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SOLVENT-ACCESSIBLE SURFACE AREA AS A PREDICTOR OF LOCAL ANESTHETIC ACTIVITY

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ABSTRACT—Quantitative structure-activity relationships (QSAR) for local anesthetics often contain experimental properties such as octanol-water partition coefficients or carbon adsorptivities. Solvent-accessible surface areas, calculated using PM3 semiempirical quantum mechanical methods and the Conductor-Like Screening Model (COSMO), alone and in combination with other calculated properties, also can serve as good predictors of anesthetic activity, as measured by the logarithm of the minimum blocking concentration (log MBC) values. For sets of 18 and 37 structurally diverse molecules, solvent-accessible surface areas produce better fits than other indicators of size and allow the effects of size on anesthetic activity to be distinguished from other factors, such as shape or other receptor-specific interactions. In addition, these calculated areas require no new laboratory work and can be related to anesthetic activity by consideration of adsorption effects.

A wide range of compounds can function as local anesthetics, making description of the receptor difficult. Recent reviews (Franks and Lieb, 1994; Gupta, 1991) identify many properties that correlate with anesthetic potency, including experimental properties such as the disruption of voltage and ligand-gated ion channels, octanol-water partition coefficients (log P), and Hammett-constant substituent effects and structural descriptors such as molecular volumes (Famini et al., 1991), connectivity indices (Kier et al., 1975; Kier and Hall, 1983), polarizability (Agin et al., 1965), and molar refractivity. The protein/water and lipid/water interfaces play essential roles in anesthetic effectiveness, and have been modeled with activated carbon (Abe et al., 1988), synthetic membranes (Okohata & Ebato, 1991; Shimooka et al., 1992), and molecular dynamics simulations (Chipot et al., 1997).

Models that account for both molecular size and electrostatic effects, such as the Molecular Transform (King et al., 1990) and the Theoretical Linear Solvation Energy Relationship (TLSER) (Famini et al., 1991), have produced good results. Hydrogen-bond formation or disruption may sometimes be involved (Hobza et al., 1981; Hobza et al., 1982; Hansch and Leo, 1995*b*). Local anesthetics destabilize membranes, increasing their water permeability (Shimooka et al., 1992), and they also increase the cytoplasmic space between membranes, which changes the speed of nerve impulse conduction (Mateu, 1997). Local anesthetic molecules must be hydrophilic enough to be transported to the active site yet hydrophobic enough (and favorably charged) to adsorb and act (Strichartz & Berde, 1994). Clinical local anesthetics (such as lidocaine and procaine) typically contain a lipophilic aromatic ring, a hydrophilic tertiary amine, and an ester or amide linkage (Strichartz and Berde, 1994). Although they are usually cationic at physiological pH, the lipid membrane may select the unionized form (Strichartz and Berde, 1994). Gupta (1991) suggested the possibility of separate sites of action for the charged and neutral species. Most recently, a groundbreaking study traced the action of alcohols and volatile anesthetics on GABA and glycine receptors to two specific amino acid residues, paving the way for description of at least one receptor site (Mihic et al., 1997). The broad spectrum of anesthetic activity points to a two-stage model; factors such as size and log P, which do not depend on receptor specificity, express the ability of a molecule to make it to the site, and only after these factors are taken into account and the drug reaches the site do receptor-specific charge and steric factors cause greater activity. The existence of specific interactions does not negate the importance of traditional non-specific factors.

Abe, Kamaya, and Ueda (1988) showed that the logarithm of the minimum blocking concentration (log MBC) of 18 local anesthetics was better correlated by the logarithm of carbon surface adsorption (log a, correlation coefficient $r = 0.994$) than by the traditional fit based on the log of the octanol-water partition coefficient (log P, $r = 0.899$). In using carbon adsorptivity, their work substituted one experimentally determined property for another in correlating log MBC. Our objective was to explore the effectiveness of calculated solvent-accessible surface area as a predictor of anesthetic potency. Molecular solvent-accessible surface area (Connolly, 1985; Hermann, 1977; Richards, 1977; Silla et al., 1991; Klamt and Schüürmann, 1993; Pacios, 1994; Ishikawa et al., 1995) offers the advantage of being a calculated property, eliminating further, sometimes extensive, experimental property determination. We used solvent-accessible surface area alone and in combination with other calculated properties for the Abe, Kamaya, and Ueda (1988) set of 18 molecules and further tested these relationships for larger sets of 37 and 39 molecules (Agin et al., 1965). The Quantitative Structure-Activity Relationships (QSAR) obtained in this work allowed us to quantify the importance of molecular size as measured by solvent-accessible surface area in local anesthetic activity.

COMPUTATION METHODOLOGY

Table 1 lists the full set of 39 molecules and their log MBC values available for this study. The subset of 18 molecules used

TABLE 1. Local anesthetic potencies and solvent-accessible surface areas.

	Drug	S (Å²)	Log MBC (mM)[a]
1	Methanol[b]	34.69	3.09
2	Ethanol[b]	43.04	2.75
3	Acetone[b]	48.73	2.60
4	2-propanol[b]	49.46	2.55
5	1-propanol[b]	50.22	2.40
6	Urethane	60.87	2.00
7	Diethyl ether[b]	59.69	1.93
8	1-butanol[b]	57.67	1.78
9	Antipyrene	98.16	1.78
10	Pyridine[b]	57.64	1.77
11	Chloroform	64.70	1.55
12	Hydroquinone	66.41	1.40
13	Aniline[b]	63.97	1.30
14	Benzyl alcohol	69.36	1.30
15	Acetanilide	81.24	1.17
16	1-pentanol[b]	65.91	1.20
17	Phenol[b]	62.59	1.00
18	Toluene[b]	65.45	1.00
19	Benzimidazole	71.52	0.80
20	1-hexanol[b]	73.25	0.56
21	Nitrobenzene[b]	70.75	0.47
22	Quinoline	77.34	0.30
23	8-OH quinoline	80.70	0.30
42	1-heptanol	80.89	0.20
25	2-napthol	81.25	0.00
26	Methyl anthranilate	83.52	0.00
27	1-octanol	88.62	−0.16
28	Thymol	86.52	−0.52
29	O-phenanthroline	94.25	−0.80
30	Ephedrine	91.89	−0.80
31	Procaine[b]	125.59	−1.67
32	Lidocaine[b]	121.06	−1.96
33	Diphenhydramine	134.55	−2.80
34	Tetracaine[b]	142.63	−2.90
35	Phenyltoloxamine	136.65	−3.20
36	Quinine	146.14	−3.60
37	Eserine	128.06	−3.66
38	Caramiphen	152.44	−4.00
39	Dibucaine[b]	173.64	−4.20

[a] Gupta, S. P. 1991
[b] Set of 18; Abe, I., H. Kamaya, and I. Ueda, 1988.

by Abe et al. (1988) is indicated. The solvent-accessible surface areas (S) shown in Table 1 were calculated using CAChe version 3.9 Project Leader software (Fujitsu, www.cache.fujitsu.com). The procedure used to calculate S first optimizes the molecule using molecular mechanics with Augmented MM2 parameters, then calculates areas using the semiempirical quantum mechanical program MOPAC with PM3 parameters and the Conductor-like Screening Model (COSMO) (Klamt and Schüürmann, 1993). COSMO calculates solvent-accessible surface areas by rolling a "probe sphere" about the molecule of interest and quantifying the resultant disturbance in the solvent dielectric. The default probe sphere values roughly approximate water, keeping water's dielectric constant of 78.40, but reducing the effective radius to 1.0 Å. Although the areas generated tend to be smaller in absolute terms than other literature solvent-accessible surface areas (which may be defined in various ways, such as Connolly, 1985; Hermann, 1977; Richards, 1977; Silla et al., 1991; Klamt and Schüürmann, 1993; Pacios, 1994; Ishikawa et al., 1995), we verified that CAChe-generated COSMO areas for six alkanes and seven alcohols correlate linearly (r = 1.000) with other solvent-accessible surface area values (Silla et al., 1991; Hermann, 1972).

Molar refractivities (MR) were calculated using the CAChe-implemented additive method. For the subset of 18, the log P values (averages of known experimental log P) of Abe et al. (1988) were used; however, the larger sets of 37 or 39 molecules used Hansch and Leo's (1995*a*) "best" experimental log P values. Differences between the two sets of log P values were minimal.

Results and Discussion

Table 2 lists several correlations for the Abe et al. (1988) set of 18 molecules. Notice that solvent-accessible surface area (S) provides a better single parameter fit (r = 0.990) than the traditional experimental value of log P (r = 0.899) and is almost as good as the Abe et al. (1988) log a (r = 0.994) fit, which requires extensive additional experimental determinations of carbon adsorption. Since measures of molecular surface area are significant correlates of adsorption on carbon, it is not surprising this calculated property can be used in place of log adsorptivity, log a, to predict log MBC. Since a carbon surface was previously considered to mimic a lipid/protein surface (Abe et al., 1988), it is reasonable to directly relate log MBC to S.

Even for this small set, S provides some improvement over another property, molecular weight (MW). While molar refractivity (MR) improves on S, it also includes implicit information on the polarizability of the molecule. Although adding an indicator for carbonyl groups (#C=O) improved the correlation slightly, adding a similar indicator for the number of nitrogen atoms had a statistically insignificant effect, and, thus, the additional variable was dropped. Combining log P values with S gives a correlation nearly as good as that of carbon adsorptivity, though the reduced F value clearly shows the effect of an additional variable.

A more structurally diverse set of 39 molecules confirmed our relationships for S alone and in combination with #C=O, yielding the following correlations:

$$\log \text{MBC} = -0.058(\text{S}) + 5.123 \qquad r = 0.963 \qquad F = 473$$

$$\log \text{MBC} = -0.062(\text{S}) + 0.611(\#\text{C=O}) + 5.277 \qquad r = 0.970 \qquad F = 291$$

Again, S provided an improvement over other strictly size-related measures, including a previous molar volume correlation on the same set with an r = 0.962 (Ishikawa et al., 1995). There were two clear outliers to the set, however. Nitrogens have always been recognized as significant to anesthetic activity; although the number of nitrogens was not a significant second variable (with solvent-accessible areas), it was significant on its own. Antipyrene was the only molecule with two nitrogens bonded to one another, thus altering the effect on size that each nitrogen has as well as altering any receptor-specific effects. It showed lower than expected activity. Eserine, on the other hand, was the only

TABLE 2. Selected correlations for the set of 18 molecules

Variables[a]	r^b	F^c	Equation
Log P	0.899	68	log MBC = −1.403(log P) + 2.558
MW	0.989	732	log MBC = −0.024(MW) + 3.577
S	0.990	762	log MBC = −0.054(S) + 4.859
MR	0.991	890	log MBC = −0.079(MR) + 3.576
S, #C=O	0.992	450	log MBC = −0.058(S) + 0.455(#C=O) + 5.047
S, log P	0.994	656	log MBC = −0.045(S) − 0.291(log P) + 4.561
Log a	0.994	1234	log MBC = −1.086(log a) + 1.500

[a] Log P is log octanol-water partition coefficient; MW is molecular weight; S is solvent-accessible surface area; MR is molar refractivity; #C=O is number of carbonyl groups; log a is log of activated carbon adsorptivity (Abe, I., H. Kamaya, and I. Ueda, 1988).

[b] Correlation coefficent.

[c] F value for full regression.

molecule to have its nitrogens conformationally restricted, and it had higher than expected activity. For further exploration of this set, we omitted these two outliers.

The correlations for this set of 37 molecules are shown in Table 3. The previous correlations are validated for this set. This set contains much more variety with respect to carbonyl groups than the smaller set of 18. Whereas #C=O alone for the set of 18 molecules showed $r = 0.729$, this decreased to $r = 0.339$ for the set of 37 molecules, yet #C=O remained a significant (partial P value of 0.0003) second correlation variable. Also, for this more varied set, S was nearly as good a correlate as MR despite the latter's inclusion of polarizability information.

Local anesthetic activity seems to be an adsorption phenomenon, an interfacial interaction between the surface of the site of action (lipid or protein) and the molecular surface of the anesthetic. The best possible description of the anesthetic's molecular surface is to be preferred, and solvent-accessible surfaces may be indicative of the actual molecule/environment interface. Solvent-accessible surface areas give better fits than other variables we have tried such as molecular weight, number of carbons, and molar volume because adsorption is better modeled by a molecule's surface area. More structurally varied sets show the most improvement with S. Although the size-based connectivity indices give fits insignificantly different from S, their exact meaning is unclear. Although MR and polarizability correlate well with log MBC values, it is difficult to separate the size effects from the electrostatic/charge element of the fit.

We tried many combinations of factors, and each fit was overwhelmingly size-based ($r = 0.985$ for log MBC versus S, set of 37). Local anesthetic action seems to be controlled by two factors: the size of the adsorbate molecule and some charge-related quality that reflects the ability to act at the receptor site. The first factor concerns the non-receptor specific actions, and the latter may come into play as more is discovered about specific sites of action. While some recent work has sought the elusive "receptors" for anesthesia, it also is important to understand non-specific aspects of anesthetic activity. This work supports the understanding that the non-specific action of local anesthetics is an adsorption phenomenon and can be quantified in terms of molecular size based on the solvent-accessible surface area. We have shown that calculated values of solvent-accessible surface area can be used in place of experimental anesthetic-carbon adsorption values to provide correlations of anesthetic minimum blocking concentrations.

TABLE 3. Selected correlations for the set of 37 molecules.[a]

Variables[b]	r^c	F^d	Equation
Log P	0.832	74.4	log MBC = −1.244(log P) + 2.393
MW	0.926	211	log MBC = −0.024(MW) + 3.7
S	0.985	1115	log MBC = −0.058(S) + 5.048
MR	0.985	1146	log MBC = −0.080(MR) + 3.586
S, log P	0.986	597[e]	log MBC = −0.050(S) − 0.224(log P) + 4.784
S, #C=O	0.990	811	log MBC = −0.061(S) + 0.508(#C=O) + 5.162

[a] Set of 39 minus antipyrene and eserine.

[b] MW is molecular weight; S is solvent-accessible surface area; MR is molar refractivity; log P is log octanol-water partition coefficient (Hansch, C. and A. Leo, 1995); #C=O is number of carbonyl groups.

[c] Correlation coefficient.

[d] F value for full regression.

[e] Two missing values.

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