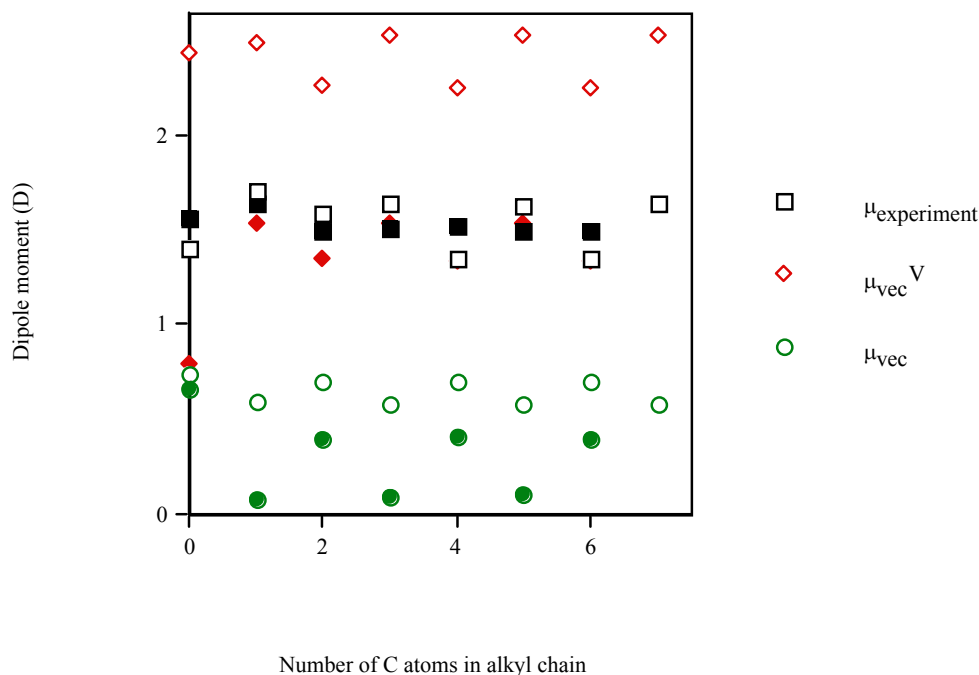
^a Taken from Reference 44.

^b Calculations carried out with program MOPAC-AM1.

In particular, 3-phenyl-2-propen-1-ol was chosen in order to compare the influence of a double bond in the alkyl chain region of a phenyl alcohol. The presence of the enol group (conjugated double bond in β -position with respect to the $-\text{OH}$ group) lent 3-phenyl-2-propen-1-ol to greater rigidity than for 3-phenyl-1-propanol. However, μ_{AM1} change was $<1\%$. For the three phenyl propanols (primary, secondary and tertiary alcohols), the primary alcohol 3-phenyl-1-propanol showed the greatest μ_{AM1} . For the three phenyl pentanols (primary, and α - and β -phenyl $-\text{OH}$ secondary alcohols), the primary alcohol 5-phenyl-1-pentanol presented a relatively large μ_{AM1} . On going from 4-propylaniline to 4-(1'-propenyl)aniline, the effect of the conjugated double bond on μ_{AM1} was again $<1\%$. For 2- and 4-methylaniline, the *para*-(4)-methylaniline showed the greatest $\mu_{\text{experiment}}$ but the smallest μ_{AM1} . For 4-propylaniline and 4-isopropylaniline, the more linear 4-propylaniline revealed the greatest μ_{AM1} . For 4-butylniline and both aminonaphthalenes, the rigid 2-aminonaphthalene displayed the greatest μ_{AM1} . For 4-hexylaniline, 4-cyclohexylaniline and 4-aminobiphenyl, the more linear 4-hexylaniline exhibited the greatest μ_{AM1} . Figure 1 illustrates how the dipole moment of both homologous series fluctuates with the number of C atoms in the alkyl chain, n . For either series, the experimental μ and calculated μ_{vec}^V vary together in an alternate fashion: for odd n , μ is greater than for even n . However, the

computed μ_{vec} presents the opposite tendency. The corresponding interpretation is that, as μ_{vec} is not sensitive to the electronic effect of either heteroatom, the steric (μ_{vec}) and electronic (μ_{vec}^V) factors are antagonistic, and the electronic effect dominates over the steric one. The $\mu_{\text{experiment}}$ decreases *ca.* 4% for either $n = 0 \rightarrow 6$ or $n = 1 \rightarrow 7$.

Figure 1. Dipole moment of phenyl alcohols (empty symbols) and 4-alkylanilines (filled symbols) as a function of the number of C atoms in alkyl chain.



The experimental dipole moments and CT indices were correlated for the homologous series. As $\mu_{\text{experiment}}$ for the 4-alkylanilines is almost constant ($\approx 1.5\text{D}$), especially for $n > 1$, it was represented by only one point in μ space. Therefore, the joint fit of phenyl alcohols and this point was performed. The best linear fit turned out to be:

$$\mu = 1.45 + 0.0906G_2 - 9.39J_4^V \quad (6)$$

$$N = 9 \quad r = 0.688 \quad \text{SD} = 0.115 \quad F = 2.7 \quad \text{MAPE} = 4.54\% \quad \text{AEV} = 0.5269$$

where MAPE is the mean absolute percentage error and AEV is the approximation error variance. All other models with greater MAPE and AEV were discarded, including those models counting the number of C atoms in the chain. The variables G_2 and J_4^V suggest the importance of electronic density distribution in the different compounds. The best quadratic model for μ turned out to be:

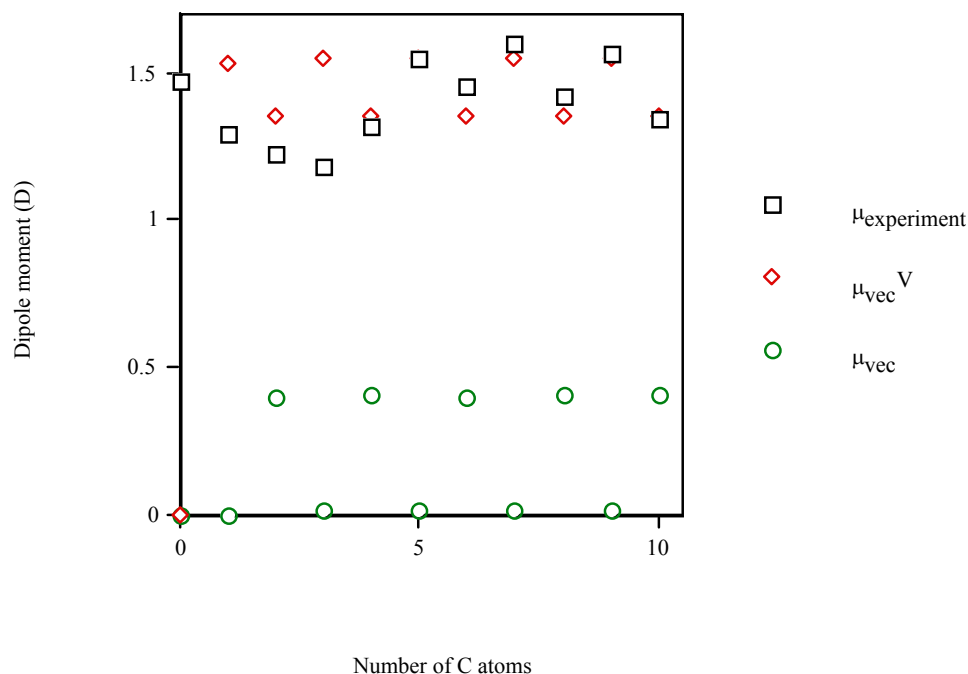
$$\mu = 17.0 - 12.8G_1^V + 2.60(G_1^V)^2 - 97.8(J_4^V)^2 \quad N = 9 \quad \text{MAPE} = 4.12\% \quad \text{AEV} = 0.5072 \quad (7)$$

and AEV decreased by 4%. The inclusion of μ_{vec} or μ_{vec}^V did not improve the fit.

As $\mu_{4\text{-alkylanilines}}$ is almost constant, a series of ammonia and 10 homologous aliphatic primary amines was chosen in order to compare the dipole moments [41]. Figure 2 shows how the dipole moment of the aliphatic amine series varies with the number of C atoms, n . In general, $\mu_{\text{experiment}}$ and μ_{vec}^V change together in an alternate fashion ($\mu_{\text{odd } n} > \mu_{\text{even } n}$) while $\mu_{\text{vec, odd } n} < \mu_{\text{vec, even } n}$. Again, the

steric and electronic factors are antagonistic, and the electronic effect dominates. Although $\mu_{\text{experiment}}$ decreases by 9% for $n = 0 \rightarrow 10$, it increases by 21% for $n = 1 \rightarrow 9$.

Figure 2. Dipole moment of ammonia and aliphatic amines as a function of the number of C atoms, n . Point $n = 9$ is AM1 calculation.



As $\mu_{4\text{-alkylanilines}}$ hardly varies, it represents only one point in the space of μ and the joint fit of the aliphatic amines and this point was performed. The best linear model for μ turned out to be:

$$\mu = 1.45 - 0.285G_1 - 0.162J_1^V + 32.6J_5^V \quad (8)$$

$$N = 12 \quad r = 0.879 \quad \text{SD} = 0.078 \quad F = 9.1 \quad \text{MAPE} = 3.60\% \quad \text{AEV} = 0.2291$$

and AEV decreased by 57%. The best quadratic model and the inclusion of μ_{vec} or μ_{vec}^V did not improve the correlation.

A comparative study was performed for each homologous series. For ammonia and the aliphatic amines, the best linear model for μ turned out to be:

$$\mu = 1.46 - 0.305J_1 + 2.17J_3 - 0.162G_1^V + 30.8J_5^V \quad (9)$$

$$N = 11 \quad r = 0.883 \quad \text{SD} = 0.086 \quad F = 5.3 \quad \text{MAPE} = 3.59\% \quad \text{AEV} = 0.2226$$

and AEV decreased by 58% from that in Equation (6).

No superposition of the corresponding G_k - J_k or G_k^V - J_k^V pairs is observed in Equations (6–9), which diminishes the risk of co-linearity in the fits, given the close relationship between each pair G_k - J_k in Equation (2) [42,43].

If the first point in Figure 2 (Equation 9) is omitted the best linear fit turns out to be:

$$\mu = 1.29 + 1.27G_3 - 2290J_4 - 0.602G_2^V + 0.584J_2^V + 4190J_5^V \quad (10)$$

$$N = 10 \quad r = 0.950 \quad \text{SD} = 0.069 \quad F = 7.3 \quad \text{MAPE} = 1.92\% \quad \text{AEV} = 0.1004$$

and AEV decreased 81%. Equation (10) is overfitted but it is given with the only purpose of showing that ammonia ($n = 0$), which is not an aliphatic amine, acts as a marginal outlier for Equation (9). The best quadratic model and the inclusion of μ_{vec} or μ_{vec}^V did not improve the correlation.

For the homologous phenyl alcohols, the best linear model turned out to be:

$$\mu = -0.799 + 0.364J_2^V + 0.871\mu_{\text{vec}}^V \quad (11)$$

$N = 8 \quad r = 0.930 \quad \text{SD} = 0.064 \quad F = 16.0 \quad \text{MAPE} = 2.59\% \quad \text{AEV} = 0.1351$

and AEV decreased by 74%. Equation (11) is overfitted but it is given with the purpose of justifying that $\mu_{4\text{-alkylanilines}}$ were represented by only one point in μ space in Equations (6–7). The best quadratic model did not improve the fit.

For the homologous 4-alkylanilines, the best linear model turned out to be:

$$\mu = 8.87 - 1.28G_2 + 1.43G_1^V \quad (12)$$

$N = 7 \quad r = 0.992 \quad \text{SD} = 0.009 \quad F = 118.1 \quad \text{MAPE} = 0.32\% \quad \text{AEV} = 0.0167$

and AEV decreased by 97%. Equation (12) is overfitted but it is given with the purpose of showing that $\mu_{\text{phenyl alcohols}}$ are difficult to fit due to their oscillating variation with the number of C atoms. The best quadratic model and the inclusion of μ_{vec} or μ_{vec}^V did not improve the correlation.

Conclusions

From the preceding results the following conclusions can be drawn:

1. Inclusion of the heteroatom in the π -electron system was beneficial for the description of the dipole moment, owing to either the role of the additional p orbitals provided by the heteroatom or the role of steric factors in the π -electron conjugation. The analysis of the electronic and steric factors in μ caused by the heteroatom showed that both factors are antagonistic, and that the electronic factor dominates over the steric one.
2. The conjugated double bond in the alkyl chain of 3-phenyl-2-propen-1-ol and 4-(1'-propenyl)-aniline lent to more rigid structures with dipole moment variations <1%.
3. Linear and quadratic correlation models were obtained for the molecular dipole moments of phenyl alcohols, 4-alkylanilines and aliphatic amines. μ_{vec}^V improved the multivariable regression equations for μ , diminishing the risk of co-linearity in the fit. Improvements in correlation suggest the general applicability of this index.

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