Table II—Values of ϕ, K, k, and I

Drug in Mixture, %	ϕ	K	k	I
40	48.6	0.1428	0.3307	−3.45
20	46.5	0.1592	0.3442	−3.77
10	44.5	0.1758	0.3566	−4.09
0	38.4	0.2337	0.3918	−4.78

where σ_1 is the maximum principal stress, ϕ is the angle of internal friction, and K is the coefficient of Rankine (5) as given by:

$$K = \frac{1 - \sin \phi}{1 + \sin \phi} \qquad \text{(Eq. 6)}$$

Thus, $\Delta\phi$ represents the probability of a packing change of the particles and is considered to be proportional to some quantities related to the state of packing in one of the several described manners. It was shown that various compression equations could be derived by making different assumptions about the properties that determine $\Delta\phi$.

If $\Delta\phi$ is proportional to the decrease in porosity and inversely proportional to the mth power of consolidation pressure, $-dn/P^m$, then:

$$-\frac{dn}{P^m} = k\frac{dP}{P} \qquad \text{(Eq. 7)}$$

where P is the consolidation pressure, m is a constant, and k is a function of the coefficient of Rankine.

Equation 7, on rearrangement, gives:

$$-dn = kP^{m-1}\,dP \qquad \text{(Eq. 8)}$$

Integration of Eq. 8 from initial porosity n_0 to porosity n, corresponding to the zero initial consolidation pressure to the consolidation pressure P, gives:

$$n - n_0 = -\frac{k}{m}P^m \qquad \text{(Eq. 9)}$$

Equation 9 is similar to Eq. 4, which is the modified form of Eq. 1. Equations 4 and 9 suggest that C is a function of $(V/V_\infty)(k/m)$.

A previous study (2) showed that, for different powder mixtures of the same drug, m was a constant. The value k is a function of the coefficient of Rankine K given by Eq. 6, and ϕ may be approximated from the angle of repose.

For the powder mixtures containing drug, spray-dried lactose, starch, and magnesium stearate, the values of ϕ, K, k, and ln C are given in Table II. A plot of C *versus* k gave a linear relationship with $r = -0.9666$. Figure 5 gives a plot of ln C *versus* k. The excellent correlation ($r = -0.998$) indicates that ln C is inversely proportional to k.

Figure 6 gives a plot of V_0/V_∞ *versus* C for the same powder mixture. A linear relationship ($r = 0.9809$) between V_0/V_∞ *versus* C suggests that these parameters are directly related.

The results of this study suggest that the consolidation ratio is a function of tensile strength and that both parameters are useful in studying flow behavior of powders and powder mixtures. The physical significance of the consolidation ratio was explored. The consolidation ratio is a function of the ratio of the initial volume to the net volume of the powder and of the coefficient of Rankine, which, in turn, is a function of the angle of internal friction in the static powder bed.

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Quantitation of Solvent Polarity Based on Molecular Structure

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Abstract □ A numerical index is proposed that ranks solvents according to their polarity. It is based entirely on structure, encoding the relative content of exterjacent electrons in the molecule. The index is the first-order valence molecular connectivity index, $^1\chi^v$. The index is modified for the number of isolated functional groups in the molecule. A comparison with solvent polarity indexes based on several experimental methods reveals a good relationship. The polarity index proposed can be quickly calculated, it does not depend on the availability of the actual molecule, and it permits prediction of solvent polarity or the polarity of mixtures.

Keyphrases □ Solvent polarity—quantitative method based on molecular structure □ Polarity index—solvents, quantitative method based on molecular structure □ Molecular structure—quantitative method for ranking solvent polarity

The term "solvent polarity" is widely used by chemists to characterize the observed manifestations of intermolecular interactions in a solution process. The processes may be chromatography, dissolution, or chemical reactions. The manifestations of the interactions are recorded as the separation or retention on stationary phases, the solubility, and the partitioning or reaction course and rate. Solvent polarity is a comparative term which the chemist uses intuitively to rank commonly employed compounds. This intuition, based on experience, permits the generalization that hydrocarbons are less polar than esters while alcohols are more polar than esters of the same molecular weight.

BACKGROUND

The quantitation of solvent polarity is difficult in practice due to the variety of intermolecular forces that may operate between molecules in a given system. Much has been written about solution theory, but the forces influencing solvent–solute interactions can be summarized as those due to dispersion and dipolar and electron donor–acceptor properties (1).

Dispersion forces account for virtually all of the attractive energy between nonbonded atoms among hydrocarbons. These compounds are regarded as nonpolar when their solvent properties are characterized. Dipolar and electron donor–acceptor interactions influence the attractive energy among molecules possessing unsaturation or atoms other than carbon or hydrogen. Solvents possessing structures capable of these interactions are characterized as being polar. Thus, molecular structure governs solvent polarity, but this relationship has yet to be quantified in any simple way.

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In contrast, several experimental observations have been used to construct a numerical ranking of solvent polarity. Hildebrand and Scott (2) reasoned that the molar heat of vaporization for the molar volume relates to the intermolecular interaction strength to give a value for a solubility parameter, δ. Since the derivation of this polarity parameter is based on the assumption of the dominance of dispersion forces, it is less accurate for more specific dipolar forces.

Snyder (3) used the eluting power of solvents on stationary phases to arrive at an eluent strength parameter, ϵ^0. The stationary phase is usually alumina, but other materials can be used with appropriate correction. Since the values for more polar solvents are quite close, the parameter is more discriminating for nonpolar solvents.

Rohrschneider (4) introduced a scale in which the solvent polarity, P', is measured for GLC retention of butane and butadiene. The quality of the parameter increases with more polar solutes.

A polarity index, Y, measuring the ionizing power of a solvent from the solvolysis rates of several compounds, was devised (5). The charge transfer band of 1-alkylpyridinium iodide complexes was used (6) as a measure of the solvent polarity, Z. Finally, the dielectric constant has been associated with molecular polarity.

Each of these proposals is based on different sets of conditions and molecular behavior, although each is ultimately a function of molecular structure. This fact was recognized by Martin (7) who attempted the prediction of the chromatographic phase distribution of a molecule from structure fragment values. The method is limited to carefully defined functional groups.

The value of a polarity index lies in its ability to predict the relative polarity of a solvent for which experimental data are not available. A second potential value lies in the ability of an index to predict the polarity of a mixture of solvents from their individual values. Thus, a wide range of solvent polarity could be achieved from various proportions of two solvents with desirable physical, chemical, and toxicological properties.

DERIVATION OF POLARITY INDEX FROM MOLECULAR STRUCTURE

Structural Influences—The structure of a molecule governs all physical and chemical phenomena. The solvent characteristics of a molecule depend on intermolecular interactions which, in turn, are dependent on structure. The generalization can be made that molecules classified as nonpolar according to any of the stated methods are molecules that possess few, if any, polar groups or bonds. Nonpolar molecules are distinguished by the absence of unsaturation or lone-pair electrons. Thus, pentane is universally regarded as nonpolar. It has only C–H and C–C bonds, which are devoid of electrons not axially directed between nuclei. In contrast, ether, with virtually the same molecular weight, is more polar. Ether has two lone pairs of electrons on the oxygen atom.

Similar comparisons between hexane and pentanol, cyclohexane and benzene, and methyl ethyl ketone and methyl acetate present the case that molecules, of about the same molecular weight, with π and lone-pair electrons are more polar than those without them. This observation is not surprising since lone-pair electrons create significant dipoles capable of intermolecular interactions associated with polar solvents. The task then is to encode this structural information into a molecular index that will quantify solvent polarity from a purely structural basis.

Calculation of Polarity Index—The presence of π and lone-pair electrons on an atom in its valence state was shown (8) to be encoded into the connectivity delta values, δ and δ^v. These connectivity deltas are not to be confused with the Hildebrand–Scott polarity index (2). The valence delta, δ^v, is assigned to an atom in its valence state according to the relationship $\delta^v = Z^v - h$, where Z^v is the count of valence electrons and h is the count of bonded hydrogen atoms. For atoms beyond the second quantum level, the expression $\delta^v = (Z^v - h)/(Z - Z^v)$, where Z is the atomic number, is used (9). The simple delta value, δ, is a count of all bonded atoms except hydrogen. It can be expressed as $\delta = \sigma - h$, where σ is a count of all σ electrons on the atom.

Since:

$$\delta^v = Z^v - h \qquad \text{(Eq. 1}a\text{)}$$

then:

$$\delta^v = \sigma + p + n - h \qquad \text{(Eq. 1}b\text{)}$$

where p is a count of π electrons and n is a count of lone-pair electrons.

Table I—Exterjacent Electrons *versus* ($^1\chi - {^1\chi^v}$)

Molecule	$^1\chi$	$^1\chi^v$	$\Delta^1\chi$	Exterjacent Electrons
$CH_3CH_2CH_2CH_2CH_3$	2.414	2.414	0.0	0
$CH_3CH_2CH_2CH_2NH_2$	2.414	2.115	0.299	2
$CH_3CH_2CH_2CH_2OH$	2.414	2.023	0.391	4
$CH_3CH_2OCH_2CH_3$	2.414	1.992	0.422	4
$CH_3CH_2CH_2CH{=}O$	2.414	1.851	0.563	6
$HOCH_2CH_2CH_2NH_2$	2.414	1.724	0.690	6
$HOCH_2CH_2CH_2OH$	2.414	1.632	0.782	8
$HOCH_2CH_2CH{=}O$	2.414	1.460	0.954	10
$O{=}CHCH_2CH{=}O$	2.414	1.288	1.126	12

It follows that:

$$\delta^v - \delta = \sigma + p + n - h - \sigma + h \qquad \text{(Eq. 2}a\text{)}$$

$$\delta^v - \delta = p + n \qquad \text{(Eq. 2}b\text{)}$$

The count of π and lone-pair electrons, called exterjacent electrons (8), is encoded in $\delta^v - \delta$.

By using these delta values assigned to each atom in a molecule, two molecular connectivity indexes are calculated by:

$$^1\chi = \Sigma(\delta_i\delta_j)^{-1/2} \qquad \text{(Eq. 3}a\text{)}$$

$$^1\chi^v = \Sigma(\delta_i^v\delta_j^v)^{-1/2} \qquad \text{(Eq. 3}b\text{)}$$

where i and j are each pair of bonded atoms and the summation is over the entire molecule.

The exterjacency on an atom, enumerated by $\delta^v - \delta$, can be encoded for the molecule by $^1\chi - {^1\chi^v}$. The subtraction of χ indexes is inverted since the reciprocal of the delta values is used in computing the molecular connectivity indexes. Kier and Hall (8) showed a derivation of the indexes from physical principles.

The effect on the calculated value of $^1\chi - {^1\chi^v}$ due to an increase of exterjacent electrons in a molecule is illustrated in Table I. With increasing numbers of exterjacent electrons in molecules in this series, the value of $^1\chi^v$ for the molecule decreases. For this series with a constant $^1\chi$ value, $^1\chi - {^1\chi^v}$ increases down the list.

In this series with a constant $^1\chi$ value, the $^1\chi - {^1\chi^v}$ value increases as the molecules increase in polarity. For molecules in an homologous series, for example the n-alkanols, the solvent polarity decreases with increasing size; however, the value of $^1\chi - {^1\chi^v}$ for such a series remains constant. To account for this effect, the use of $^1\chi - {^1\chi^v}$ to reflect solvent polarity must be modified by a term describing increasing molecular weight. This can be accomplished by diminishing the value of $^1\chi - {^1\chi^v}$ by $^1\chi$, which increases with size in an homologous series.

The index reflecting polarity thus may be described as:

$$\text{polarity} = {^1\chi} - {^1\chi^v} - {^1\chi} = -{^1\chi^v} \qquad \text{(Eq. 4)}$$

To restate this relationship, it is proposed that solvent polarity is inversely related to $^1\chi^v$. Table II shows the calculated values of $^1\chi^v$ for common solvents. Also included are other polarity indexes, $\epsilon^0(Al_2O_3)$, δ, and P', as well as the octanol–water partition coefficient, dielectric constant, and water solubility.

Functional Group Number Weighting—A number of molecules in Table II, such as ethylene glycol and dioxane, possess two isolated functional groups. These solvents are more polar than their monofunctional counterparts of about equal molecular weight, propanol and pyran. The two functional groups may be regarded as having twice the opportunity or probability of engaging in dipolar or electron donor–acceptor interactions with a solute.

For purposes of defining this solvent polarity index, a functional group is defined as an ensemble of atoms with exterjacent electrons that engage, as a unit, in essentially a single type of intermolecular interaction. Thus, the two oxygens and the carbon atom of an ester group constitute a functional group in this definition. Similarly, the three atoms of a nitro group represent one functional group in nitrobenzene. The six carbon π electrons of the benzene ring also constitute a discrete functional group that acts in concert with the nitro group. Thus, nitrobenzene has two functional groups.

A nitrogen atom in pyridine participates in the π-electron annulus and contributes to van der Waals interaction. The nitrogen also may participate in hydrogen bonding through the lone-pair electrons. Thus, pyridine has two functional groups by this definition. To account for this, it is proposed that the calculated $^1\chi^v$ value be divided by a factor, f, describing the number of discrete, isolated functional groups. This method was

Table II—Ranking of Solvent Polarity Using $^1\chi^v/f$ Index

Molecule	$^1\chi^v/f$	P'[a]	Hildebrand–Scott δ[b]	$\epsilon^0(Al_2O_3)$[c]	Octanol–Water log P[d]	Dielectric Constant[e]	Water Solubility[f], g/100 g
Cyclohexane	3.000	0.0	8.2	0.04	3.44	2.0	0.01
Hexane	2.914	0.0	7.3	0.01	—	1.9	Insoluble
Isopropyl ether	2.781	2.2	7.0	0.28	—	3.9	—
Chlorobenzene	2.508	2.7	9.6	0.30	2.46	5.6	0.05
Toluene	2.411	2.3	8.9	0.29	2.80	2.4	0.05
Carbon tetrachloride	2.390	1.7	8.6	0.18	2.72	2.2	0.08
Ethylene dichloride	2.190	3.7	9.7	0.49	1.48	10.4	—
Tetrahydrofuran	2.077	4.2	9.1	0.45	0.73	7.6	∞
Chloroform	2.070	4.4	9.1	0.40	1.97	4.8	0.82
Butanol	2.023	3.9	11.3	—	0.88	12.5	7.45
Benzene	2.000	3.0	9.2	0.32	2.13	2.3	0.18
Ether	1.992	2.9	7.6	0.38	0.80	4.3	6
Ethyl acetate	1.904	4.3	8.6	0.58	0.70	6.0	8.1
Methyl ethyl ketone	1.765	4.5	9.3	0.51	0.27	18.5	24
Methylene chloride	1.690	3.4	9.6	0.42	1.25	8.9	1.3
Propanol	1.523	3.9	10.2	0.82	0.30	20.3	∞
Carbon disulfide	1.414	1.0	10.0	0.15	—	2.6	0.29
Isopropanol	1.413	4.2	10.2	0.82	0.05	19.9	∞
Dimethylformamide	1.388	—	11.5	—	−1.01	36.7	∞
Methyl acetate	1.316	—	9.2	0.60	0.30	6.7	—
Nitrobenzene	1.250	4.5	11.1	—	1.85	34.8	0.19
Acetone	1.204	5.4	9.4	0.56	−0.24	20.7	∞
Benzonitrile	1.192	4.6	10.7	—	1.56	—	—
α-Picoline	1.135	4.8	—	—	—	—	∞
Dioxane	1.073	4.8	9.8	0.56	−0.35	2.2	∞
Ethanol	1.023	5.2	11.2	0.88	−0.30	24.6	∞
Acetic acid	0.928	6.2	12.4	1.00	−0.25	6.2	∞
Pyridine	0.925	5.3	10.4	0.71	0.65	12.4	∞
Nitromethane	0.812	6.8	11.0	0.64	−0.34	35.9	11.1
Methoxyethanol	0.757	5.7	—	—	−0.77	16.9	∞
Acetonitrile	0.724	6.2	11.8	0.65	−0.34	37.5	∞
Ethanolamine	0.678	—	13.5	—	−1.31	—	∞
Formamide	0.569	7.3	17.9	—	—	109	∞
Ethylene glycol	0.566	5.4	13.5	1.11	−1.93	37.7	∞
Methanol	0.447	6.6	12.9	0.95	−0.65	32.7	∞
Water	0.0	9.0	21	—	−1.38	80.2	∞

[a] Reference 4. [b] Reference 2. [c] Reference 3. [d] C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," Wiley, New York, N.Y., 1979. [e] "CRC Handbook of Chemistry and Physics," R. C. Weast and M. J. Astle, Eds., CRC Press, Boca Raton, Fla., 1979, E-56. [f] "Vogels' Textbook of Practical Organic Chemistry," 4th ed., B. S. Furniss, A. J. Hannaford, V. Rogers, P. Smith, and A. R. Tatchell, Eds., Longman Press, London, England, 1978, p. 1302.

applied to nitrobenzene, benzonitrile, α-picoline, dioxane, pyridine, methoxyethanol, ethanolamine, and ethylene glycol (Table II).

The exception to this rule is the case where one or more halogen atoms is present on different carbon atoms, *i.e.*, ethylene dichloride. Chlorine does not make a significant contribution to a molecule in terms of enhancing its solvent polarity. Aryl and alkyl halides are classified among the more nonpolar solvents, *i.e.*, carbon tetrachloride, chlorobenzene, *etc.* Thus, the value of $^1\chi^v$ computed for a halogen-containing molecule would be used unmodified.

Table II lists 36 of the more common solvents, ranked according to increasing solvent polarity computed as a diminishing value of $^1\chi^v/f$. This polarity index, based solely on molecular structure, can be compared with the experimental polarity indexes derived by several methods. In addition, the table lists physical properties associated with solution phenomena. Several observations emerge from comparisons of these indexes.

DISCUSSION

The diminishing value of $^1\chi^v/f$, associated with increasing solvent polarity, parallels the increase in the values of P', δ, and $\epsilon^0(Al_2O_3)$, with the P' values having perhaps the best correlation. Each of these experimentally derived polarity indexes is based on different experimental methods; thus, a close correlation is not expected among them or with $^1\chi^v/f$. Nevertheless, for a broad definition of solvent polarity, $^1\chi^v/f$ performs quite well in comparison. The distinct advantage of using $^1\chi^v/f$ as a solvent polarity index is the fact that it is based exclusively on structure, so it is nonempirical. It can be computed quickly and simply for any molecule, including those that may not be available.

The physical properties in Table II correlate fairly well with $^1\chi^v/f$. The aqueous solubility is minimal for molecules with $^1\chi^v/f$ values above 2.0, intermediate for $^1\chi^v/f$ values of 1.5–2.0, and miscible for practically all molecules with $^1\chi^v/f$ values of $<\sim$1.5.

There are exceptions to these observations, but generally the calculated $^1\chi^v/f$ index ranks the molecules according to solvent polarity as well as any of the experimental indexes, the advantage clearly being in the purely structural basis for the calculation.

An additional application of the $^1\chi^v/f$ solvent polarity index is obvious when binary solvent mixtures are considered. If it is assumed that when two nonreacting solvents are mixed the solvent polarity is an average of their polarities, weighted by their mole fractions, then it should be possible to calculate the solvent polarity of any mixture or, conversely, to design a solvent mixture with a specific solvent polarity. This latter course often is desirable when one solvent may possess unfavorable physical, chemical, or toxicological properties.

As an example, ether may have optimum solvent polarity for a particular application; however, its volatility and flammability preclude its use from safety considerations. It is desirable to reproduce approximately the $^1\chi^v/f$ = 1.992 ether polarity with a mixture of two solvents. Calculations show that a 1:1 mixture of toluene and propanol has a $^1\chi^v/f$ value of 1.967, while a 2:1 mixture of methyl ethyl ketone and chlorobenzene has a $^1\chi^v/f$ value of 1.973.

Other applications of the index include the basis of selection of a relatively nonpolar solvent that is heavier or lighter than water or miscible, all with about the same polarity. Chloroform, butanol, and tetrahydrofuran, respectively, meet these specific criteria.

Finally, the index will prove useful in estimating the polarity of a molecule not commonly considered as a solvent or perhaps a polymeric structure such as the polyethers. Thus, the $^1\chi^v/f$ values lead to polarity rankings for some additional liquids: methylformamide, 1.024; diethylene glycol, 0.737; dimethoxy polyethylene glycol, $^1\chi^v/f$ approaches a limit of 1.10 with increasing size; morpholine, 1.142; various fluorinated ethanols, 0.0–0.5; glycerol, 0.569; and aniline, 1.100.

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Structure–Activity Studies on Sulfamate Sweeteners II: Semiquantitative Structure–Taste Relationship for Sulfamate ($RNHSO_3^-$) Sweeteners—The Role of R

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Abstract ☐ With the use of Corey–Pauling–Koltun space-filling models, measurements of defined parameters (x, y, and z) were made of the R groups in a large number of carbosulfamates, $RNHSO_3^-$. The correlation between sweet and nonsweet sulfamates and the defined parameters for R is good. As a test, 12 new carbosulfamates were synthesized and tasted. The predictions of their sweetness or nonsweetness based on the correlation were >90% correct. To elicit a sweet taste, the R group of the sulfamate should have $x \geq 5.2$ Å and ≤ 7.2 Å and V (*i.e.*, xyz) ≤ 250 Å^3 and probably ≥ 90 Å^3. The receptor site is seen (as for aspartame) as a rather narrow cleft into which R has to fit "properly" or be "locked" so that the AH,B mechanism for initiating the sweet stimulae can operate. Possible applications of this approach are indicated.

Keyphrases ☐ Sweeteners—structure–activity analysis of sulfamates, the role of R side chains ☐ Sulfamates—sweeteners, structure–activity analysis, the role of R side chains ☐ Structure–activity relationships—the role of R side chain on sulfamate sweeteners

Synthetic studies of alternative sweeteners have been given impetus since the ban on cyclamates in 1970 and the apparently unresolved question of the toxicity of saccharin, the only synthetic sweetener presently used worldwide. These studies, aimed at the design of new synthetic sweeteners and a fuller understanding of sweetness, have led to the establishment of structure–taste relationships for some classes of alternative sweeteners (1–3).

Most workers have concentrated on the development of intraclass structure–taste relationships since there is good evidence that different classes of sweeteners act by binding at different receptor sites in the taste buds of the tongue (4). Thus, structure–taste information from one class is not transferable to another class.

BACKGROUND

The structure–activity relationships of sulfamate sweeteners were reviewed in Part I of this study (5). Other investigators (6, 7), using Corey–Pauling–Koltun (CPK) space-filling atomic models, showed that the best $NHSO_3^-$ group conformation for sweet taste stimulation involved an angle (θ) of 60° between the N–H and S–O bonds. The necessity of maintaining this optimal 60° torsional angle for sweetness explains why substitution of an α-hydrogen by an alkyl group at C-1 of an alicyclic ring or aliphatic chain destroys sweetness. Similarly, the lack of sweetness of phenylsulfamate is ascribed to steric hindrance due to an *ortho*-hydrogen of the phenyl ring forcing the aminosulfonate group to adopt a conformation with $\theta \approx 0°$.

Pautet and Nofre (6) measured the lengths of various R groups in $RNHSO_3^-$ and found that for sweetness, R should lie between 5 and 7 Å. In their second paper (7), they suggested, on the basis of a few measurements, that R should have a "half-width" of <4 Å. While this approach is satisfactory for simpler aliphatic and alicyclic systems, it appeared to us to be inadequate for various substituted systems for several reasons:

1. Taste response is a function of the size, shape, and functionality of a molecule, *i.e.*, taste response = f(size, shape, functionality), and any assessment of size and shape should take into account the three-dimensional structure and conformation of the molecule.
2. Several molecules whose R groups have dimensions falling within the limits given by Pautet and Nofre (6, 7) were prepared (and tasted for sweetness), and it was found that they are not sweet (Table I, Compounds 15, 18, 47, and 49).

In the present work, 12 new sulfamates were synthesized. With the use of CPK space-filling models, measurements were taken on these and other sulfamates reported (and tasted) previously. A good correlation existed between sweet/nonsweet sulfamates and the defined parameters for R, so it is possible to predict whether unknown sulfamates will be sweet. Predictions based on the correlation were >90% correct for the 12 sulfamates synthesized.

RESULTS AND DISCUSSION

Measurements were carried out on all known carbosulfamates for which taste data were available. Only those sulfamates whose lack of sweetness could be ascribed to a distortion of the angle θ from 60°, *e.g.*, those substituted at C-1 of a chain or a bridgehead (6, 7), were excluded.

Parameters x, y, and z were defined and measured for each R group; from these values, a measure of the size or three-dimensional structure (V) of R is obtained from the product xyz (see *Experimental*).

Table I lists the sulfamates on which measurements were made. The x, y, z, and V parameters are given together with the literature references. The compounds are listed (Table I) in certain convenient groupings, *e.g.*, straight chain, branched, and increasing ring size.

In Fig. 1, a plot of x (the "length" of R) against V was made using the data for the previously reported sulfamates in Table I. The sulfamates synthesized in the present work (Compounds 15, 18, 20, 21, 35, 41, 43, and 45–49) and those about which predictions were made (Compounds 26–28) were excluded. Figure 1 reveals that nearly all of the sweet sulfamates fall into a rectangle (Fig. 1A) whose boundaries are reasonably well defined on three sides, being ~5.2 and ~7.2 Å on the x axis and ~250 Å^3 on the V axis. The fourth boundary appears to be ≤ 90 Å^3 on the V axis. Almost all of the sulfamates lying outside A are not sweet. Some bitter or faintly sweet sulfamates lie at or near one of the three defined boundaries.

Of the 12 sulfamates synthesized, it could be predicted on the basis of Table I and Fig. 1 that 10 of them would not be sweet and two of them would be sweet (*i.e.*, Compounds 46 and 48). Tasting indicated that these predictions were correct in 11 cases. The one exception was the apocamphane compound (Compound 48), which was bitter. All 12 compounds are shown in Fig. 2. Compound 48 might have been excluded since it is an example of a C-1 substituted sulfamate and, therefore, would not be expected to be sweet due to distortion of the angle θ from 60°. However, it is included because it is bitter and it does lie on a boundary.

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