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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

STRUCTURE-TASTE RELATIONSHIPS FOR SULFAMATE SWEETENERS (RNHSO₃⁻)

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To cite this Article Spillane, William J. and Sheahan, Maryanne(1991) 'STRUCTURE-TASTE RELATIONSHIPS FOR SULFAMATE SWEETENERS (RNHSO₃⁻)', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 59: 1, 255 — 258

To link to this Article: DOI: 10.1080/10426509108045736

URL: <http://dx.doi.org/10.1080/10426509108045736>

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STRUCTURE-TASTE RELATIONSHIPS FOR SULFAMATE SWEETENERS (RNHSO_3^-)

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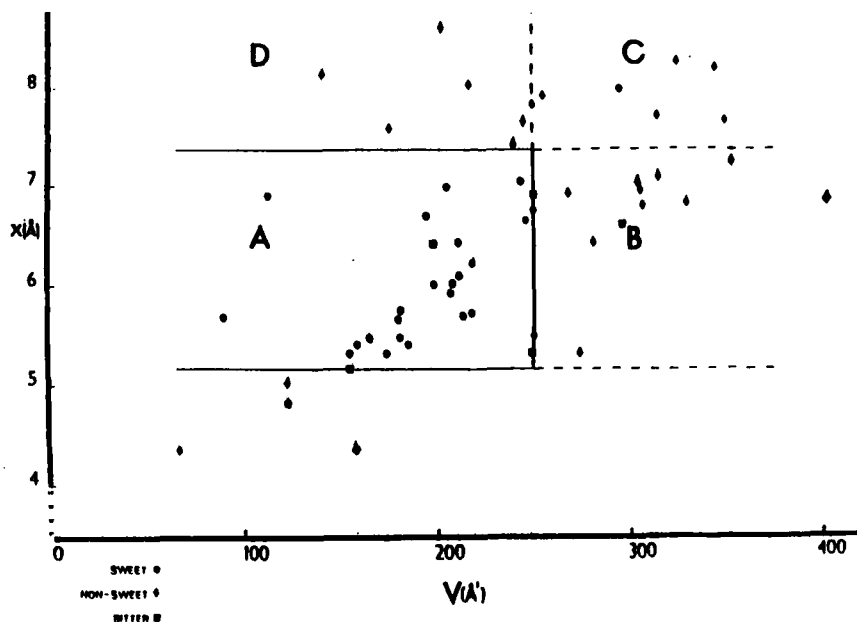
Abstract Structure-taste relationships for sulfamate sweeteners have been derived. The sulfamates have been grouped into four categories: (i) alicyclic, aliphatic-carbosulfamates, (ii) heterosulfamates, (iii) carboaromatic and (iv) disubstituted aromaticsulfamates.

Key words : Structure-taste, sulfamate, sweetener, QSAR.

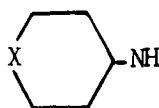
Syntheses in the above and various laboratories worldwide has resulted in the availability of taste data for about 170 sulfamates of which about 40 are sweet and the remainder are described simply as being non-sweet or tasteless or sometimes more specifically as bitter or salty. Since relative sweetness data is only available for about 12 of the sweet compounds structure-taste analysis has tended to be qualitative or semi-quantitative. Using principally Corey-Pauling-Koltun molecular models we have been able to develop semi-QSAR's for carbosulfamates^{1,2}, heterosulfamates^{2,3} carboaromatic⁴ and disubstituted aromaticsulfamates.

Carbosulfamates. - The space-filling properties of the R group in $\text{RNHSO}_3^- \text{Na}^+$, in which R possesses a carbon skeleton (carbosulfamates), have been assessed from measurements of the 'length' ($x\text{A}^0$), the 'height' ($y\text{A}^0$) and the 'width' ($z\text{A}^0$) of R using CPK models.¹ The volume ($V\text{A}^0$) which the R group might occupy is defined by the product $x.y.z$. This is not the molecular volume but a larger and perhaps more significant volume for SAR studies into which R may be thought of as fitting comfortably. Plots of $x\text{A}^0$ vs. $V\text{A}^0$ (see Figure) turn out to be very meaningful since the sweet sulfamates more or less all fall into area A. The lack of sweetness of the sulfamates which fall into areas B, D and C can be rationalized readily if one supposes that those in B are too large, those in D too long and those in C both too large and too long to fit tightly at the receptor site in order that the Shallenberger mechanism may operate. A few sulfamates with $x < 5\text{A}^0$ fall below area A and their non-sweetness may be due to the fact that though they do fit into the receptor site, the fit is too loose and they cannot be 'locked'.

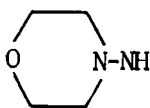
The correlation was originally established with 35 compounds whose taste data had been reported in the literature. Since then we and others have synthesised a further 29 compounds.² About 60 are shown in the Figure.



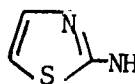
Heterosulfamates. - Plots of x vs. V for various heterosulfamates (here the R group possesses a carbon skeleton which includes one or more heteroatoms) e.g. I - IV did not group the compounds into sweet and non-



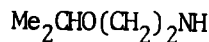
I, X = O, S



II



III



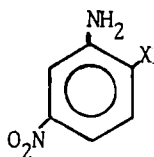
IV

sweet categories indicating that a further parameter(s) would be required to distinguish between the two categories. Molecular connectivities of the first order ($^1x^V$) were calculated for the 33 compounds forming the data base and the application of the statistical technique of linear discriminant analysis allowed the compounds to be successfully grouped into sweet/non-sweet categories utilising a subset containing the three variable x , z and $^1x^V$. This subset was superior to all others examined in that it only misclassified five compounds (three

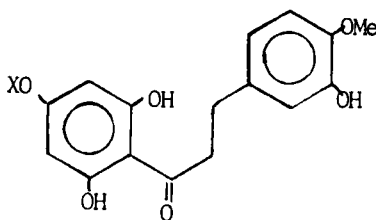
sweet and two non-sweet). With the more recent synthesis of 23 new heterosulfamates it has been possible to reapply the linear discriminant analysis and interestingly for these 23 compounds the same subset $(x, z, 'x^V)$ turns out to be the best in that it misclassifies two sweet compounds and one non-sweet.²

Carboaromaticsulfamates. - The rather surprising discovery that meta-chlorophenylsulfamate, sodium salt, was sweet led to an extensive synthetic study in this area and eventually the discovery of four further sweet meta-compounds (F, Br, CH₃ and CN).⁴ A dihedral angle theory to account for the taste of these compounds was also disputed and in its place an x/V plot was suggested and this seems to indicate that the bulk of R (in this case $X-C_6H_4-$) is crucial in deciding whether or not a compound will be sweet. R is required to be $\sim 5.7A^0$ in 'length' (x) and its 'volume' (V) should lie in the range ~ 120 to $175 A^{03}$ for sweetness to occur.

Disubstituted Aromaticsulfamates. - Nineteen sulfamates of this type have been synthesised in the above laboratory and all are not sweet. Utilising the criteria for sweetness of the monosubstituted aromatics above the lack of sweetness of 18 of the compounds can be rationalized. However, 3,5-dichlorophenylsulfamate, with $x = 5.7 A^0$ and $V = 178 A^{03}$, ought perhaps to be sweet. Another interesting aspect of this work was that five of the starting amines, namely ortho-X, m-nitroanilines, (V) ($X = F, Cl, Br, CH_3, OMe$) were sweet. It is worth noting that some years ago DuBois⁵ was successful in retaining sweetness when he sulfamated the sweet dihydrochalcone (VI, $X = CH_2CH_2NH_2$) to obtain the sweet derivative (VI, $X = CH_2CH_2NHSO_3K$). We suspect that in our sulfamation of compound V we interfered with the operation of the Shallenberger AH,B mechanism and this destroyed sweetness. While on the other hand the sulfamation of the side-chain of compound (VI, $X = CH_2CH_2NH_2$) probably does not interfere with the Shallenberger 'sites'.



(V)



(VI)

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