states that anesthesia occurs when the volume of a hydrophobic region is caused to expand beyond a certain critical amount by the absorption of molecules of an inert substance. These results also are in agreement with a previous study of a mixed group of anesthetics (5) for which a size effect interpretation was proposed. More structure–activity studies of anesthetics are being completed to generalize these findings.

REFERENCES

(1) J. C. Miller and K. W. Miller, in "MTP International Review of Science, Biochemistry Series One," vol. 12, H. K. F. Blaschko, Ed., Butterworths, University Park Press, Baltimore, Md., 1975, p. 33.

(2) K. W. Miller, W. D. M. Paton, E. B. Smith, and R. A. Smith, *Anesthesiology*, **36**, 339 (1972).

(3) C. Hansch, A. Vittoria, C. Silipo, and P. Y. C. Jow, *J. Med. Chem.*, **18**, 546 (1975).

(4) W. R. Glave and C. Hansch, *J. Pharm. Sci.*, **61**, 589 (1972).

(5) T. Di Paolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, **13**, 31 (1977).

(6) D. F. Marsh and C. D. Leake, *Anesthesiology*, **11**, 455 (1950).

(7) L. B. Kier and L. H. Hall, "Molecular Connectivity in Chemistry and Drug Research," Academic, New York, N.Y., 1976.

(8) C. Hansch and J. M. Dayton, *J. Pharm. Sci.*, **62**, 1 (1973).

(9) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

Molecular Connectivity in Quantitative Structure–Activity Relationship Study of Anesthetic and Toxic Activity of Aliphatic Hydrocarbons, Ethers, and Ketones

THÉRÈSE Di PAOLO

Received April 11, 1977, from the *Massachusetts College of Pharmacy, Boston, MA 02115.* Accepted for publication June 10, 1977. Present address: Department of National Defence, DMFR-4, Ottawa, Ontario, K1A 0K2, Canada.

Abstract □ The nonempirical molecular connectivity indexes of 27 aliphatic hydrocarbons, ethers, and ketones were calculated. Very good correlations were obtained between anesthetic (AD_{100}) and toxic (LD_{100} and LD_{50}) activities of these compounds and their molecular connectivity indexes. These quantitative structure–activity relationships are discussed briefly in the light of general anesthesia theories.

Keyphrases □ Molecular connectivity indexes—various aliphatic hydrocarbons, ethers, and ketones, related to anesthetic activity and toxicity □ Structure–activity relationships—various aliphatic hydrocarbons, ethers, and ketones, anesthetic activity and toxicity related to molecular connectivity indexes □ Anesthetics—various aliphatic hydrocarbons, ethers, and ketones, activity related to molecular connectivity indexes □ Toxicity—various aliphatic hydrocarbons, ethers, and ketones, related to molecular connectivity indexes □ Topological indexes—mclecular connectivity, various aliphatic hydrocarbons, ethers, and ketones, related to anesthetic activity and toxicity

Molecular connectivity is a method of quantitating the topological structure of organic molecules. This method derives numerical descriptors encoded with information about the number and kind of atoms and their bonding relationships to each other. It has been used successfully to arrive at structure–activity relationships with many classes of biological agents (1).

In a previous study with a mixed group of anesthetics, an excellent correlation was obtained between the relative anesthetic potency and a molecular connectivity term in addition to a term for the charge on the polar hydrogens (2).

To test further the validity of these findings and to gain more information for the interpretation of these results, structure–activity relationships of 27 anesthetic aliphatic hydrocarbons, ethers, and ketones were studied. Anesthetic and toxicity data for this group of molecules had been measured previously (2), and confidence limits of the experimental values are given. In this group, the polarity of the hydrogens does not vary much, so the effect of this factor on activity is fairly constant. In going to higher congeners of each alkane, ether, and ketone, the anesthetic and toxic activity increases, reaches a maximum, and then decreases. A parabolic relationship was found between the activity and the logarithm of the octanol–water partition coefficient or the molecular weight (3).

This group of compounds is a good example of nonlinear structure–activity relationships and will broaden the study of anesthetic activity. Since there are many measurements beyond the maximum, it can be determined accurately whether the structure–activity relationship is parabolic. Previous work on a series of ethers could not confirm this hypothesis (4).

EXPERIMENTAL

Molecular connectivity indexes were calculated, in the usual manner (1), for the molecules in Tables I and II and statistically analyzed with a system of programs developed to find the best set of variables.

The anesthetic (AD_{100}) and toxic (LD_{50} and LD_{100}) activities of the compounds studied are those of Jeppsson (3). The alkanes, ethers, and ketones were dissolved in an emulsion and administered intravenously to mice. The confidence limits given at $p = 0.05$ for the experimental data were used to compute the experimental standard error. Expressed as log $1/c$, these are values 0.17 for the AD_{100} activity and 0.13 and 0.06 for LD_{100} and LD_{50} activities, respectively.

RESULTS

The statistical analysis shows that ${}^1\chi$ and ${}^4\chi_p{}^v$ are the best connectivity terms to correlate with the AD_{100} anesthetic activity. The following equation was formulated from the data in Table I:

$$\log {}^1/c' = +2.895\ (\pm 0.324) - \frac{8.539\ (\pm 0.875)}{{}^1\chi} - 1.487\ (\pm 0.114){}^4\chi_p{}^v \quad \text{(Eq. 1)}$$

$$r = 0.943 \quad s = 0.170 \quad n = 27$$

$$F = 96.5,\ p < 0.001$$

Table I—AD_{100} Values for Loss of Righting Reflex of Mice by Aliphatic Hydrocarbons, Ethers, and Ketones

Compound	$^1\chi$	$^4\chi_p^v$	$-\log 1/c'$ Obs.[a]	$-\log 1/c'$ Calc.[b]	$\lvert\Delta \log 1/c'\rvert$
Pentane	2.414	0.354	1.052	1.167	0.115
Hexane	2.914	0.500	0.941	0.777	0.164
Heptane	3.414	0.677	0.458	0.614	0.156
Octane	3.914	0.854	0.391	0.552	0.161
Nonane	4.414	1.030	0.428	0.575	0.147
Decane	4.914	1.207	0.613	0.633	0.020
Undecane	5.414	1.384	0.810	0.743	0.067
Dodecane	5.914	1.561	1.124	0.869	0.255
Tridecane	6.414	1.737	1.119	1.020	0.099
Tetradecane	6.914	1.914	1.294	1.189	0.105
Pentadecane	7.414	2.091	1.516	1.367	0.149
Hexadecane	7.914	2.268	1.566	1.554	0.012
Heptadecane	8.414	2.444	1.538	1.755	0.217
Ethyl ether	2.414	0.204	1.036	0.944	0.092
Propyl ether	3.414	0.391	0.305	0.188	0.117
Butyl ether	4.414	0.595	0.104	−0.072	0.176
Pentyl ether	5.414	1.010	0.297	0.187	0.110
Hexyl ether	6.414	1.364	0.535	0.465	0.070
Heptyl ether	7.414	1.717	0.869	0.811	0.058
Octyl ether	8.414	2.071	1.188	1.201	0.013
3-Pentanone	2.808	0.250	0.657	0.517	0.140
4-Heptanone	3.808	0.683	0.121	0.366	0.245
5-Nonanone	4.808	0.873	−0.081	0.179	0.260
6-Undecanone	5.808	1.269	0.076	0.461	0.385
7-Tridecanone	6.808	1.623	0.978	0.774	0.204
8-Pentadecanone	7.808	1.976	1.127	1.136	0.009
9-Heptadecanone	8.808	2.330	1.455	1.543	0.088

[a] From Ref. 3; drug dose in millimoles per kilogram. [b] Calculated using Eq. 1.

where c' is the AD_{100} millimolar concentration of the anesthetic. This equation accounts for 89% (r^2) of the variance in $\log 1/c'$, and the standard deviation is at the level of experimental error.

The analysis for the toxic doses LD_{100} (c'') and LD_{50} (c''') of Table II led to the following equations:

$$\log 1/c'' = +3.903\ (\pm 0.442) - 1.195\ (\pm 0.097)^3\chi_p^v - \frac{17.77\ (\pm 1.81)}{^0\chi^v} \quad \text{(Eq. 2)}$$

$$r = 0.938 \quad s = 0.173 \quad n = 27$$

$$F = 87.3,\ p < 0.001$$

$$\log 1/c''' = +3.188\ (\pm 0.385) - 3.246\ (\pm 0.345)^6\chi_p^v - \frac{16.57\ (\pm 1.74)}{^0\chi^v} \quad \text{(Eq. 3)}$$

$$r = 0.941 \quad s = 0.149 \quad n = 15$$

$$F = 46.6,\ p < 0.001$$

For the LD_{100} toxicity, Eq. 2 accounts for 88% (r^2) of the variance in $\log 1/c''$, and the standard deviation is close to the experimental error. For the LD_{50} toxicity, Eq. 3 accounts for 89% (r^2) of the variance, and the standard deviation is larger than that experimentally calculated.

Nonlinear relationships were obtained in these three cases with different connectivity terms.

DISCUSSION

Equation 1, correlating the AD_{100} activity, contains $^1\chi$ and $^4\chi_p^v$. As shown in Table I, both these terms increase as the molecules become larger. When comparing the connectivity term values in Eq. 1, it is seen that $^1\chi$ is the important factor for the smaller congeners of these molecules up to a maximum and then $^4\chi_p^v$ becomes the main factor for the larger congeners. No parabolic relationship with connectivity terms gave as good results as these two terms.

Jeppsson (3) fitted parabolic relationships with log P and the molecular weights with these anesthetic activities. He did not group each class of molecules for his correlations but studied them in separate classes. To compare the present results with those of Jeppsson, the parabolic relationship with log P was calculated for the whole set to give $r = 0.814$, $s = 0.296$, $n = 27$, and $F = 23.6$; with the molecular weights, the values were $r = 0.762$, $s = 0.331$, $n = 27$, and $F = 16.6$. Clearly, the correlation with the connectivity terms is superior.

These results are also consistent with previous findings for a group of ethers (4) where the scarcity of points past the maximum did not permit a choice between an inverse or a parabolic relationship with $^1\chi$.

The equations correlating the LD_{100} and LD_{50} activities show similar dependence as functions of connectivity terms compared to Eq. 1 for AD_{100}. For smaller congeners, $^0\chi^v$ is the important factor up to a maximum; then $^3\chi_p^v$ for LD_{100} and $^6\chi_p^v$ for LD_{50} become the main factors for the larger congeners. Similarly, for these two cases, no parabolic relationships with connectivity terms gave as good results as these different connectivity terms. Again, the parabolic relationships with log P or the molecular weights calculated from Jeppsson's work are less satisfactory. For the parabolic LD_{100} correlation with log P, the following statistical values were obtained: $r = 0.761$, $s = 0.324$, $n = 27$, and $F = 16.5$; similarly, the molecular weight gave $r = 0.763$, $s = 0.323$, $n = 27$, and $F = 16.7$. The

Table II—Toxic Doses (LD_{50} and LD_{100}) of Some Alkanes, Ethers, and Ketones after Intravenous Administration to Mice

Compound	$^0\chi^v$	$^3\chi_p^v$	$-\log 1/c''$ Obs.[a]	$-\log 1/c''$ Calc.[b]	$\lvert\Delta \log 1/c''\rvert$	$^6\chi_p^v$	$-\log 1/c'''$ Obs.[a]	$-\log 1/c'''$ Calc.[c]	$\lvert\Delta \log 1/c'''\rvert$
Pentane	4.121	0.707	1.287	1.261	0.026	0.000	0.792	0.840	0.048
Hexane	4.828	0.957	0.984	0.920	0.064				
Heptane	5.535	1.207	0.660	0.757	0.097	0.177	0.346	0.387	0.041
Octane	6.243	1.456	0.574	0.683	0.109				
Nonane	6.950	1.707	0.672	0.697	0.025	0.338	0.233	0.296	0.063
Decane	7.657	1.957	0.807	0.765	0.042				
Undecane	8.364	2.207	1.020	0.869	0.151	0.515	0.520	0.473	0.047
Dodecane	9.071	2.457	1.195	0.990	0.205				
Tridecane	9.778	2.707	1.332	1.146	0.186	0.692	0.800	0.749	0.051
Tetradecane	10.485	2.956	1.466	1.321	0.145				
Pentadecane	11.192	3.207	1.660	1.513	0.147	0.869	1.217	1.109	0.108
Hexadecane	11.899	3.457	1.637	1.723	0.086				
Heptadecane	12.607	3.707	1.611	1.933	0.322				
Ethyl ether	3.822	0.408	1.329	1.241	0.088	0.000	1.129	1.155	0.026
Propyl ether	5.237	0.697	0.322	0.325	0.003	0.102	0.301	0.309	0.008
Butyl ether	6.651	1.284	0.297	0.298	0.001				
Pentyl ether	8.065	1.784	0.508	0.434	0.074	0.297	0.017	−0.168	0.185
Hexyl ether	9.479	2.284	0.677	0.694	0.017				
Heptyl ether	10.891	2.784	1.068	1.061	0.007	0.607	0.342	0.308	0.034
Octyl ether	12.308	3.284	1.386	1.463	0.077	0.784	0.689	0.700	0.011
3-Pentanone	4.322	0.789	1.125	1.146	0.021	0.000	0.776	0.641	0.135
4-Heptanone	5.737	1.058	0.375	0.455	0.080				
5-Nonanone	7.151	1.618	0.262	0.520	0.258	0.239	−0.013	−0.091	0.078
6-Undecanone	8.565	2.118	0.328	0.709	0.381	0.466	−0.161	0.264	0.425
7-Tridecanone	9.979	2.618	1.248	1.005	0.243				
8-Pentadecanone	11.394	3.118	1.702	1.389	0.313	0.760	0.723	0.738	0.015
9-Heptadecanone	12.808	3.618	1.596	1.809	0.213				

[a] From Ref. 3; drug dose in millimoles per kilogram. [b] Calculated using Eq. 2. [c] Calculated using Eq. 3.

parabolic LD_{50} correlation with log P or the molecular weight also gave poorer results as compared to the molecular connectivity correlations. The parabolic relationship between LD_{50} and log P gave $r = 0.826$, $s = 0.249$, $n = 15$, and $F = 12.9$; with the molecular weight, the values were $r = 0.653$, $s = 0.334$, $n = 15$, and $F = 4.5$.

The very good correlations for the anesthetic and toxic activities were obtained with nonempirically based molecular connectivity terms. The equations describing the activity variations were not parabolic but contained two different connectivity terms. It is questionable whether the same structural features quantitatively affect the activity uniformly in a homologous series. The same features probably govern activity for smaller congeners up to the maximum activity; but beyond it, these factors may be somewhat different. In this respect, nonlinear correlations bring to light the flexibility and discriminating power of molecular connectivity as compared to the usual quadratic form of log P.

Many mechanistic explanations for parabolic relationships have been given (5–7). The usual explanation is based on a partitioning model. Alternative mechanistic explanations include the principle of bulk tolerance, limited solubility of the higher members of a congeneric series, conformational distortion of the active site, and metabolic transformation. These explanations imply that molecular size is the governing influence. The molecular connectivity indexes that mirror molecular connectedness are most readily identified with the size and shape of molecules. Murray *et al.* (8) obtained excellent parabolic relationships between molecular connectivity and biological activity. They discussed and endorsed the molecular size explanation, as modeled by molecular connectivity.

That the molecular connectivity indexes reflect the size and shape of molecules also can be seen when going through the congeneric series of Tables I and II. Thus, the correlations obtained would also support the mechanistic explanation for parabolic relationships implying molecular size. More specifically for the anesthetic activity, this molecular size explanation is in line with the Mullins critical volume hypothesis (9). This hypothesis states that anesthesia occurs when the volume of a hydrophobic region is caused to expand beyond a certain critical amount by the absorption of molecules of an inert substance. The results obtained here are also in agreement with previous studies of a mixed group of anesthetics (2) and a group of ethers (4) for which a molecular size explanation of the correlations with molecular connectivity indexes was proposed.

REFERENCES

(1) L. B. Kier and L. H. Hall, "Molecular Connectivity in Chemistry and Drug Research," Academic, New York, N.Y., 1976.

(2) T. Di Paolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, **13,** 31 (1977).

(3) R. Jeppsson, *Acta Pharmacol. Toxicol.*, **37,** 56 (1975).

(4) T. Di Paolo, *J. Pharm. Sci.*, **67,** 564 (1978).

(5) C. Hansch and J. M. Clayton, *ibid.*, **62,** 1 (1973).

(6) E. J. Lien, in "Medicinal Chemistry," vol. IV, J. Mass, Ed., Elsevier, Amsterdam, The Netherlands, 1974.

(7) T. Higuchi and S. S. Davis, *J. Pharm. Sci.*, **59,** 1376 (1970).

(8) W. J. Murray, L. B. Kier, and L. H. Hall, *J. Med. Chem.*, **19,** 573 (1976).

(9) J. C. Miller and K. W. Miller, in "MTP International Review of Science, Biochemistry Series One," vol. 12, H. K. F. Blaschko, Ed., Butterworths, University Park Press, Baltimore, Md., 1975, p. 33.

Correlation of Quinidine Absorption with Disintegration and Dissolution Rates

JEFFREY D. STRUM, JOHN W. EBERSOLE, JAMES M. JAFFE, JOHN L. COLAIZZI, and ROLLAND I. POUST ˣ

Received April 25, 1977, from the *Department of Pharmaceutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261.* Accepted for publication July 13, 1977.

Abstract □ The dissolution profiles of four commercial quinidine sulfate tablets were determined using the USP rotating-basket dissolution apparatus. Substantial differences in dissolution half-times were noted and compared to previously reported disintegration times, absorption rate constants, and times of appearance of peak serum concentrations. Rank-order correlations were observed among all combinations of *in vivo* and *in vitro* parameters, indicating that the absorption rates of these tablets are controlled by both disintegration and dissolution.

Keyphrases □ Quinidine sulfate—four commercial tablets, dissolution profiles determined and related to disintegration and absorption □ Dissolution—quinidine sulfate, four commercial tablets, profiles determined and related to disintegration and absorption □ Disintegration—quinidine sulfate, four commercial tablets, related to dissolution profiles □ Absorption—quinidine sulfate, four commercial tablets, related to dissolution profiles □ Cardiac depressants—quinidine sulfate, four commercial tablets, dissolution profiles determined and related to disintegration and absorption

A recent report (1) presented the results of a comparative bioavailability study of four commercially available, chemically equivalent brands of quinidine sulfate. No statistically significant differences in the extent of absorption from the four brands were observed. However, significant differences in the times of peak serum concentration and absorption rate constants were found, indicating differences in the absorption rate among certain pairs of products. A rank-order correlation was observed when mean disintegration times for the four tablet formulations were compared with values for peak time and the absorption rate constant. It seemed appropriate, therefore, to determine the dissolution profiles of these four brands of quinidine sulfate tablets and to investigate the relationships among disintegration, dissolution, and absorption rate.

EXPERIMENTAL

The dissolution properties of six tablets of each of the four brands[1] of quinidine sulfate tablets employed in the study of Strum *et al.* (1) were determined in 900 ml of 0.1 *N* HCl at 37° using the USP rotating-basket dissolution apparatus[2] at 25 rpm. Following preliminary trials, sampling

[1] Treatment A: quinidine sulfate tablets USP, lot 76F83A, Eli Lilly & Co., Indianapolis, Ind.; Treatment B: quinidine sulfate tablets USP, lot 7088A, Philips Roxane Laboratories, Columbus, Ohio; Treatment C: Quinora tablets, lot 72755, Lakeside Laboratories, Milwaukee, Wis.; Treatment D: quinidine sulfate tablets USP, lot 15840, Stanlabs, Portland, Ore. These lots are the same as those used by Strum *et al.* (1).

[2] Hanson Research Corp., Northridge, Calif.