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Is the Negative Charge on $RNHSO_3^-M^+$ an Essential Requirement for Sulfamate Sweetness?

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Although many structure−taste studies have been carried out on sulfamate (cyclamate) sweeteners, there are still some unanswered questions—notably whether the sulfamate anion, $-NHSO_3^-$, is essential for sweetness in this class of compounds. The literature is contradictory on this point; therefore, 14 sulfamate esters $RNHSO_3R'$, which contain the sulfamate moiety but without the negative charge, i.e., $-NHSO_3^-$, have been synthesized and tasted under standard conditions. Almost all of the esters were found to possess strong sweetness accompanied by bitterness. Because the esters had to be heated in water to 60 °C to dissolve them, it was necessary to check for partial hydrolysis to the free sulfamic acids, $RNHSO_3H$, since they would be sweet and would invalidate the tasting results if formed. This was done by monitoring (gas−liquid chromatography) the formation of alcohol after heating. Negligible or very low hydrolysis to acid was found for all 14 esters. This work, in addition to answering an important structure−taste question, points the way to the potential use of suitable sulfamate esters as additives in situations where the more usual sodium sulfamate salts are unsuitable, for example, in hydrophobic media.

KEYWORDS: Sweetness; sulfamates; esters; bitterness; cyclamates

INTRODUCTION

The nonnutritive sweeteners cyclamate (*N*-cyclohexylsulfamate) as its sodium salt (**1**; **Figure 1**) and calcium salts and cyclamic acid are now permitted in tabletop, food, and beverage usage in over 40 countries including the European Union. A number of other countries allow limited usage (*1*). Many structure−taste studies have been carried out, but almost all of these have concentrated on the effects of changing R in compund **2** (*2*), and a few have looked at the effects of changing the cation M^+ (*3*). An intact sulfamate anion, $-NHSO_3^-$, has long been considered essential for sulfamate sweetness based on the seminal work of Audrieth and Sveda (*4*) and some work in our laboratory (*5*), which showed that alkylation at the amino hydrogen to give **3** destroyed sweetness. This view has been reinforced by work that has demonstrated that cyclohexylsulfamoyl chloride (**4**) (*5*), sulfamides of type **5** (*6*), and sulfonamides of type **6** (*7*) are all nonsweet.

A key question however remains as to the nature of the sulfamate, i.e., is it necessary to have a sulfamate anion, $-NHSO_3^-$, to elicit sweetness? The literature is contradictory on this matter, and there are various reports that sulfamate esters (**7**) are "strongly sweet with an accompanying sharp bitter taste" (*8*), "tasteless" (*9*), and "nonsweet" (*6*). If sulfamate esters are sweet, the possibility that they could be used as additives in situations where the usual sodium sulfamate salts are unsuitable, i.e., hydrophobic media, arises. In this paper, we have resynthesized the esters reported and tasted in references *6*, *8*, and *9* in order to address the questions raised above.

MATERIALS AND METHODS

Chemistry. All 14 sulfamates have been prepared from the appropriate sulfamoyl chlorides (*10*−*13*) and alcohols (*14*). The yields varied from 9 to 41%. The compounds had been made previously by this method (*8*) (**7a**−**e**) and the method in reference *6* (**7g**−**n**), and compound **7f** was made by reaction of 2-methylcyclohexylsulfamic acid with diazomethane. The esters, which we made, were purified by distillation under reduced pressure in a Kugelrohr apparatus (liquids) or by flash chromatography (solids). The Kugelrohr did not allow accurate readings of boiling point/pressure to be made so comparison with earlier reported data was not possible. For the solids, we found that the melting points agreed well with reported values: **7g**, 56−58 °C (lit. 56 °C (*6*)); **7j**, 45−46 °C (lit. 48 °C (*6*)); and **7n**, 52−54 °C (lit. 54 °C (*6*), 49−51 °C (*14*)).

All ester products gave C, H, and N microanalysis within ±0.5% except compounds **7a**,**k**. Their analyses are as follows. Compound **7a**: theory: C, 43.06; H, 8.77; N, 7.17. Found: C, 42.41; H, 8.30; N, 6.94. Compound **7k**: theory: C, 51.06; H, 8.94; N, 5.96. Found: C, 51.70; H, 8.16; N, 6.25. All esters were characterized by ^1H and ^{13}C NMR, IR, and gas chromatography−mass spectrometry (GC-MS). The typical peaks expected were observed in proton and carbon-13 NMR. All of the esters gave the following characteristic IR frequencies (15): N−H, 3250−3380; 1320−1380; and 1100−1190 cm^{-1}. N−S: 880−980 cm^{-1}. In the mass spectrum, the expected fragments were observed. Molecular ions were not observed due to the lack of stability of the esters at the operating temperature.

Instrumentation. A JEOL 400 mHz spectrometer was used for NMR, a Perkin-Elmer FT-IR spectrum 100 was used for IR, and a Shimadzu QP5000 was used for mass spectrometry (electron impact low resolution at 70 kV). Column: 5% phenyl−95% methylpolysiloxane (30 m × 0.25 mm i.d.); temperature, 80 °C. For gas−liquid

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Table 1. Taste Data on Sulfamate Esters

compd	ester R	ester R′	(M)	no.[a]	predominant taste[b]
7a	Bu^i	Pr^n	0.002	10	sweet(60)/bitter(70)
7b	Bu^i	Et	0.002	11	bitter(50)[c]
7c	Bu^n	Pr^n	0.003	11	sweet(50)[d]/bitter(80)
7d	Bu^n	Et	0.003	10	sweet(50)/bitter(50)
7e	Pr^n	Pr^n	0.003	11	sweet(60)/bitter(50)
7f	2-Me-cyc-C_6H_{10}[e]	Me	0.002	8	bitter(67)
7g	cyc-C_6H_{11}	Me	0.002	10	sweet(50)[f]/bitter(50)
7h	cyc-C_6H_{11}	Et	0.002	11	sweet(50)[g]/bitter(60)
7i	cyc-C_6H_{11}	Pr^n	0.002	11	sweet(50)[h]/bitter(60)
7j	cyc-C_6H_{11}	Pr^i	0.002	10	sweet(80)/bitter(80)
7k	cyc-C_6H_{11}	Bu^n	0.001	10	sweet(90)/bitter(60)
7l	cyc-C_6H_{11}	Bu^i	0.001	10	sweet(80)/bitter(70)
7m	cyc-C_6H_{11}	Bu^s	0.001	10	sweet(50)/bitter(70)
7n	cyc-C_6H_{11}	cyc-C_6H_{11}	0.001	10	sweet(80)/bitter(80)

[a] Number of tasters. [b] Taste found by ≥50% of the tasters. [c] Thirty percent of tasters reported sweetness. [d] Six tasters reported the sweetness as being aniseed (or liquorice)-like. [e] 2-Methylcyclohexyl. [f] Six tasters reported the sweetness as being fruity/vanilla-like. [g] Three tasters described the sweetness as being fruity (similar to wine gums). [h] Six tasters found the sweetness to be caramel (toffee)-like.

chromatography (GLC), Pye-Unicam 104 and Shimadzu GC-8A chromatographs were used. Column: 10% Carbowax 20 M on Chromosorb W mesh size 80/100; temperature 50−115 °C (depending on the alcohol being analyzed); carrier gas, N_2 1.2 kg cm^{-2}. A Perkin-Elmer 2400 series II analyzer was used for C, H, and N analysis.

Sensory Analysis of Esters (7). The standards used were 1.5, 2.5, and 3.0% (g/mL) sucrose, 0.01 and 0.02% (g/mL) citric acid, and 0.00005 and 0.000075% (g/mL) quinine sulfate dihydrate. At least eight tasters and usually 10 or 11 were used in assessing the taste portfolio of each of the compounds. Each taster was first trained using the standards. Checking for saltiness and umami tastes was not included since a preliminary screening did not reveal the presence of either of these tastes. All solutions including the various standards were made up with deionized water of pH 5.7 ± 0.2. The ester solutions had to be heated to 60 °C and were maintained at this temperature for 20 min in order to dissolve all of the ester at the concentration levels given in **Table 1**. This heating was carried out in 5 mL round-bottomed glass flasks with tight-fitting rubber septa used to ensure that no evaporation of alcohol occurred during heating. The ester solutions were then allowed to cool back down to ∼20 °C before tasting. Initially, some preliminary tasting was carried out for all of the esters at 0.003 M concentrations, but in a number of cases, the taste panellists found the taste to be too strong. Therefore, in these cases, the concentrations were decreased so that each panellist could tolerate the taste and therefore give a better description of the taste portfolios of the compounds.

GLC Analysis of Sulfamate Hydrolysates. Aliquots (3 mL; made up in deionized water, pH 5.7 ± 0.2) of 0.1 M solutions of each ester in the presence of 0.05 M of the appropriate internal standard (see **Table 2**) were heated to 60 °C and maintained at this temperature for 20 min. After they were cooled, 3 μL samples of the hydrolyte were injected (injection/detection temperature 125−200 °C) on to a column using column temperatures of 50−115 °C (depending on the respective alcohol that would be produced on hydrolysis). **Figure 2A** shows a typical result, for compound **7c**, where it is estimated that less than 0.3% hydrolysis has occurred.

However, when the same solution was heated at 90 °C for 75 min, substantial hydrolysis (∼18%) occured (**Figure 2B**). The results for the other esters were obtained in the same manner; it is seen that the maximum percent hydrolysis (after heating at 60 °C for 20 min) is ∼4%, and this arises only with esters **7b**,**d**. The percent hydrolysis figures in **Table 2** were obtained from a series of standard curves in which peak area ratios (PARs) for the alcohol being liberated/internal standard were plotted against the concentration (0−0.1 M) of the "liberated" alcohol in water. To check for possible alcohol evaporation, some test solutions containing known amounts of alcohol and 0.05 M internal standard were injected before heating at 60 °C for 20 min, and after they were heated, they fell on the same position on the standard curve, thus showing that evaporation of alcohol is not a problem.

Table 2. GLC Analysis[a] of Hydrolysates of Esters (**7**)

ester R	ester R′	alcohol liberated	internal standard	% hydrolysis
Bu^i	Pr^n	Pr^nOH	Bu^nOH	<0.3
Bu^i	Et	EtOH	Pr^nOH	∼4.0
Bu^n	Pr^n	Pr^nOH	Bu^nOH	<0.3
Bu^n	Et	EtOH	Pr^nOH	∼4.0
Pr^n	Pr^n	Pr^nOH	Bu^nOH	<0.3
2-Me-cyc-C_6H_{10}	Me	MeOH	Pr^nOH	∼3.0
cyc-C_6H_{11}	Me	MeOH	Pr^nOH	∼2.5
cyc-C_6H_{11}	Et	EtOH	Pr^nOH	∼0.8
cyc-C_6H_{11}	Pr^n	Pr^nOH	Bu^nOH	<0.3
cyc-C_6H_{11}	Pr^i	Pr^iOH	Bu^nOH	∼2.8
cyc-C_6H_{11}	Bu^n	Bu^nOH	Pr^nOH	<0.3
cyc-C_6H_{11}	Bu^i	Bu^iOH	Pr^nOH	<0.3
cyc-C_6H_{11}	Bu^s	Bu^sOH	Bu^nOH	∼3.0
cyc-C_6H_{11}	cyc-C_6H_{11}	cyc-$C_6H_{11}OH$	Bu^nOH	<0.6

[a] Full details of GLC conditions are in the Materials and Methods.

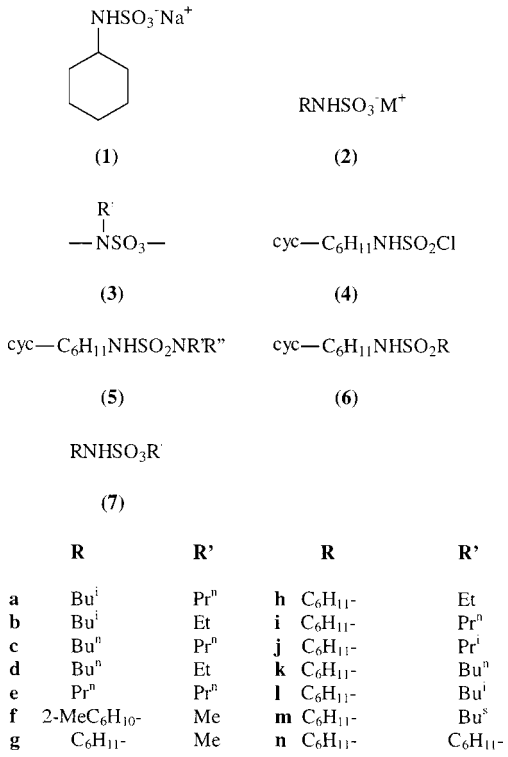

Figure 1. Molecular structures of sodium cyclamate (**1**), general sulfamate salt (**2**), alkylated sulfamate (**3**), cyclohexylsulfamoyl chloride (**4**), cyclohexylsulfamides (**5**), cyclohexylsulfonamides (**6**), and sulfamate ester (**7**).

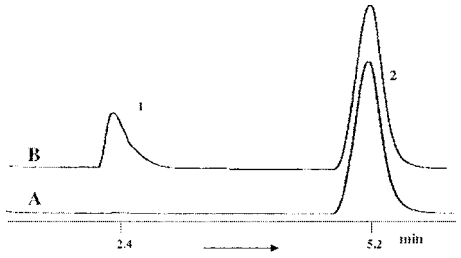

Figure 2. GLC of hydrolysates of *n*-propyl *n*-butylsulfamate (**7c**) (**A**) after heating at 60° C for 20 min and (**B**) after heating at 90 °C for 75 min. Retention times: *n*-propanol, 2.4 min; *n*-butanol (internal standard), 5.2 min.

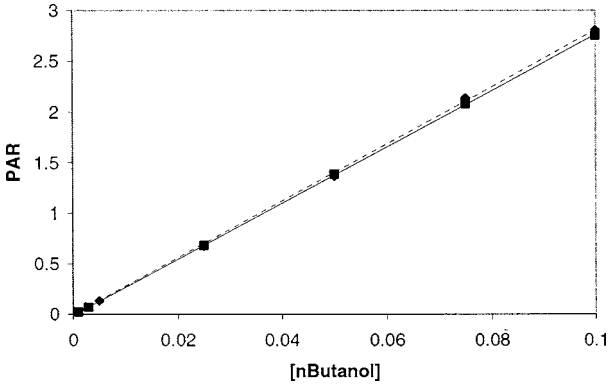

Figure 3. PARs of *n*-butanol/*n*-propanol (0.05 M internal standard) against the concentration of *n*-butanol: lower solid line (—, ■) derived in water only and upper dashed line (- - -, ◆) derived in the presence of 0.1 M *n*-butyl cyclohexylsulfamate (**7k**).

In an additional set of experiments to test the efficiency of the extractability of alcohols in the presence of organic sulfamate ester, esters/internal standards were used as follows: **7d**/Pr^{n}OH, **7k**/Pr^{n}OH, **7m**/Bu^{n}OH, and **7n**/Bu^{n}OH. In a typical run, a set of 0.1 M solutions (3 mL aliquots) of ester in the presence of 0.05 M internal standard were injected with the appropriate liberated alcohol in amounts varying from 0.005 to 0.1 M. Samples (3 μL) of each solution were then injected, and a new standard curve was generated. The agreement between the previous standard curve and the new one was excellent, and a typical result is shown for ester **7k** (**Figure 3**).

Attempt To Determine Sweetness of a Cyclamic Acid Spiked Solution. A 0.00009 M cyclamic acid solution in deionized water (pH ~ 5.7) was prepared. This would be the cyclamic acid content of one of the ester solutions if 3% hydrolysis of any of the cyclohexyl esters had occurred during the heating at 60 °C. The 10 tasters used to assess this solution all emphasized the difficulty of detecting any taste at all. Four could get no trace of a sweet or bitter taste; two noted a very faint sweet taste; two found a very slight bitter taste; and two reported a barely discernible sour taste. These tastes were at extremely low levels as compared to the taste intensities displayed by solutions of the cyclohexyl esters (**7g**−**n**; **Table 1**); therefore, even if 3% hydrolysis had taken place during the heating procedure, it would not have effected the taste results in **Table 1**.

RESULTS AND DISCUSSION

Many sulfamate esters have been synthesized (*16*), and interest in them has risen sharply over the last 12 years due to their importance in medicinal chemistry (*17*, *18*). Only a small number however have been made with a view to ascertaining their tastant properties. Sowada (*8*) synthesized five sulfamate esters (**7a**−**e**) in 1965, and he described them as having "a strong sweet taste accompanied by a sharp bitter taste." Unterhalt (*9*) in 1975 made the ester **7f** and cited it as being "tasteless", and finally, in 1982, Pautet et al. (*6*) made nine more esters and found them to be "not sweet" (*16*). Many years ago, we made one of these latter esters, i.e., **7h**, and found that it was sweet (*19*). The information available therefore on the precise structural requirements needed to elicit sweetness in the sulfamate moiety of cyclamates is inconclusive and contradictory. Against this background, it was decided to repeat the previous synthesis; thus, 14 sulfamate esters (**7a**−**n**) have been made and tasted under controlled conditions. The esters were synthesized by standard literature methods and purified by distillation (liquids) and flash chromatography (solids) (see Materials and Methods). An array of methods was used to characterize the compounds. Three of the esters were solids (**7f**,**j**,**n**), and the remainder were liquids.

Virtually all tastant studies involving sodium or other metallic sulfamates have been carried out in water, and it was felt that it would be important to assess the tastes of the sulfamate esters under similar conditions in order to allow possible future comparisons of data. Pautet and co-workers tasted the esters that they made in "concentrated aqueous solutions" (*6*) and Sowada (*8*) and Unterhalt (*9*) may have tasted the neat compounds. To dissolve the esters in water, it was necessary to heat the aqueous solutions to 60 °C (sonication failed to dissolve them properly) and this has the attendant risk that partial hydrolysis of the esters could occur (*20*, *21*) according to eq 1.

$$RNHSO_2OR^1 + H_2O \rightarrow RNHSO_2OH + HOR^1 \quad (1)$$

If this was to occur, it would invalidate the tasting results because the acids produced have inherent sweet tastes. For example, cyclohexylsulfamic acid has a relative sweetness (RS) of 46 (*22*) measured against a 3% sucrose solution as the standard. The sodium salts of *i*-butyl-, *n*-butyl-, and *n*-propylsulfamates have reported RS values of 3.5, 2.9, and 0.6, respectively (*23*), and their free acids would very likely also exhibit some sweetness. It therefore becomes critical to the present work to establish the degree of hydrolysis, if any, occurring when the esters are heated to 60 °C for 20 min in the dissolution process. This was checked by a GLC method for all 14 esters and independently by using a spiked solution of cyclamic acid, which duplicated the amount of this acid that would be produced if as little as 3% hydrolysis of the tastant solution of **7g**−**n**) occurred. The results in **Table 2** show that the level of hydrolysis is negligible or very low, and the sensory data from the study of the spiked solution of cyclamic acid showed that the tasters had great difficulty picking up any tastes at all and all found that the faint tastes present were of far lower intensity than those they encountered when tasting the 14 ester solutions (**Table 1**).

In the GLC analysis, it would not be possible to pick up the small amounts of alcohols produced for the 0.001−0.003 M solutions of esters used in the sensory analysis (**Table 1**); therefore, more concentrated aqueous solutions of esters (0.1 M) were used in the heating procedure at 60 °C. The data in **Table 2** show that only very small or negligible amounts of hydrolysis occurred (see **Figure 2A**); however, when these ester solutions were heated more strongly at 90 °C for 75 min, appreciable hydrolysis was observed in all cases; a typical result for **7c** is shown (see **Figure 2B**). Because the hydrolysis of sulfamate esters under a variety of conditions is first-order in substrate (*20*, *21*), the rate of the hydrolysis is independent of the initial concentration of ester; thus, there is no possibility that the more concentrated ester solutions used for the GLC work might hydrolyze more extensively (faster rate of reaction) than the less concentrated solutions. The procedures where different concentrations of esters were used for tasting and for GLC analysis can therefore be compared.

One other matter needs to be addressed. Because the 0.1 M solutions of the esters used above are not completely homogeneous, the possibility exists that some alcohol, if formed by hydrolysis, might be absorbed into the organic ester phase and this could lead to some of it not being detected. To check this possibility, four standard curves were set up using aqueous solutions containing 0.1 M ester, 0.05 M internal standard, and varying amounts of alcohol (0−0.01 M). The standard curves set up for the analysis above used only 0.05 M internal standard and varying amounts of alcohol (0−0.01 M) in water. If alcohol was being absorbed or occluded in some way, a different standard curve would be expected. The esters chosen for this study were selected in order to try to maximize this absorption

if it did occur. As both *n*-butanol and *s*-butanol have somewhat greater solubilities in organic media (e.g., ether, ethanol) than in water (*24*), we used esters **7k** and **7m**, which if hydrolyzed, would give rise to one of these alcohols. In this way, we hoped to facilitate the operation of the above effect, and if absorption of alcohol occurred, it would manifest itself in the generation of a new and different standard curve, which might exhibit discontinuities and/or scatter. Two more esters, i.e., **7d** and **7n**, were also included in the study since they had a lower and a higher molecular weight, respectively, of the esters synthesized for this work. **Figure 3** shows a typical result for ester **7k**. The upper dashed line (- - -, ■) is the original standard curve derived in water, and the lower solid line (—, ◆) was obtained by carrying out an experiment in which varying amounts of *n*-butanol were added to solutions that were 0.1 M in ester (**7k**) and 0.05 M in *n*-propanol (internal standard). It is readily seen that the two lines are very close to one another; thus, there appears to be no evidence for partial extraction of alcohol. Similar results were obtained with esters **7d**,**m**,**n** by adding varying amounts of the appropriate alcohol to solutions of ester and the appropriate internal standard. In conclusion, it is clear that the absorption of alcohol by ester in these experiments is not a problem and the results in **Table 2** give an accurate estimate of the upper limits of detection of alcohol; thus, if any hydrolysis occurs, it must be less than the percentages in the table.

The taste data in **Table 1** show good agreement with Sowada's data (*8*) for esters **7a**−**e** except for **7b**, which he found to be sweet/bitter and we found to be predominantly bitter although some sweetness was detected (see **Table 1**, footnote c). Unterhalt reported (*9*) that **7f** was "tasteless", but we found it to be bitter. We found the esters **7g**−**n**, reported by Pautet and co-workers (*6*) as "nonsucre" (i.e., not sweet), to be clearly sweet/bitter (**Table 1**). These discrepancies in the tasting analysis could be due to several factors: (i) because **7f** was not sweet, Unterhalt may have been content to describe it as tasteless ("geschmacklos") or nonsweet (this is common in "sweet taste" literature and may indicate a lack of interest in nonsweet tastes); and (ii) Pautet et al. used "concentrated aqueous solutions" (strength not specified), and the sweet taste (as we found, see Materials and Methods) may have been masked by bitterness in such concentrated solutions.

This present work has now clearly established that a sulfamate anion, $-NHSO_3^-$, is not essential for sulfamate sweetness. This is an important point, hitherto unclear, in our understanding of structure−taste relationships for the broad class of sulfamate (cyclamate) sweeteners. Furthermore, it points to the possibility of obtaining and using a sweet sulfamate ester in hydrophilic media—a finding that would greatly extend the use of sulfamates as sweet additives.

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