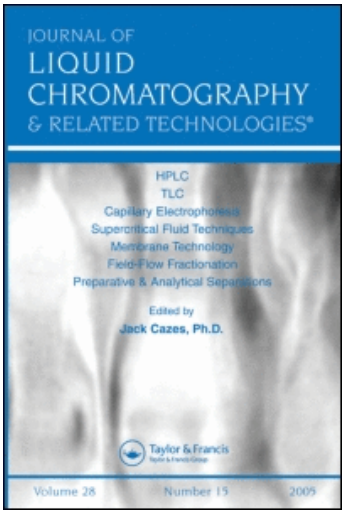

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Fractal Dimension of Transdermal-Delivery Drug Models: 4-Alkylanilines

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Abstract: The pathways that exist in porous membranes used to deliver drugs form *fractal* percolating paths. For a homologous series of 4-alkylanilines, the *fractal dimension D* is calculated as a model for transdermal-delivery drugs. Program TOPO is used for the calculation of the *solvent-accessible surface* AS, which is denoted by the centre of a probe, which is allowed to roll on the outside while maintaining contact with the *bare* molecular surface *S*. AS depends on the probe radius *R*. For 4-alkylanilines, the quadrupole moment Θ is doubled. The hydrophobic contribution to AS is doubled while its hydrophilic part remains constant. *D* increases 11%. Geometric descriptor and topological index results are in agreement with reference calculations. The 1-octanol-water partition coefficient $\log P$ increases. The molar concentration of organic compounds necessary to produce a 1:1 complex with bovine serum albumin *via* equilibrium dialysis, $\log 1/C$ increases. The hydrophile–lipophile balance (HLB) decreases. The linear correlation between *D* and Θ, and non-linear correlations between *D*, $\log P$, $\log 1/C$ and HLB point to a homogeneous molecular structure of the 4-alkylanilines. The comparison with phenyl alcohols shows that their greater dipole moments cause lower hydrophobicity.

Keywords: 4-alkylaniline, Fractal dimension, Percutaneous absorption, Percutaneous enhancer, Phenyl alcohol, Transdermal drug delivery

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INTRODUCTION

Given that the skin offers an excellent barrier to molecular transport, the rationale for transdermal drug delivery needs to be carefully identified.[1] During the last decades, there has been great interest in developing systems for controlled delivery of drugs and other bioactive substances.[2] A suggested technique was to join a specialized patch on the skin, which will deliver pre-specified and reproducible dosages over a wide spectrum of conditions and required durations of therapeutic treatment.[3] The simplest devised scheme utilized uncoated polymer matrices containing the embedded drug.[4] The pathways that exist in a porous membrane used to deliver drugs over a continuous period form a percolating path.[5] The pathways available for the delivery of the medication are usual fractal structures.[6] Several groups developed computational methods for predicting fluxes, including several models based on multiple regression methods.[7] Barry reviewed some selective ways for circumventing the *stratum corneum* barrier, all of which provide areas for future research.[8] There was a significant effort directed to finding new drug release systems in which bioactive molecules contained in a reservoir can be supplied to a host system while controlling the rate and period of delivery.[9] Pernaut and Reynolds performed a redox chemistry approach to the use of conducting electroactive polymers for drug delivery and sensing of bioactive molecules.[10]

Díez-Sales et al. proposed a drug-delivery system consisting of a specialized patch joined to the skin.[11] In previous papers, the dipole moment and valence topological charge-transfer indices of a homologous series of 4-alkylanilines were computed.[12] The fractal dimension of a homologous series of phenyl alcohols was evaluated.[13] In this work, the calculation of the fractal dimension for the 4-alkylanilines has been performed. The next section defines the geometric descriptors and topological indices, and presents the computational method. Following that the calculation results for electrostatic, geometric, topological and solvation descriptors of 4-alkylanilines are discussed. The last section summarizes the conclusions.

EXPERIMENTAL

In our program TOPO, molecular surface is represented by the external surface of a set of overlapping spheres with appropriate radii, centred on the atomic nuclei.[14] The molecule is defined by tracing spheres about the nuclei. It is computationally enclosed in a graduated rectangular box, and geometric descriptors evaluated by counting points within the solid or close to chosen surfaces. The molecular volume is concurrently

approximated as $V = P \cdot \text{GRID}^3$, where P is the number of points within the molecular volume and GRID is the size of the mesh grid. As a first approximation, the molecular *bare* surface area should be calculated as $S = Q \cdot \text{GRID}^2$, where Q is the number of points close to the bare surface. Two topological indices of molecular shape can be calculated: G and G'. Consider S_e as the surface area of a sphere whose volume is equal to the molecular volume. The ratio $G = S_e/S$ is interpreted as a descriptor of molecular globularity. The ratio $G' = S/V$ is interpreted as a descriptor of molecular *rugosity*.

The properties of solvated systems are strongly related to the contact surface between solute and solvent molecules.[15,16] The *solvent-accessible surface* AS is defined by means of a probe sphere, which is allowed to roll on the outside while maintaining contact with the molecular bare surface S.[17] AS can be calculated in the same way as S by means of

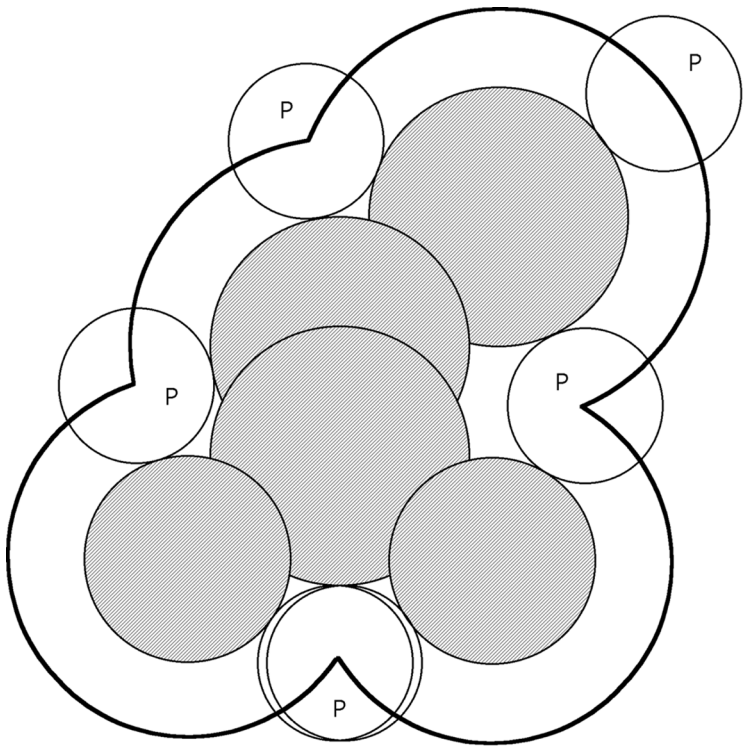

Figure 1. Molecular surface models for a set of spheres. The contour of the shaded area represents the bare molecular surface and the bold contour defines the solvent-accessible surface. Circles labelled "P" represent probe spheres simulating the solvent.

pseudoatoms, whose van der Waals radii have been increased by the probe radius R (cf. Fig. 1).[18] The *fractal dimension* D of the molecules may be obtained as[19]

$$D = 2 - \frac{d(\log A_s)}{d(\log R)}$$

D measures surface accessibility toward different solvents. TOPO analyzes D in its atomic contributions D_i, which are calculated as described above on each atom i. In order to calculate each D_i, a set of atomic contributions to $A_{s,i}$ are calculated with different probes. D_i can be averaged to obtain a new fractal dimension $D' = \left(\sum_i A_{s,i} D_i\right)/A_s$. D' represents an average for *non-buried* atoms. A version of TOPO has been implemented in programs AMYR[20] and GEPOL.[21]

RESULTS AND DISCUSSION

The fractal dimension and other descriptors have been calculated for homologous series of phenyl alcohols[13] and 4-alkylanilines, as models for drugs that can be administrated in a patch joined to the skin. Table 1 shows the dipole $\bar{\mu}$ and tensor quadrupole Θ moments calculated with our program POLAR for the 4-alkylanilines.[22] In the series, the dipole moment remains constant except for aniline, which is 2% greater. However, the mean quadrupole moment is doubled. The dipole and mean quadrupole moments fluctuate a little with the number of C atoms in the alkyl chain, n. The comparison of the results for phenyl alcohols and 4-alkylanilines shows that the former are more polar (μ *ca.* 1.7D) while the latter exhibit less polar character (μ *ca.* 1.1D in Table 1).

Table 2 lists the geometric descriptors for the 4-alkylanilines. The results for the molecular volume V are in agreement with reference

Table 1. Dipole (μ) and quadrupole (mean Θ and eigenvalues Θ_i) moments for 4-alkylanilines

Molecule	Number of C atoms in alkyl chain	μ [D]	Mean Θ [$D \cdot$ Å]	Θ_1 [$D \cdot$ Å]	Θ_2 [$D \cdot$ Å]	Θ_3 [$D \cdot$ Å]
aniline	0	1.116	4.799	8.229	6.168	0.000
4-methylaniline	1	1.090	6.033	10.566	6.850	0.683
4-ethylaniline	2	1.093	7.174	12.158	7.526	1.838
4-propylaniline	3	1.085	8.407	14.540	8.201	2.479
4-butylaniline	4	1.097	9.540	16.147	8.880	3.594
4-pentylaniline	5	1.086	10.767	18.565	9.556	4.180
4-hexylaniline	6	1.098	11.944	20.316	10.231	5.285

Table 2. Geometric descriptors for 4-alkylanilines. Reference calculations performed with program GEPOL

Molecule	Volume [Å^3]	V ref. [Å^3]	Surface [Å^2]	S ref. [Å^2]	Water accessible surface [Å^2]	AS ref. [Å^2]	Hydrophobic AS [Å^2]	Hydrophilic AS [Å^2]	Side-chain AS [Å^2]	AS′ ref. [Å^2]
aniline	98.4	99.1	123.17	127.17	247.20	250.70	171.07	76.13	568.84	572.38
4-methylaniline	114.0	114.7	141.78	147.28	274.29	278.92	198.78	75.51	612.95	617.60
4-ethylaniline	129.5	130.4	160.61	167.29	300.26	305.78	225.31	74.95	651.86	658.12
4-propylaniline	145.1	146.1	179.14	187.56	328.69	335.53	253.65	75.04	699.67	704.16
4-butylaniline	160.5	161.7	198.81	207.56	357.45	364.83	282.20	75.25	744.80	751.57
4-pentylaniline	176.1	177.4	217.64	227.60	386.01	394.42	310.44	75.57	789.81	798.07
4-hexylaniline	191.6	193.0	237.35	247.75	415.09	424.11	339.64	75.45	837.35	845.44

calculations performed with GEPOL (error *ca.* −0.7%). Although the errors for the molecular surface areas are greater (i.e., −4% for the bare molecular surface area *S*), this error drops for the water-accessible surface area AS (−2%) and even for the side-chain accessible surface area AS′ (−0.8%). The comparison between GEPOL and TOPO is of great interest because the former does not perform an atom-to-atom analysis of the geometric descriptors of the molecule. For instance, the partition of the accessible surface area AS shows that its hydrophobic term HBAS trebles the hydrophilic component part HLAS. In the series, *V* and *S* are doubled, while the side-chain accessible-surface area AS′ increases 47%. As expected, the increase in the water accessible-surface area AS is due to HBAS, which is doubled, while HLAS remains almost constant.

Table 3 reports the topological indices for the 4-alkylanilines. In the series, the molecular globularity *G* decreases 19%, molecular rugosity *G′* remains almost constant, fractal dimension *D* increases 11% and fractal dimension averaged for non-buried atoms *D′* increases 13%. On going from *D* to *D′*, the $D - D'$ increment rises from 2% to 4% in the series. This indicates the presence of more buried atoms in 4-hexylaniline. The comparison with the results for the phenyl alcohols shows that index *G′* distinguishes quantitatively these (*G′ ca.* 1.20Å^{-1}) from 4-alkylanilines (*G′ ca.* 1.24Å^{-1}).

Table 4 resumes the solvation descriptors for the 4-alkylanilines calculated with SCAP.[23] In the series, minus Gibbs free energy of solvation in water $\Delta G^0_{\mathrm{solv,w}}$ decreases and minus $\Delta G^0_{\mathrm{solv,o}}$ in 1-octanol increases. Therefore, the 1-octanol-water partition coefficient $\log P$ increases. This is caused by the augmentation of HBAS through Table 2. Notice that for values of $\log P > 3$, more than 99.9% of the solute is in the organic phase. Therefore, most results predict a negligible quantity of solute in the aqueous phase. In the series, the molar concentration of organic compounds necessary to produce a 1:1 complex with bovine serum albumin (BSA) *via* equilibrium dialysis, $\log 1/C$ increases. On the other hand, the hydrophile–lipophile balance (HLB) decreases in the series. These trends are in line with reference calculations performed with a method developed by Kantola et al.[24] The comparison with the results for the phenyl alcohols shows that these are less hydrophobic ($\log P$ in the range 0.6–7.9) than the 4-alkylanilines ($\log P$ 1.4–8.5). This is in agreement with the less negative $\Delta G^0_{\mathrm{solv,w}}$ and the smaller dipole moment of the 4-alkylanilines (Table 1).

A linear model for the molecular quadrupole moment of the 4-alkylanilines vs. fractal dimension gives:

$$\Theta = -61.3 + 55.2D \quad r = 0.993 \tag{1}$$

Table 3. Topological indices for 4-alkylanilines. Reference calculations performed with program GEPOL

Molecule	Molecular globularity	G ref.	Molecular rugosity ($Å^{-1}$)	G' ref. ($Å^{-1}$)	Fractal dimension of the solvent-accessible surface	D ref.	D averaged for non-buried atoms
aniline	0.837	0.814	1.251	1.283	1.191	1.199	1.217
4-methylaniline	0.802	0.775	1.244	1.284	1.220	1.229	1.255
4-ethylaniline	0.771	0.743	1.241	1.283	1.249	1.256	1.290
4-propylaniline	0.745	0.715	1.235	1.283	1.267	1.280	1.310
4-butylaniline	0.719	0.692	1.238	1.284	1.286	1.299	1.337
4-pentylaniline	0.698	0.671	1.236	1.283	1.305	1.316	1.359
4-hexylaniline	0.677	0.652	1.239	1.283	1.320	1.330	1.374

Table 4. Solvation descriptors for 4-alkylanilines. Reference calculations performed with a method by Kantola et al.

Molecule	Water ΔG^0_{solv} [a] ($kJ \cdot mol^{-1}$)	1-Octanol ($kJ \cdot mol^{-1}$)	ΔG^0_{solv} log P^b	log P ref.	log$(1/C)^c$	log $(1/C)$ ref.	Hydrophile-lipophile balance	HLB ref.	Cavity volume in water (Å^3)
aniline	−14.59	−22.36	1.36	2.67	3.32	4.30	5.87	4.79	595.4
4-methylaniline	−9.50	−28.16	3.28	3.11	4.76	4.63	4.28	4.42	957.7
4-ethylaniline	−7.84	−32.52	4.34	3.33	5.55	4.80	3.41	4.24	1107.2
4-propylaniline	−6.39	−36.95	5.37	3.52	6.33	4.94	2.55	4.08	1234.0
4-butylaniline	−4.96	−41.42	6.40	3.73	7.10	5.10	1.69	3.91	1362.7
4-pentylaniline	−3.52	−45.93	7.45	3.94	7.89	5.26	0.82	3.73	1485.1
4-hexylaniline	−2.05	−50.45	8.50	4.14	8.68	5.41	−0.05	3.57	1633.5

[a]Gibbs free energy of solvation.
[b]P is the 1-octanol/water partition coefficient.
[c]C is the molar concentration necessary to produce a 1:1 complex with BSA via equilibrium dialysis.

Non-linear models for $\log P$, $\log 1/C$ and HLB of the 4-alkylanilines vs. fractal dimension result:

$$\log P = -4.15 - 39.1D + 36.8D^2 \quad r = 0.998 \tag{2}$$

$$\log 1/C = 0.613 - 31.6D + 28.5D^2 \quad r = 0.998 \tag{3}$$

$$\text{HLB} = 8.04 + 36.2D - 32.0D^2 \quad r = 0.998 \tag{4}$$

The best linear model for the fractal dimension of the 4-alkylanilines vs. different physicochemical parameters results:

$$\begin{gathered} D = 1.35 + 0.0000161 V_W^{\text{cav}} + 0.00858V - 0.00409\text{AS} \quad \text{MAPE} = 0.05\% \\ \text{AEV} = 0.0003 \quad n = 7 \quad r = 0.9998 \quad SD = 0.001 \quad F = 3113.9 \end{gathered} \tag{5}$$

where V_W^{cav} is the volume of the hydration cavity. The mean absolute percentage error (MAPE) is 0.05% and the approximation error variance (AEV) is 0.0003. The best non-linear model for the fractal dimension gives:

$$\begin{aligned} D = {} & 2.72 - 0.00153\text{AS}' + 0.177\Delta G^0_{\text{solv,w}} - 0.000131\text{AS}' \cdot \Delta G^0_{\text{solv,w}} \\ & + 0.00391(\Delta G^0_{\text{solv,w}})^2 \\ & \text{MAPE} = 0.02\% \quad \text{AEV} = 0.0001 \end{aligned} \tag{6}$$

and AEV decreases 67%.

CONCLUSIONS

From the preceding results the following conclusions can be drawn.

1. The method offers an accurate, stable, spatially invariant and fast algorithm to obtain the fractal dimension of the solvent-accessible surface.
2. The difference between both fractal indices D' and D increases in both phenyl alcohol and 4-alkylaniline series. The difference $D' - D$ is a sensitive method to elucidate the occurrence of atoms that are hidden to the solvents in the range of sizes used to calculate D and D'.
3. The linear correlation between D and Θ, and non-linear correlations between D, $\log P$, $\log 1/C$ and HLB point not only to homogeneous molecular structures of the phenyl alcohols and of 4-alkylanilines but also to the ability to predict and tailor drug properties. The latter is nontrivial in pharmacology.
4. The comparison 4-alkylanilines/phenyl alcohols shows that the smaller polar character of the former causes their less negative $\Delta G^0_{solv,w}$ and greater hydrophobicity. Both series are distinguished by molecular rugosity G'.

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