reference to the venous blood sampling site, this flow will result in a first-pass effect and the actual systemic clearance will be overestimated (24). Even after correcting for this effect by assuming a hepatic extraction of 0.97 (12), the mean systemic clearance of 28.8 ml/min still is greater than the normal liver blood flow. This result could indicate extrahepatic elimination in the rat or an acute hemodynamic effect of lidocaine on its own disposition as a result of an increase in liver blood flow. Such an increase in flow was observed in humans following steady-state intravenous infusion (25).

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Use of Molecular Negentropy to Encode Structure Governing Biological Activity

LEMONT B. KIER

Received October 5, 1979, from the *Department of Pharmaceutical Chemistry, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298.* Accepted for publication February 12, 1980.

Abstract □ A drug molecule is considered to be an information source with an information content available to receptive tissue. In nonspecific interactions, much of the information content has quality as judged by the receptor. Quantitation of the information content using Shannon's equation gives the molecular negentropy. This index is shown to rank molecules according to symmetry and to encode structural characteristics influencing physical properties and biological activity in certain cases.

Keyphrases □ Structure–activity relationships—quantitation of molecular information content by negentropy calculations, correlation between biological activity and molecular structure □ Negentropy—mathematical analysis of correlation between biological activity and molecular structure, molecular information content available to receptor molecule □ Drug–receptor interaction—structure–activity relationships, negentropy of molecules, mathematical analysis of molecular structure and biological potency

A drug molecule may be regarded as a message containing information in the form of electron probability fields distributed in space around a framework of atomic nuclei. Therefore, drug–receptor interaction may be viewed as a presentation of the message, with its information content, to a receiver. Some information in the message may be interpretable by the receiver or receptor, leading to the beginning of events culminating in a biological response.

It follows that the efficacy of a drug depends on the information content and its quality as judged by the receptor. The quality of the information content in the drug molecule depends on the ability of the receptor to interpret the fields and to translate the interactions into a significant change in the receptor and its adjacent structures.

BACKGROUND

Under some circumstances, most if not all of the information content of a drug molecule has quality; that is, a receptor may be capable of interpreting the entire message presented by the drug. These circumstances are commonly referred to as nonspecific actions. In this category are molecules which, by virtue of the mere presence of atoms and bonds, are capable of eliciting a biological response. There usually is a rough correlation between size, expressed as the number of atoms, and the potency. However, various isomers frequently have different potencies. For example, in *in vitro* studies, there often is a decline in activity for the isomer series butanol > isobutanol > *tert*-butanol. Several physicochemical correlates have been presented to explain this trend, but all point to bulk phase phenomena, not to events occurring at the molecular level between the drug and the receptor.

If the information content of a nonspecific-acting molecule is of considerable importance to the potency, then quantitation of this characteristic would be a productive approach in analyzing the structure–activity relationships and the molecular level mechanism.

The information content of a message, whether it is a molecule, a book, or communication network, can be quantitated through information theory (1), particularly by use of the equation developed by Shannon and Weaver (2). This equation has its roots in the probabilities of choice among items classified into sets of equivalent items. A specific example using the propane molecule illustrates the assignment of equivalent atoms

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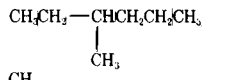
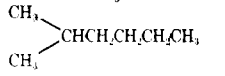
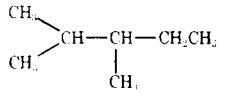
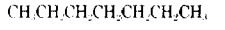
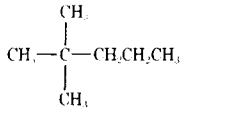
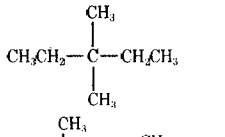
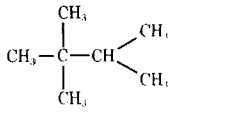
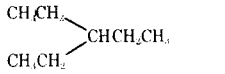
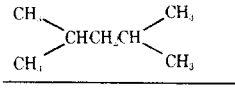
Table I—Molecular Negentropy and Redundancy of Isomeric Heptanes

Heptane	I	R
	25.219	0.195
	22.811	0.272
	22.584	0.279
	19.426	0.379
	18.665	0.404
	17.768	0.432
	16.029	0.488
	15.200	0.515
	14.155	0.548

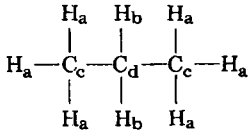
into sets and the calculation of the information content. Before proceeding with this illustration, the term molecular negentropy, the negative of information entropy, will be adopted as a measure of the information content of a molecule as suggested previously (1, 3).

THEORETICAL

Calculation of Molecular Negentropy—An approach to the calculation of the negentropy of a molecule can be derived from a consideration of molecular graphs as shown by Rashevsky (4), who pointed out the biological implications of such a parameter. Consider the propane molecule (Fig. 1) as an assemblage of atoms where the six methyl hydrogens are regarded as equivalent. This equivalence is apparent from the performance of symmetry operations on a model and from experimental evidence such as NMR. Each methyl hydrogen possesses the same physical and chemical properties as the other five by virtue of its equivalent topology relative to all of the other atoms.

These six hydrogens comprise a set. Similarly, the two methylene hydrogens are equivalent and comprise a different set with a multiplicity (number in the set) of two. The two methyl carbons comprise a third set with a multiplicity of two. The methylene carbon is in a fourth set with a multiplicity of one. Figure 1 shows the molecule labeled by sets with multiplicities.

The probability of a random selection of a methyl hydrogen is 6/11



sets	[aaaaaa]	[bb]	[cc]	[d]
multiplicity	6	2	2	1
probabilities of random selection	6/11	2/11	2/11	1/11

Figure 1—*Decomposition of the propane molecule into sets of topologically equivalent atoms, their multiplicities, and probabilities of random selection.*

Table II—Enzyme Inhibitory Potency of Alcohols and Molecular Negentropy

Molecule	I	pC Found	pC Calc.
Methanol	3.24	3.36	3.45
Ethanol	6.55	3.85	3.73
Propanol	10.32	4.28	4.05
Butanol	14.40	4.43	4.39
Pentanol	18.76	5.05	4.76
Hexanol	23.32	5.31	5.15
Heptanol	28.08	5.75	5.55
Octanol	33.00	6.05	5.97
3-Methylbutanol	17.93	4.77	4.69
3-Pentanol	14.31	4.26	4.39
2-Pentanol	18.53	4.40	4.74
2-Methylbutanol	18.53	4.70	4.74
Nonanol	38.07	6.30	6.40
1,2-Dimethyl-propanol	15.89	4.08	4.52
1-Methyl-3-phenyl-propanol	29.91	5.55	5.71
1-Phenylethanol	20.46	4.98	4.91
1-Phenylpropanol	25.09	5.35	5.30

while that for a methylene hydrogen is only 2/11. The complete array of probabilities, P_j, for the four sets is shown in Fig. 1.

The negentropy per atom, i, is computed for propane from Shannon's formula:

$$i = -K \sum_j P_j \log P_j \qquad \text{(Eq. 1)}$$

where K is a constant depending on the logarithmic base and j is the set. For propane, the calculation is:

$$i = -\frac{6}{11}\log\frac{6}{11} - \frac{2}{11}\log\frac{2}{11} - \frac{2}{11}\log\frac{2}{11} - \frac{1}{11}\log\frac{1}{11} \qquad \text{(Eq. 2)}$$

where $i = 0.507$. The molecular negentropy, I for $N = 11$ atoms, is $iN = 5.582$. Note that $\log_{10}$ is used for convenience. Use of $\log_2$ leads to negentropy expressed in bits.

Several properties of negentropy are apparent:

1. The negentropy is maximal when all parts of a structure are unique, resulting in equal probabilities for all parts.

2. The negentropy is zero when all parts of a structure are equivalent.

3. The numerical value of the negentropy decreases with greater multiplicity within each set or for a smaller number of sets. This observation translates into awareness that molecular negentropy ranks molecules according to symmetry. Bonchev *et al.* drew a relationship between negentropy and symmetry only among homologs (5). An example is shown in Table I, in which the nine isomers of heptane are ranked by molecular negentropy. It is apparent that this ranking is the same as that by symmetry and presents the possibility of quantitating the degree of symmetry among molecules. An alternative quantitation would be the use of redundancy, R (1), where $R = 1 - i/\log N$.

Molecular Negentropy as a Structure–Activity Relationship Parameter—If it is hypothesized that in some cases of biological activity the entire information content of a molecule is of quality to the receptor, then the molecular negentropy is a potentially useful parameter of structure. This approach is possible because molecular structure obviously governs the information content (Table I).

Table III—Lipoxygenase Inhibition and Molecular Negentropy

Alcohol	I	pK_I Found	pK_I Calc.
Methanol	3.24	−0.18	−0.10
Ethanol	6.55	0.18	0.26
Isopropanol	7.68	0.37	0.38
Propanol	10.32	0.68	0.67
tert-Butanol	7.62	0.49	0.37
sec-Butanol	14.18	0.86	1.08
Isobutanol	11.77	1.13	0.82
Butanol	14.40	1.15	1.11
Isopentanol	17.93	1.34	1.49
Pentanol	18.76	1.61	1.58
Hexanol	23.33	2.10	2.07
Heptanol	28.08	2.60	2.59

Table IV—Tadpole Narcosis Potency *versus* Molecular Negentropy

Molecule	I	log 1/c		
		Found	Calc.	Calc.[a]
Methanol	3.24	0.24	0.46	0.32
Ethanol	6.55	0.54	0.80	0.66
Propanol	10.32	0.96	1.18	1.05
Butanol	14.40	1.42	1.60	1.48
Octanol	33.00	3.40	3.49	3.41
Isopropanol	7.68	0.89	0.91	0.77
Isobutanol	11.77	1.35	1.33	1.21
tert-Butanol	7.62	0.89	0.91	0.77
Isopentanol	16.13	1.64	1.77	1.66
tert-Pentanol	11.87	1.24	1.35	1.23
Acetone	4.73	0.54	0.61	—
Butanone	11.02	1.04	1.25	—
3-Pentanone	10.99	1.54	1.25	—
2-Pentanone	15.20	1.72	1.68	—
Acetal	14.81	1.98	1.64	—
Ethyl ether	9.36	1.57	1.08	—
Methyl acetate	8.59	1.10	1.01	1.18
Ethyl formate	9.42	1.15	1.09	1.25
Ethyl acetate	12.58	1.52	1.41	1.54
Ethyl propionate	16.85	1.96	1.85	1.93
Propyl acetate	16.85	1.96	1.85	1.93
Ethyl butyrate	21.35	2.37	2.31	2.34
Ethyl isobutyrate	18.72	2.24	2.04	2.10
Butyl acetate	21.35	2.30	2.31	2.34
Isobutyl acetate	18.72	2.24	2.04	2.10
Ethyl valerate	26.05	2.72	2.79	2.76
Amyl acetate	26.05	2.72	2.79	2.76
Butyl valerate	35.93	3.60	3.79	3.66
Methyl carbamate	7.97	0.57	0.94	—
Ethyl carbamate	11.85	1.39	1.34	—
Acetonitrile	3.24	0.44	0.46	—
Acetaldehyde oxime	7.16	0.93	0.86	—

[a] Alcohols calculated from Eq. 6, and esters calculated from Eq. 7.

Sheep Liver Esterase Inhibition—One example of such a relationship is the inhibition of sheep liver esterase by several alcohols (6). In this study, the concentration required to inhibit the enzyme *in vitro* by 25% was deduced from plots of concentration *versus* percent inhibition (Table II). The low activities for 2-butanol and 2-methyl-2-butanol are suspicious. An examination of the original study revealed that these two molecules never achieved 25% inhibition within the concentration range reported. The reported concentration values for these two molecules were extrapolations beyond the concentration range studied. The large uncertainty in those values indicates that they should be deleted in a structure–activity relationship analysis.

The molecular negentropies were computed for each alcohol in Table II. The assignment of atoms into sets and their multiplicities was based on the topological equivalence of the atoms. The equation and statistics are:

$$pC = 0.085(\pm 0.000)\, I + 3.174(\pm 0.16) \qquad \text{(Eq. 3)}$$

$$r = 0.970 \quad s = 0.200 \quad n = 17 \quad F = 239$$

By comparison, a correlation with molecular weight gives $r = 0.940$; a correlation with log P yields $r = 0.931$. The predicted values from Eq. 3 are found in Table II.

Lipoxygenase Inhibition—A second example of alcohol enzyme inhibitors in which molecular negentropy encodes structural features governing potency is found with the enzyme lipoxygenase (7). The data are shown in Table III with *in vitro* potencies predicted from:

$$pK_I = 0.108(\pm 0.000)\, I - 0.450(\pm 0.12) \qquad \text{(Eq. 4)}$$

$$r = 0.986 \quad s = 0.140 \quad n = 12 \quad F = 353$$

A correlation with molecular weight gives $r = 0.974$; a correlation with log P gives $r = 0.984$.

Nonspecific Narcotic Agents—Kier and Hall (8) analyzed several compounds of diverse structure that exhibited narcosis on frog tadpoles (9). The original list of compounds was factorable into two distinct lists based on the relationship between potency (log 1/c) and molecular structure, described by a molecular connectivity index. Two separate nonspecific mechanisms influencing the potency of each list were postulated.

Table V—Vapor Toxicity of Alcohols and Molecular Negentropy

Alcohol	I	pC	
		Found	Calc.
Methanol	3.24	2.80	2.88
Ethanol	6.55	3.00	3.13
Propanol	10.32	3.32	3.43
Isopropanol	7.68	3.26	3.22
Butanol	14.40	3.77	3.74
Pentanol	18.76	4.09	4.08
sec-Butanol	14.18	3.62	3.72
Isopentanol	17.93	4.09	4.01
tert-Pentanol	11.97	3.75	3.55
3-Pentanol	14.31	3.81	3.73
2-Pentanol	18.53	3.90	4.06
2-Methylbutanol	18.53	3.96	4.06
Isobutanol	11.77	3.72	3.54
tert-Butanol	7.62	3.28	3.22

In the present study, 32 molecules (10 alcohols, four ketones, two ethers, 12 esters, two carbamates, one nitrile, and one oxime) were analyzed (Table IV). Dichloropropanol was omitted from the list. The relationship between the negentropy (I) and potency (log 1/c) and the statistics are:

$$\log \frac{1}{c} = 0.102(\pm 0.000)\, I + 0.130(\pm 0.09) \qquad \text{(Eq. 5)}$$

$$r = 0.975 \quad s = 0.187 \quad n = 32 \quad F = 582$$

Analyses of the alcohol and ester subclasses show a definite improvement in the correlations:

$$\log \frac{1}{c}\,(\text{alcohols}) = 0.104(\pm 0.000)\, I - 0.019(\pm 0.077) \qquad \text{(Eq. 6)}$$

$$r = 0.994 \quad s = 0.101 \quad n = 10 \quad F = 654$$

and:

$$\log \frac{1}{c}\,(\text{esters}) = 0.091(\pm 0.000)\, I + 0.396(\pm 0.09) \qquad \text{(Eq. 7)}$$

$$r = 0.994 \quad s = 0.083 \quad n = 12 \quad F = 768$$

Predicted values based on the calculated I values are shown in Table IV for the entire list of compounds (Eq. 5) and for the alcohols (Eq. 6) and esters (Eq. 7).

Toxicity of Alcohols—A number of alcohols have a toxic effect on red spiders when they are exposed to the vapors (10). The potency, expressed as pC, is related to the molecular negentropy by:

$$pC = 0.077(\pm 0.000)\, I + 2.630(\pm 0.14) \qquad \text{(Eq. 8)}$$

$$r = 0.959 \quad s = 0.119 \quad n = 14 \quad F = 136$$

The values calculated from Eq. 8 are shown in Table V.

Heat of Vaporization of Alcohols—A test of the relationship between molecular negentropy and dispersion forces can be made using heats of vaporization available for alcohols found in the described studies. This property is related to molecular negentropy by:

$$\Delta H_{vap} = 0.265(\pm 0.000)\, I + 8.566(\pm 0.29) \qquad \text{(Eq. 9)}$$

$$r = 0.989 \quad s = 0.414 \quad n = 15 \quad F = 563$$

The values calculated from Eq. 9 are shown in Table VI.

DISCUSSION

The significant correlations of molecular negentropy with enzyme inhibitory potencies suggest that this structural index encodes an appreciable description of the structure influencing the activity. Variation in nonspecific activity in these *in vitro* studies may be proposed to result from variation in the receptor interaction rather than the effects on accumulation at, or disturbance of, the receptor environment. This conclusion evolved from a comparison with log P or molecular weight.

In these studies, the receptor may be viewed as responding to the hydroxyl group in a specific way. The response of the receptor to the remainder of the molecule probably is nonspecific; that is, there is no particular need for a specific atom or group to enhance the interaction. The receptor responds to all bonds and atoms in a roughly cumulative way, which is characteristic of dispersion forces among nonpolar moieties.

Table VI—Heat Vaporization of Alcohols and Molecular Negentropy

Alcohol	I	ΔH_{vap}, kcal/mole	
		Found	Calc.
Methanol	3.24	8.94	9.45
Ethanol	6.55	10.18	10.29
Propanol	10.32	11.34	11.25
2-Propanol	7.68	10.90	10.58
Butanol	14.40	12.50	12.29
2-Butanol	14.18	11.89	12.23
2-Methylpropanol	11.77	12.15	11.62
2-Methyl-2-propanol	7.62	11.14	10.56
Pentanol	18.76	13.61	13.40
2-Pentanol	18.53	12.56	13.34
3-Pentanol	14.31	12.36	12.27
2-Methylbutanol	18.53	13.04	13.34
3-Methylbutanol	17.93	13.15	13.19
3-Methyl-2-butanol	15.89	12.27	12.67
Hexanol	23.33	15.00	14.56
Heptanol	28.08	16.20	15.77
Octanol	33.00	17.00	17.03
2-Ethylhexanol	32.77	16.12	16.97
Nonanol	38.07	18.60	18.32
Decanol	43.26	19.82	19.64

Dispersion forces are notable only at close distances, are maximized between similar structural features, and are always attractive (11). Therefore, a molecule with a greater variety of structural features (a molecule with little topological equivalence or symmetry) should be capable of interaction with a greater variety of structural features on a receptor. Stated quantitatively, the greater the information content (negentropy) in a molecule, the greater is its potential for dispersion-type interaction with nonspecific receptive surfaces. Negentropy, which encodes the information content in the molecule, quantitates the variety of structural features and the associated probabilities of interaction with the receptor.

As a test of the relationship between negentropy and dispersion forces, a good correlation can be found between the molecular negentropy of alcohols and the heat of vaporization. This property reflects intermolecular forces in this series due to structural variation, in addition to the common hydroxyl group, for the 15 alcohols in Table VI.

Equations 5–8, which correlate molecular negentropy and the biological activity, show that this index has encoded molecular information of importance to the activity. The operating model of nonspecific interaction admittedly is simplistic. Nevertheless, the probabilities leading to the calculated molecular negentropy values are of great importance to the potencies. The quality of the correlations is good.

In the narcosis study, the greater the variety of information or negentropy, the greater is the potency. The receptive tissue responds to a greater degree to a molecule possessing a greater mix of atoms in differing structural environments. Isomers are ranked correctly by potency with the I value. As an example, the rankings for the observed and calculated potencies for the isomers may be compared (Table IV): propanol > isopropanol, butanol > isobutanol > *tert*-butanol, isopentanol > *tert*-pentanol, 2-pentanone > 3-pentanone, ethyl propionate = propyl acetate, ethyl valerate = isoamyl acetate, and ethyl isobutyrate = isobutyl acetate.

The subclassification into alcohols (Eq. 6) and esters (Eq. 7) (Table IV) considerably improves the correlations. The slopes in Eqs. 6 and 7 are nearly identical and are close to the slope in Eq. 5. It can be concluded that the mechanism is quite similar for alcohols and esters but that there is a uniform difference in potency running through both types of molecules. This difference undoubtedly is due to the roles played by the hydroxyl group and the carbonyl group at receptive tissue, apart from a completely nonspecific definition. Thus, a nonspecific model is useful as a first approximation, and molecular negentropy can encode most of the salient structural characteristics among both types of molecules.

The discussion of the mechanism of action in these studies takes on a probability description. It is evident why, in some studies of nonspecific effects (10, 12, 13), the range of potencies is butanol > isobutanol > *tert*-butanol since the negentropies of these molecules are 14.40, 11.77, and 7.62, respectively. Butanol is composed of 12 different sets of equivalent atoms, isobutanol has eight sets, and *tert*-butanol has five sets. Butanol, with its greater variety of topologically different atoms, can interact with a greater variety of features on a receptor. Its potency would be expected to be higher based on its structure, which governs the probabilities.

A similar situation can be found in observations of the relative affinity contributions of onium groups of muscarinic antagonists (14): $N(CH_3)_3 < N(CH_3)_2(C_2H_5) < N(CH_3)(C_2H_5)_2 > N(C_2H_5)_3$. The calculated negentropies for these moieties parallel the affinity contributions; they are 4.462, 11.962, 14.583, and 13.413, respectively. A similar trend and negentropy relationship can be found in the onium group contribution to affinities among nicotinic agents (15).

It is proposed here that a molecule of biological interest also may be regarded as a message made up of atoms and bonds containing information transmitted to a receptor or receptive tissue. The information content or negentropy is a meaningful parameter in some structure–activity relationship analyses such as in some nonspecific interactions.

It remains to be seen whether molecular negentropy as a structure–activity relationship parameter needs to be confined exclusively to drug molecules postulated to act in a nonspecific manner. Drug molecules that are active at highly structured, specific receptors certainly contain information. The probabilities of atom interaction are altered in a complex way from purely random choice due to marked differences in interaction forces between certain atoms in an agonist molecule and complementary portions of a receptor. Thus, acetylcholine engages its receptor through strong dipolar forces centered on the carbonyl oxygen and the onium group. The statistical picture describing the information content in the previous discussion must be altered to reflect the much greater probability of the onium group and the carbonyl oxygen atom of acetylcholine engaging the receptor. This issue remains for future study.

In conclusion, the calculation of the molecular negentropy of a molecule leads to the quantitation of its relative information content. Molecular negentropy encodes the salient structural characteristics of molecules in some cases where biological activity is nonspecific. It correctly ranks them according to nonspecific biological potency and provides a mechanistic interpretation of action at the molecular level based on probability considerations.

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