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Sulfamate sweeteners

William J. Spillane,* Caroline A. Ryder, M. Rachel Walsh, Patrick J. Curran, Danny G. Concagh & Siobhan N. Wall

Chemistry Department, University College, Galway, Ireland

After a short introduction to the subject of sulfamate (cyclamate) sweeteners, recent work on structure-taste aspects is reviewed. Some revisitation to well known classes, such as the heterosulfamates and the disubstituted aromatic sulfamates, is made and updates are provided. Several entirely new and novel types of sulfamates including carbinyl sulfamates (ureasulfonates) (I), sulfonyl sulfamates (sulfonamide sulfonates) (II), sulfamidyl sulfamates (sulfamide sulfonates) (III) and iminyl sulfamates (hydrazonyl sulfonates) (IV) are introduced.

$RNHCONHSO_3^-Na^+$ (I)

$RSO_2NHSO_3^-Na^+$ (II)

$RNHSO_2NHSO_3^-Na^+$ (III)

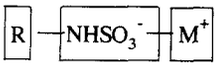
$Ar-C(R)=N-NHSO_3^-Na^+$ (IV)

Finally, the development of QSARs for sweet sulfamates is discussed, using a data base of 20 different sulfamates of widely varying structural types and having a relative sweetness (RS) spread of over 100. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

This paper will consist of a general introduction to sulfamate structure–taste relationships, followed by a discussion of our work on a number of different classes of sulfamate tastants, and finally a summary of our efforts to establish a Quantitative Structure Activity Relationship (QSAR) for sweet-tasting sulfamates.

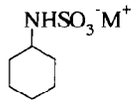
Sulfamates are of the general structural formula:



Sulfamate structure–taste relationships can be viewed under the headings of:

- Role of the cation, M^+
- Role of the sulfamate function, $NHSO_3^-$
- Role of the R group.

The first sulfamate molecule found to display sweet taste was cyclohexylsulfamate (cyclamate) reported by Audrieth & Sveda (1944). Sodium cyclamate has been found to have a relative sweetness (RS) of ~40, compared to a 3% w/v sucrose solution (Benson & Spillane, 1976).



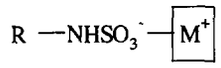
Cyclamate was used commercially for many years as an artificial sweetening agent, but was banned in the US, Canada and the UK in 1970 because of suspected carcinogenic effects. Cyclamate, however, is currently available in more than 50 countries world wide, including several European countries, and is being used in food, drink and pharmaceuticals (Grenby, 1991). In June 1994 the Sweeteners Directive of the European Union was introduced. This directive seeks to harmonize the use of low-calorie sweeteners throughout the European Union once it has been implemented into law by the Member States. The regulations had to be adopted by each country by the end of 1995. The directive allows the use of six low-calorie sweeteners: acesulfame K, aspartame, cyclamate, neohesperidine DC, saccharin and thaumatin, and specifies how much of a sweetener may be used in each type of food or drink. Many Central and Eastern European countries plan to align their regulatory systems with those of the EU (Sweetener Update, 1994).

*To whom correspondence should be addressed.

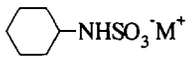
Table 1. Relative sweetness values

M^+	RS
NH_4^+	39.6
Ca^{2+}	39.5
K^+	40.2
Na^+	39.8

Role of the cation, M^+



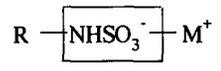
The influence of the cation, M^+, on the taste of cyclamate, has been investigated. The silver, sodium, ammonium and cyclohexyl ammonium salts of cyclamate were all reported to display a 'marked sweetness' by Audrieth & Sveda (1944).



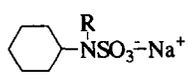
M=Ag, Na, NH_4, cyc-$C_6H_{11}NH_3$
All sweet

Recently, in our own laboratory, the RS values of a number of different cyclamate salts have been measured (Table 1). It would appear that the cation has very little effect on the sweet taste of cyclamate, from these results. However, in all our synthetic work we normally isolate the sulfamates as sodium salts.

Role of the sulfamate function

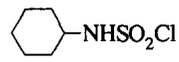


From the very first study of sulfamate structure–taste relationships (Audrieth & Sveda, 1944) it was recognized that the sulfamate function was essential for sulfamate sweetness. The sodium salts of *N*-methyl-*N*-cyclohexylsulfamate, *N*-ethyl-*N*-cyclohexylsulfamate and *N*-dicyclohexylsulfamate, in which the amino hydrogen has been replaced by an alkyl group, were synthesized and tasted. None of these compounds was sweet, indicating that a free amino hydrogen is a prerequisite for sweetness. Similar work, in which the amino hydrogen of other sweet-tasting sulfamates has been replaced by other R groups, has also yielded non-sweet tasting sulfamates.

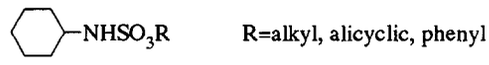


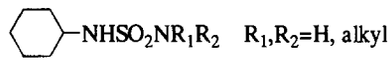
R=CH_3, CH_3CH_2, cyc-C_6H_{11}
Non-sweet

The $NHSO_3^-$ sulfamate function is presumed to contain the Shallenberger AH/B centres necessary for the elicitation of sweet taste by these compounds. The NH probably represents the AH entity. The SO_3^- moiety has been proposed as the B centre of the sulfamate function (Benson & Spillane, 1976). The tastelessness of *N*-cyclohexylsulfamyl chloride, a molecule in which the SO_3^- entity of cyclamate has been replaced by SO_2Cl, was seen as supporting this theory (Benson & Spillane, 1976).

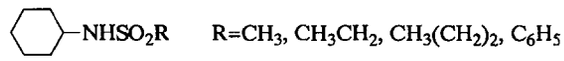


Also, a series of cyclohexylsulfamic acid esters where R represents an alkyl group, alicyclic ring or phenyl ring, and amides, in which R_1 and R_2 are hydrogen atoms or alkyl groups have been synthesized and tasted. All were found to be non-sweet (Pautet *et al.*, 1982).





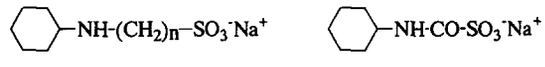
In a further investigation of the role of the sulfamate function in taste determination, a number of sulfonamides were examined and found to be non-sweet (Pautet & Daudon, 1986). Again, this demonstrates the importance of the intact sulfamate anion to sweet taste.



Of course, certain compounds containing the sulfonamide and cyclic sulfamate group in a ring structure are sweet, e.g. saccharin and acesulfame K.

Saccharin Acesulfame K
Free acid forms

A number of cyclamate analogues in which the NH and SO_3 entities of the sulfamate function are separated by an alkyl or carbonyl group were also tested and found to be non-sweet (Pautet & Daudon, 1986).



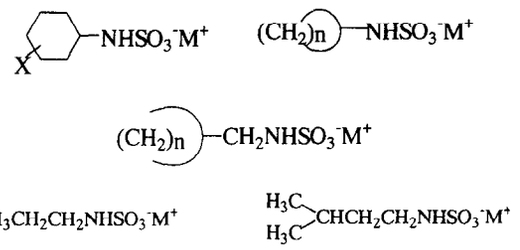
n = 1, 2

Role of the R group

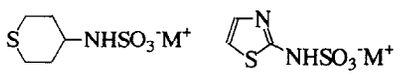
Much work has been done on the study of the role of the R group in sulfamate taste, and sulfamates can be classified according to the nature of the R group, e.g. carbosulfamates, heterosulfamates and aromatic sulfamates.

Various substituted cyclohexylsulfamates were investigated and it was found that substitution is limited to certain ring positions if sweet taste is to occur. The size of the substituent X group is also a factor of importance (Audrieth & Sveda, 1944; Unterhalt & Böschmeyer, 1972; Spillane & McGlinchey, 1981). Different sized ring compounds were also examined. It was found that only 5 to 9 membered rings display sweetness (Blicke *et al.*, 1954; Unterhalt & Böschmeyer, 1972; Benson & Spillane, 1976). Compounds in which a methylene group has been inserted between the cycloalkyl ring and the sulfamate function have been examined by a number of researchers (Nofre & Pautet, 1975; Unterhalt & Böschmeyer, 1972; Spillane & McGlinchey, 1981).

Open-chain compounds have also been investigated, both branched and unbranched. It was discovered that the carbon ring can be replaced by open-chain carbosystems without destroying sweet taste. The two open-chain compounds illustrated here are sweet (Nofre & Pautet, 1975).



Heterosulfamates, in which R is composed of a chain or ring of atoms, containing one or more heteroatoms (sulfur, nitrogen or oxygen) have also been examined and some structure–taste relationships, which shall be examined later in this paper, derived. Both heterosulfamates illustrated here are sweet (Benson & Spillane, 1976; Hurd & Kharasch, 1946).

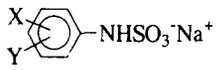


Aromatic sulfamates, in which R consists of a phenyl ring — which can be monosubstituted or multi- (usually di-) substituted — have also been studied.

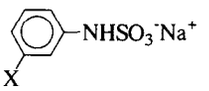
Sulfamates synthesized in our laboratory can be classified according to their R groups.

DISUBSTITUTED AROMATIC SULFAMATES

The first reported structure–taste study on disubstituted aromatic sulfamates was published by our research group in Galway (Spillane *et al.*, 1993). Over 60 compounds have now been studied. The general structure is shown here.



As well as opening up a new area of sulfamate structure–taste study the aim of this work was also partly to examine the effect of structural modification of known sweet-tasting monosubstituted aromatic sulfamates, with special emphasis on completing individual sets of compounds, e.g. synthesis and taste analysis of all six di-fluoro, di-chloro and di-methyl isomers.

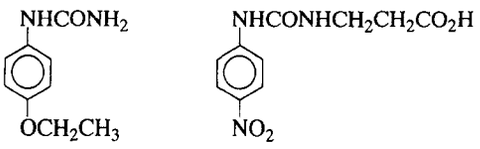


X=Cl, Br, CH_3, F, CN
All sweet

The disubstituted aromatic sulfamates were analysed by a taste panel as previously described (Spillane *et al.*, 1993). Several tastes were displayed (Table 2), with most of the compounds giving bitter tastes. Some structure–taste relationships were developed for the compounds displaying predominant sweetness or sweet aftertaste (Spillane *et al.*, 1993).

CARBINYL SULFAMATES

There are a number of sweet-tasting ureido-containing compounds known, e.g. para-ethoxy phenylurea (dulcin) and suosan and derivatives of suosan.

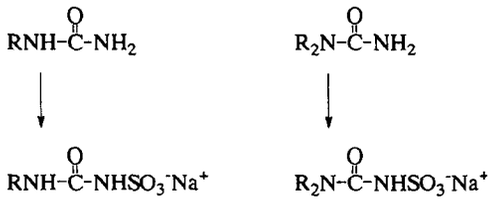


Dulcin Suosan

Table 2. Tastes of disubstituted aromatic sulfamates

Sulfamate taste	Number of compounds
Sweet	7
Sour	8
Bitter	21
Salt	0
Bitter with sweet aftertaste	23
Sour with sweet aftertaste	3
Bitter/sour	1

Derivatives of ureas of the general formulae shown below are under study. The products are known as carbinyl sulfamates or urea sulfonates.

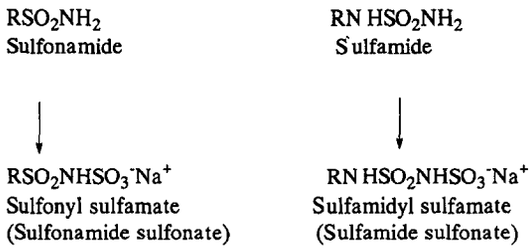


R = aliphatic,aromatic

Taste assessments were carried out on these compounds, but at present the data base of information is too limited to allow structure–taste relationships (SARs) to be derived.

SULFONYL SULFAMATES AND SULFAMIDYL SULFAMATES

The sulfamation of other new N functionalities, sulfonamides and sulfamides of the general structure shown below have been studied. The products are known as sulfonyl sulfamates or sulfonamide sulfonates and sulfamidyl sulfamates or sulfamide sulfonates.

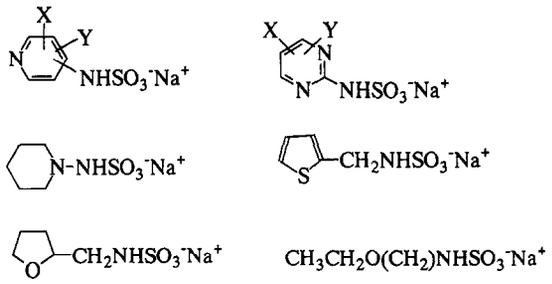


R= alicyclic, aromatic

Taste assessments were carried out on these new sulfamates. Again, the data base of sulfonyl sulfamates and sulfamidyl sulfamates is too limited to develop SARs. As more compounds of this type are synthesized some relationships may emerge.

HETEROSULFAMATES

Heterosulfamates are defined as those sulfamates in which the R group contains one or more heteroatoms: S, N or O. Shown here are a few examples of the heterosulfamates synthesized by our research group: pyridine, pyrimidine, amino piperidine derivatives and other S- and O-containing compounds, both cyclic and open-chain (Spillane & Sheahan, 1989; Spillane *et al.*, 1983).



As can be seen from these examples, this class of sulfamates contains compounds of widely different structures. It is thought that the factors which affect sweet taste activity in the heterosulfamates are different from those which affect carbosulfamate taste. For example, one difference in structure–taste relationships of heterosulfamates is the fact that the requirement for a free amino hydrogen in these compounds for sweet taste is not apparently always necessary, e.g. the S-containing heterocyclic sulfamates shown here are reported as sweet (Wendt & Winkley, 1974).

R=C_2H_5, $CH_3(CH_2)_3$, $HOCH_2CH_2$ Sweet

R=C_2H_5, $CH_3(CH_2)_3$ Sweet

It was found that the structure–taste relationships developed for carbosulfamates are not useful in analysing heterosulfamate taste. In developing an SAR for these compounds Corey Pauling Koltun (CPK) measurements of the length (x), height (y) and width (z) of each molecule were made (Spillane *et al.*, 1983). Volume (V_{CPK}) and first order molecular connectivity ($^1x^v$) values were calculated.

Using the statistical technique of linear discriminant analysis a discriminant function was then obtained which best separated the two categories, sweet and non-sweet. An accuracy of 84% is obtained when this discriminant function is applied to the complete set of 92 compounds.

$$d = -0.86x - 0.81z + 1.31\,{}^1x^v$$

where $d < -8.18$ for sweet compounds, and $d > -8.18$ for non-sweet compounds.

It is observed, however, that many of the misclassified compounds contain S atoms. It has been noted that the S atom behaves differently from N or O atoms when introduced into the sulfamate structure. Replacing a C atom in a sweet carbosulfamate by a S atom has been found to give a compound of reduced sweetness potency, whereas replacement by N or O atoms results in the loss of sweetness. Therefore, it seems logical to examine the S-containing heterosulfamates as an individual group. Taste studies have now been carried out on 28 S-containing heterosulfamates. A graph of the x vs V_{CPK} parameters of these compounds is shown in Fig. 1. This plot was found useful in analysing the tastes of these molecules. The sweet compounds are generally found

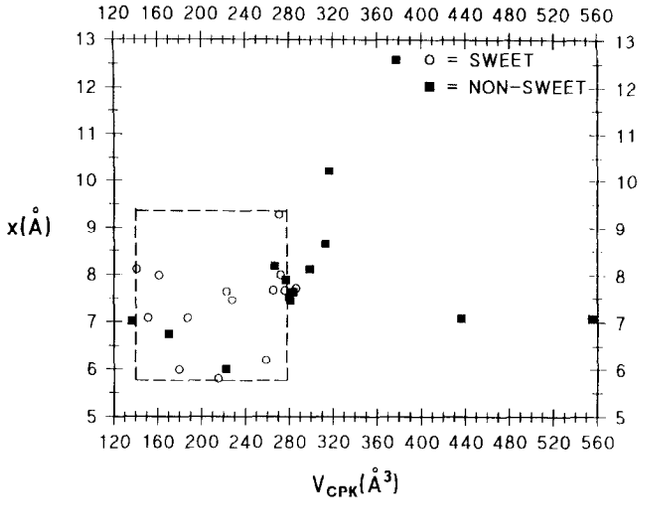


Fig. 1. Plot of x (Å) vs V_{CPK} (Å^3) for S-containing heterosulfamates.

in the rectangle with boundaries: $x \approx 5.8$–9.3 Å and $V_{CPK} \approx 140$–276 Å^3. The non-sweet compounds are largely found outside this area.

IMINYL SULFAMATES

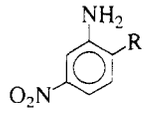
Recently we have become interested in extending the basic sulfamate function by synthesizing iminyl sulfamates (or hydrazonyl sulfonates) of the type shown here:

This work has been fully reported earlier (Spillane & Walsh, 1995).

QSARs

The use of QSARs has a major role to play in helping our understanding of the taste reception mechanism. A QSAR study involves using information on the electronic, hydrophobic and steric properties of a compound as represented by a number of constants. This information is used to investigate the effect of these variables on the activity of an homologous series.

One of the first attempts to develop a QSAR for sweet-tasting compounds is the Deutsch & Hansch (1966) study. The RS of a series of 2-substituted 5-nitroanilines was investigated. Nine compounds were used in the investigation. Equations correlating the RS of these compounds with the Hammett σ constant and the hydrophobic bonding constant, π, of the R substituent were developed. The equation found to give the best correlation is given as:

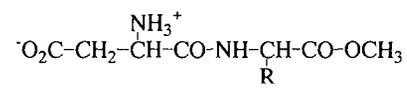


$$\log \text{R.S.} = 1.61\,\pi - 1.83\,\sigma + 1.73$$

$$r = 0.936,\ s = 0.282,\ n = 9$$

It can be inferred from this equation that both the hydrophobic and electronic effects of the substituent, R, are important in determining the RS of these compounds. Since this initial study in 1966, a number of other QSAR investigations have been carried out on the 2-substituted 5-nitroanilines.

Another important QSAR study on taste was that of van der Heijden *et al.* (1979). The work was performed on the aspartyl dipeptide methyl esters, including aspartame. This investigation was restricted to compounds in which only the side-chain R varied and so only its effect on RS was measured. Forty compounds were used in this study. The parameters used were a number of steric STERIMOL parameters which measure the length and width of the R group, the hydrophobic fragmental constant, f, and the parachor parameter, P, which is related to volume.



The best correlation was given by:

$$\log \text{RS} = 0.194f + (1.472 \times 10^{-2}P) - 3.357B_5$$

where $r = 0.909$, $s = 0.40$, $n = 31$.

Here B_5 is a STERIMOL width parameter. This was obtained when some of the compounds were excluded, reducing the data set to 31. This equation demonstrates the influence of a molecule's hydrophobicity and size on sweetness potency.

A QSAR study of a number of compounds from different chemical classes and having different functional groups was carried out by Greenberg (1980). The parameters used in this work were E_s (Taft steric constant), σ^* (Taft polar constant) and log P (hydrophobicity parameter). Using sweetness threshold data for a number of sulfamates obtained in our research laboratory, Greenberg developed the relationship shown here, where c = the taste threshold, between sweetness and hydrophobicity. Seven compounds were used in this study.

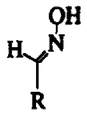
$$\log 1/c = 0.68 \log \text{P} + 0.05$$

where $r = 0.86$, $s = 0.33$, $n = 7$.

The relationship between structure and taste potency of perillartine derivatives was investigated quantitatively by Iwamura (1980), using a number of STERIMOL parameters and log P. Forty-nine compounds were used in this study.

Table 3. Parameters used in deriving QSAR

Parameter	Source
Log P	Calculated using HyperChem and Chem Plus
k_w	Experimentally measured using reversed-phase HPLC
$^3\chi^m$	Calculated from δ^v values
V_{CPK}	Calculated from CPK measurements
GEPOL generated volumes	
V_w	Van der Waals volume
V_a	Accessible volume
V_m	Molecular volume
Molar refractivity	Calculated using HyperChem and Chem Plus
Surface area (approx. and grid)	Calculated using HyperChem and Chem Plus
σ^*	Reported data from literature or calculated



The equation shown here was developed, when the data set was reduced to 38 compounds.

$$\log A = 0.63 \log P + 0.19 L - 0.48 W_1 - 0.62 W_u + 2.87$$

where $r = 0.91$, $s = 0.32$, $n = 38$.

In this equation A represents the activity of the compound, as regards taste potency, irrespective of whether sweet or bitter. The parameters, L and W, are STERIMOL parameters. Again, hydrophobicity is significant in determining taste intensity.

We are attempting to develop a QSAR which correlates the RS of the sulfamates with a parameter/parameters describing their properties. Twenty compounds were used in the present study. All 20 compounds were synthesized and their RS values measured in our own laboratory. A spread of ~110 exists between the sweetest compound, exo-2-norbornylsulfamate (RS = 70.5) and the least sweet compound, *n*-propylsulfamate (RS = 0.63). The parameters used in deriving this QSAR are listed in Table 3.

Interrelationships between parameters

When attempting to derive a QSAR for the set of 20 sulfamates, care was taken to employ combinations of variables that were independent of each other. For example combinations of log k_w and log P cannot be used as both are hydrophobic parameters and are interrelated. There is also a correlation between log k_w (i.e. log capacity factor) and $^3\chi^m$. As expected, V_{CPK} correlates with other calculated volumes. Also, there is a correlation between log k_w and all volumes.

The following equation, which relates log RS to log k_w, for the 20 compounds was derived:

$$\log RS = 0.81 \log k_w + 1.09$$

where $r = 0.67$, $s = 0.39$, $n = 20$.

If the heterosulfamate, 2-thiazolylsulfamate, is excluded from the analysis, the data set is reduced to 19 compounds and the following correlation found:

$$\log RS = 1.234 \log k_w + 1.02$$

where $r = 0.79$, $s = 0.31$, $n = 19$.

Again, these equations demonstrate that hydrophobicity is significant in sweet taste determination.

In view of the structural diversity encompassed by the 19 compounds for which RS data is available, it would be surprising if RS could be accommodated in an equation containing only one independent variable.

We have also found the following correlations:

$$\log RS = 1.85 \log k_w - 0.011 SA(g) + 4.71$$

(where SA = surface area)

where $r = 0.81$, $s = 0.3$, $n = 19$.

$$\log RS = 1.19 \log k_w + 0.11\sigma^* + 0.99$$

where $r = 0.84$, $s = 0.27$, $n = 17$.

The correlation between log RS and k_w and σ^* applies to only 17 compounds. The exo- and endo-2-norbornyl sulfamates are not included in this analysis as σ^* values for these two compounds were not at hand. This is unfortunate as the exo-2-norbornylsulfamate is the sweetest in our data set. It is hoped that when these two compounds are included in the analysis the correlation will be further improved.

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