Thermodynamic Roles of Solubility in Taste Responses of Amino Acids

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Abstract

Bitter, sour and sweet responses of amino acids were related to their solubilities S_w, which are virtually equal to the reciprocals of activity coefficients at infinite dilution in water γ_w, and also related to their excess partial molar entropies of transfer $T\Delta S_t^E$. **Chem. Senses 21: 405–409, 1996.**

Hydrated solute is the form of the sapid substance that is actually presented to the receptors because a sapid substance must be in solution to exert its effect (Birch, 1987). The thermodynamic description of the actual behavior of tastant molecules in the receptor environment has been a point of concern in gustatory chemoreception. The change in hydration entropy reflects the water-structure formed around solute species for both electrolytes and non-electrolytes (Frank and Evans, 1945). The solute behavior of amino acids and proteins highly diluted in aqueous phase was evaluated in terms of the free energy of transfer, ΔF_t, measured from the relative solubility of the same solute between ethanol and water solvents (Tanford, 1962).

The bitterness of amino acids and peptides was related to this free energy (Ney, 1971; Weiser and Belitz, 1976), and also to molecular connectivity (Gardner, 1980). Parachors (apparent molar volumes) were also used as a parameter to describe solute–water interaction in gustation (Birch, 1987). Recently, for monofunctional methylene homologs, the values of γ_w (activity coefficient of solute at infinite dilution in water) were related to the odor and flavor detection thresholds, D, with constant values of apparent threshold activities $D\gamma_w$ (Yamanaka, 1995). The γ_w represents the magnitude of solute–water interaction in solutions at infinite dilution, and is defined for non-electrolytes as the deviation from ideal solute behavior in the pure liquid solute; $\gamma_w \rightarrow 1$ as the solution composition approaches the pure liquid solute. For solid amino acids, the γ_w can be regarded as the deviation from ideal solute behavior in the hypothetical pure liquid of the amino acid which would be produced by supercooling the saturated solution of the solid amino acid to the desired temperature below the melting point (Shinoda, 1978).

When a liquid compound and water are incompletely miscible, the activities of the compound are the same in the two phases which are in equilibrium with each other, or $S_s\gamma_s = S_w\gamma_w$. Where S_s, S_w represent the solubilities of the compound (expressed in mole fraction) in the compound-rich phase and in the aqueous phase respectively, and γ_s, γ_w are their activity coefficients, defined as the deviation from ideal solute behavior in the pure liquid of the compound.

Then a relation $\gamma_w = 1/S_w$ holds for compounds that are slightly soluble in water since the activity $S_s\gamma_s$ is unity in the compound-rich phase, which is practically regarded as the pure liquid (Butler *et al.*, 1933).

In the above binary mixture, the partial molar free energy change ΔF_t for transfer of 1 mol of compound, at the same concentration, from the compound-rich phase to the saturated aqueous phase is described as $\Delta F_t = RT\ln S_s/S_w + RT\ln\gamma_s/\gamma_w$ (Nozaki and Tanford, 1971). The term $RT\ln\gamma_s/\gamma_w$ is easily recognized as the non-ideal free energy of transfer in excess over the ideal free energy of transfer $RT\ln S_s/S_w$. Thus, for compounds that are slightly soluble in water, the excess partial molar free energy of transfer ΔF_t^E can be expressed as $\Delta F_t^E = -RT\ln\gamma_w$ or $\Delta F_t^E = RT\ln S_w$ since $\gamma_w = 1/S_w$ and $\gamma_s \approx 1$ at $S_s \approx 1$. The entropy term $T\Delta S_t^E$ and the enthalpy ΔH_t^E corresponding to the ΔF_t^E can also be described in terms of γ_w (or $1/S_w$) respectively. The purpose here is to apply the relation $\gamma_w = 1/S_w$ as a first approximation to elucidate the functions of the γ_w and the term $T\Delta S_t^E$ in the chemoreception for the bitter, sour and sweet amino acids that are slightly soluble in water.

The data on solubility in water S_w (used as $\log 1/S_w$ in mole fraction) were taken for each amino acid listed in the references (cf. footnotes to Table 1). The taste recognition threshold values D (used as $\log 1/D$ in mole fraction) for L-amino acids and the classification of their taste qualities were quoted from Kirimura *et al.* (1969). According to the previous work (Yamanaka, 1995), the apparent threshold activity (A_{thr} or $D\gamma_w$) for each amino acid was calculated as the value of $\log S_w/D$ (corresponding to $\log 1/D\gamma_w$).

For the 12 amino acids that have an A_{thr} value higher than 1.7, the pairs of $\log 1/D$ versus $\log 1/S_w$ were subjected to a simple regression of $\log 1/D = a\log 1/S_w + b$, regardless of their disparate taste qualities. Figure 1 shows that the value of log 1/D for each of the amino acids tested is related to the corresponding $\log 1/S_w$ with the slope a of 0.877 ± 0.10 and the intercept b of 2.510 ± 0.24 ($r = 0.94$; $s = 0.242$). The isoelectric points of most amino acids are not far away from the pH range of saliva (Bradly, 1991). In the isoelectric solutions, the predominant species are neutral dipole species, i.e. zwitterions (Greenstein and Winitz, 1961b). Thus, as discussed in the previous work, the values of A_{thr} (an apparent recognition threshold activity) reflect the activity of zwitterions in receptor environment where the zwitterions actually interact with the gustatory receptors in equilibrium. Furthermore the decrease in the $\log 1/D$ for bitter, sour and sweet responses may be compensated by increasing $\log\gamma_w$ (or $\log 1/S_w$).

The values of ΔF_t^E, $T\Delta S_t^E$ and ΔH_t^E were calculated at 25°C. The excess partial molar free energy of transfer ΔF_t^E was obtained from $\Delta F_t^E = RT\ln S_w$ using the value of solubility at 25°C. The corresponding entropy term $T\Delta S_t^E$ was given by $T\Delta S_t^E = RT\ln S_w + RT^2\partial\ln S_w/\partial T$ derived from $-(\partial\Delta F_t^E)/\partial T = \Delta S_t^E = R\ln\gamma_w + RT\partial\ln\gamma_w/\partial T$ which was obtained by differentiating $\Delta F_t^E = -RT\ln\gamma_w = \Delta H_t^E - T\Delta S_t^E$ with respect to T. For each amino acid, the slope of solubility versus temperature was taken to determine $\partial\ln S_w/\partial T$ around 25°C. The corresponding enthalpy ΔH_t^E was obtained as a sum of the calculated values of ΔF_t^E and $T\Delta S_t^E$ on the basis of $\Delta H_t^E = \Delta F_t^E + T\Delta S_t^E$.

The values of ΔF_t^E, ΔH_t^E and $T\Delta S_t^E$ at 25°C are summarized in Table 1. For each of the amino acids tested, the values of ΔF_t^E, ΔH_t^E and $T\Delta S_t^E$ are always negative. The negative value of ΔF_t^E for each amino acid indicates that the transfer of zwitterions from the hypothetical pure liquid to the saturated solution is moderately favorable. In fact, all the amino acids tested are slightly soluble in water since their solubilities fall in the range 0.67–3.17.

In Table 1, the differences of the ΔF_t^E value are observed for an additional CH_2 or CH_3 group between the homologous amino acids. The differences are 820 cal per CH_2 between valine and leucine, 350 cal per CH_3 between glycine and alanine, and 410 cal per CH_3 between serine and threonine. These differences are comparable to a mean value of 806 cal per CH_2 and a value of 400 cal per CH_3 obtained from the solubilities by using the relation $\gamma_w = 1/S_w$ by Butler *et al.* (1933) for the differences of the excess partial molar free energy between the successive members of n-alkanols. This suggests the validity for applying the relation $\gamma_w = 1/S_w$ to a series of amino acids. On the contrary, the deviations of ΔF_t^E are the same negative values of –260 cal per CH_2 between asparagine and glutamine, and between aspartic acid and glutamic acid, which may be caused by that one additional CH_2 group between polar groups increasing the solubility S_w to the same extent.

Figure 2 shows the relationship between the negative values of $T\Delta S_t^E$ and ΔH_t^E for each amino acid. The parallel lines indicate that there is one rather good straight line which represents sweet or bitter monobasic amino acids, and another which represents the amino acids that have a tendency to increase solubility on account of the additional CH_2 group between the polar groups. The deviation of methionine from a group of bitter amino acids might be

Table 1 Activities coefficients, thermodynamic properties, taste recognition thresholds and recognition threshold activities for L-amino acids

	$\log \gamma_w$[a] (log $1/S_w$)	$-\Delta F_t^E$[b]	$-T\Delta S_t^E$[c]	$-\Delta H_t^E$[d]	log $1/D$[e]	A_{thr}[f] $-\log D\gamma_w$	Ref.
Sweet amino acids[e]							
Glycine	1.25	1.72	0.44	2.16	3.50	2.25	R1
Alanine	1.49	2.07	1.25	3.32	3.92	2.43	R1
Serine	1.23	1.68	–	–	3.50	2.27	R2
Threonine	1.53	2.09	0.73	2.82	3.40	1.89	R3
Proline	0.69	0.94	0.49	1.43	3.00	2.31	R1
Hydroxyproline	1.32	1.80	1.17	2.97	4.16	2.84	R1
Bitter amino acids[e]							
Valine	1.87	2.55	2.34	4.89	4.21	2.34	R5
Leucine	2.47	3.37	2.82	6.19	3.58	1.11	R1
Isoleucine	2.25	3.07	2.57	5.64	3.91	1.66	R1
Arginine	1.81	2.47	–	–	4.28	2.47	R4
Histidine	2.30	3.14	–	–	4.64	2.33	R6
Methionine	2.38	3.25	0.92	4.17	4.44	1.79	R7
Phenylalanine	2.49	3.40	2.19	5.59	4.00	1.51	R1
Tryptophan	3.02	4.12	2.82	6.94	4.10	1.08	R1
Sour and MSG-like amino acids[e]							
Asparagine	2.47	3.36	0.51	3.87	3.80	1.33	R1
Glutamine	2.27	3.10	1.34	4.44	3.51	1.24	R8
Aspartic acid	3.17	4.32	1.81	6.13	5.17	2.00	R1
Glutamic acid	2.98	4.06	1.49	5.55	5.21	2.23	R1

The data on solubility were quoted from the following sources for L-amino acids. R1, Greenstein and Winitz (1961a) in which the original references were cited. R2, Brockmann and Muss (1956). R3, West and Carter (1937). R4, Vickery and Leavenworth (1928). R5, the data on D-valine were quoted from Dalton and Schmidt (1936). R6, Dunn *et al.* (1942). R7, Hill and Robson (1933). R8, Eisenschimmel.

[a] The value of activity coefficient γ_w was taken as the reciprocal of solubility $1/S_w$ (in mole fraction) for each amino acid at 25°C except serine at 20°C and arginine at 21°C.

[b] Excess partial free energy of transfer (kcal/mol) calculated from $\Delta F_t^E = RT\ln S_w$ at 25°C.

[c] Excess partial molar entropy term of transfer (kcal/mol) obtained from $T\Delta S_t^E = RT\ln S_w + RT^2 \partial \ln S_w/\partial T$ at 25°C.

[d] Excess partial molar enthalpy of transfer (kcal/mol) obtained from $\Delta H_t^E = \Delta F_t^E + T\Delta S_t^E$ at 25°C.

[e] Recognition threshold expressed in the form of log1/D (in mole fraction) and the classification of their taste qualities were quoted from Kirimura *et al.* (1969)

[f] Recognition threshold activity expressed as logS_w/D equivalent to $-\log D\gamma_w$.

caused by the fact that the two methylene groups between the two polar groups of SCH_3 and $CH(NH_2)COOH$ do not measurably decrease its solubility. The negative value of $T\Delta S_t^E$ for each amino acid results from a sum of contributions from productive or disruptive changes in 'ice-like-ness' in the water evoked by the structure-making or breaking tendency distinctive of structural groups in the zwitterion. Also, the negative value of ΔH_t^E implies that heat evolves on account of the production of 'ice-like-ness' in the water adjacent to each zwitterion. That is, each amino acid acts as a structure-maker. All of the amino acids tested behave very much like non-electrolytes; the zwitterions carry not only electric charges but also a wide variety of electrically uncharged groupings. These results are

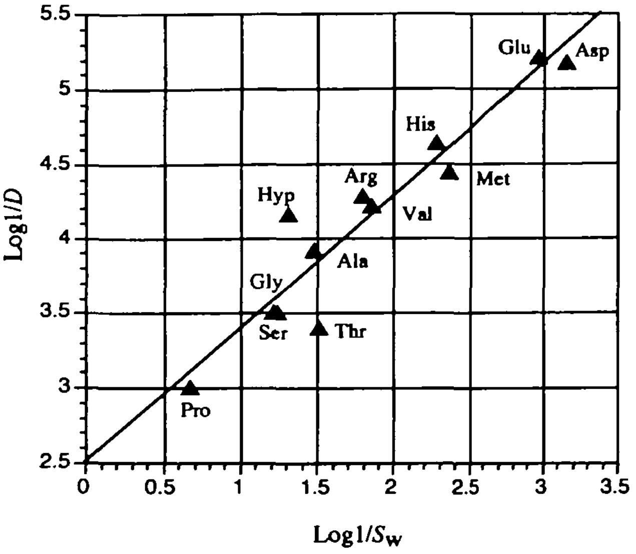

Figure 1 Relation between log1/S_w and log1/D for the L-amino acids that have an A_{thr} value >1.7. The solid line represents the regression line of log1/D = 0.877log 1/S_w + 2.51 (r = 0.94, s = 0.242).

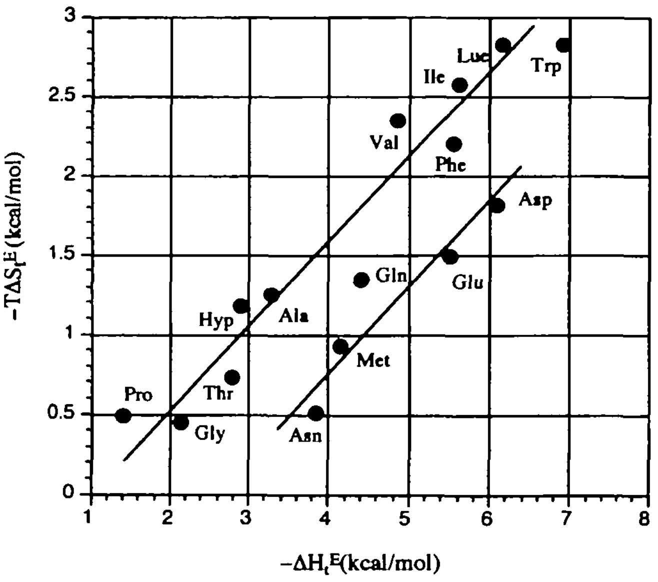

Figure 2 Relation between ΔH_t^E and $T\Delta S_t^E$ for the L-amino acids listed in Table 1. The two solid lines respectively represent one group having a tendency to decrease solubility with increase in bulkiness of side chain of the monobasic amino acids and another group having a tendency to increase solubility with increase in the number of CH_2 groups between two polar groups

consistent with the concept of hydration entropy proposed by Frank and Evans (1945).

The bitter amino acids, except methionine, have relatively large negative values of $T\Delta S_t^E$, compared with those of the amino acids which elicit sweet, sour or monosodium glutamate (MSG)-like tastes (see Table 1). This does not conflict with the conclusion by Ney (1971) that the bitterness of amino acids depends on the lipophilicity of their side chains. Besides, the value of $T\Delta S_t^E$ or of γ_w quantitatively indicates the degree of lipophilicity for each amino acid.

So far, the activity coefficients employed for amino acids have been customarily defined so that they indicate the magnitude of solute–solute interaction which increases with departure from the infinite dilution, and its value is unity for every amino acid at infinite dilution (Nŏzaki and Tanford, 1971). The value of γ_w reflects the sum of inherent contributions from individual interactions between pairs of structural groups in the solute and water molecules, and its value deviates from unity as the solution composition approaches the infinite dilution where solute–water interaction exclusively prevails over solute–solute interaction (Yamanaka, 1995).

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