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Solvation Effects on the Tautomerization of N,N-Dimethylvaline

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Abstract: The effects that solvents have on the tautomerization of N,N-dimethylvaline were analyzed using a linear solvation energy relationship (LSER) approach. In solution, the population of the zwitterionic tautomer is dictated mainly by the nature of the medium. Acidic solvent molecules appear to be more concentrated near the carboxylate functionality of the zwitterionic tautomer compared to the concentration of basic solvent molecules in the region of the dimethylammonium functionality.

The study of the factors that affect the acidity and basicity of compounds has been one area of interest to our research group.[1] It is known that many drugs must first be ionized in order to achieve biological activity.[2] For amino acids, knowledge of their tautomeric equilibria in different media is essential for the development of quantitative structure-activity relationships (QSAR) which are capable of reliable predictions of the activity of these important molecules. For the development of reliable QSAR, accurate property measurements are needed. The limited solubility of most amino acids in a wide variety of solvents however, precludes accurate measurements of different properties, including the tautomerization, and thus the determination of the effects that solvents have on their properties proves to be very difficult. For the limited number of amino acids that are soluble in polar solvents, such as water, the tautomeric equilibrium overwhelmingly favors the zwitterionic tautomer,[3] and subtle solvation effects on the tautomerization cannot be determined precisely. Compared to unmethylated amino acids, N,N-alkylated amino acids are very soluble in a wide variety of solvents,[4] and as a result, they are ideal molecules to study the effects that solvents have on the tautomerization of amino acids. In addition, it is known that N-alkylation of amino acids increases the population of the neutral tautomer in solution[5] thus, for N-alkylated amino acid, the tautomeric equilibrium is more sensitive to subtle solvation effects than that of the unmethylated amino acids. Based on the zwitterionic distribution of N,N-dimethylvaline in different solvents, the effects that solvents have on the tautomerization are evaluated in this study.

Table 1 shows the distribution of the zwitterionic tautomer of N,N-dimethylvaline (along with predicted distribution) in different solvents.[6]

Table 1. Solvatochromic Parameters[a] and % Zwitterion of N,N-Dimethylvaline in Different Solvents.

No.	Solvent	α	β	% Zwitterion (experimental)	% Zwitterion (calculated)[b]
1.	(Gas)	-	-	0[c]	-2
2.	AN	0.15	0.31	14	18
3.	DMSO	0.00	0.76	17[d]	18
4.	AQ	1.17	0.51	97	100
5.	MeOH	0.98	0.62	95	90
6.	Acetone	0.07	0.48	19	16
7.	DMF	0.00	0.69	16	16

[a]Reference 11; [b]Using Equation 1; [c]Headley, A. D.; Giam, C. S. (unpublished results); [d]Reference 1d.
Key: Gas, gas phase; AN, acetonitrile; DMSO, dimethyl sulfoxide; AQ, water; MeOH, methanol; DMF, dimethylformamide.

It is obvious from the results shown in Table 1 that the tautomerzation is dependent on the nature of the solvent. In the absence of any solvent, i.e., the gas phase, it is known that amino acids also exist as neutral tautomers.[7] The distribution of the different tautomers of amino acids in solution is dictated largely by the stabilization of the individual tautomeric species by the medium.[8] Linear solvation energy relationships (LSER) are routinely used to analyze such solvation effects.[9] Equation 1 shows the dual parameter LSER obtained from the results shown in Table 1.[10]

$$\% \text{ Zwitterion} = (77\pm4)\alpha + (27\pm6)\beta - 2\pm3 \qquad (1)$$
$$N = 7;\ R = 0.997;\ SD = 0.4$$

For Equation 1, the solvatochromic parameters,[11] α and β represent the solvents' hydrogen bond acidity (HBA) and basicity (HBD) properties, respectively. The goodness of the 'fit' of Equation 1 is reflected by the regression coefficient (R), standard deviation (SD) and the ability of the equation to predict accurately the experimental values. Thus, the relative magnitude and sign of the coefficients for this equation reveal aspects of the nature and extent of zwitterion/solvent interactions. Since the coefficients for the two solvation properties are positive, the indication is that the solvation modes considered serve to stabilize the zwitterion. From the magnitude of the coefficients however, the contributions of acidic and basic solvents to the stability of the zwittirion are not the same.

The effects that solvents have on the stability of the zwitterionic tautomer of N,N-dimethylvaline can be achieved from examination of solvation effects on the component ionic molecules. It is known that solvation of alkyl substituted dimethylammonium ions occurs primarily via an effective hydrogen bond from the acidic hydrogen of the ion to essentially one molecule of a basic solvent.[12] On the other hand, the carboxylate functionality is fairly large[13] and requires more solvent molecules for effective solvation. It has been shown that more than one water molecules do solvate the carboxylate functionality.[14] Thus, based on the different

values for the coefficients of Equation 1 for the solvation of the zwitterionic tautomer of N,N-dimethylvaline, more solvent molecules appear to cluster around the carboxylate functionality compared to the dimethylammonium functionality. Figure 1 illustrates the solvation of the zwitterion.

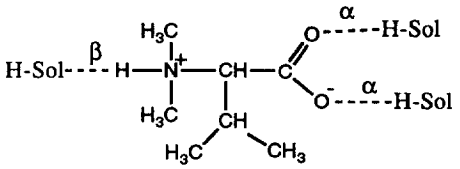

Figure 1. Solvation of the Zwitterionis Tautomer of N,N-Dimethylvaline. α and β Represent the HBA and HBD Abilities of the Solvent, Respectively.

In summary, the QSAR, developed from the solvatochromic parameters, is a very good model for the prediction of the tautomeric equilibrium of N,N-dimethylvaline, and should reflect the solvation effects on the tautomeric equilibria of other similar amino acids. The population of the zwitterionic tautomer of N,N-dimethylvaline is dictated mainly by specific zwitterion/solvent interactions. Owing to the greater size of the carboxylate functionality, compared to that of the dimethylammonium functionality, a greater concentration of solvent molecule is found in the region of the carboxylate functionality, compared to that of the dimethylammonium functionality.

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