Diverse Interactions of N-Methyl Glycine in Aqueous Paracetamol Solution with the Manifestation of Solvation Consequences

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1. Introduction

The native conformations of proteins depend on several non-covalent interactions such as hydrogen bonding, electrostatic and hydrophobic interactions which may originate from surrounding solute and solvent molecules [1, 2]. So physicochemical properties of the proteins are influenced greatly by the presence of surrounding solute and solvent molecules. Physicochemical study of proteins provides many valuable information like hydration, solubility, stabilization and enzyme activity which are taking place in biochemical and physiological processes of living organism [3-5]. The nature of interaction of drug molecules with protein may also be understood from Physicochemical measurements.

World’s most popular and most commonly used analgesic and anti-inflammatory medicine by McNeil Laboratories mainly for children. After 1961 it became the most frequently sold analgesic available and inexpensive also [6-8]. Chemical name of paracetamol is N-par-α-methyl amino phenol. It was introduced into the market by an analgesic and antipyretic medicine by McNeil Laboratories mainly for children. After 1961 it became the most frequently sold analgesic medications. Its use as an analgesic is most tolerable than the other non-steroidal drugs (NSAIDs) which should not be used by the people with bronchial asthma, hemophilia, salicylate-sensitive people, peptic ulcer disease, pregnant or breastfeeding women and children under 12 years of age [9, 10]. Currently the use of aspirin as antipyretic and analgesic has been declined due some adverse effects and parallelly the use of paracetamol has increased. Paracetamol has now been an appropriate analgesic for all age groups.

In continuance of our earlier works [11-15], we attempted to examine the nature of solute-solvent/co-solute interactions of N-methyl glycine in aqueous solutions of paracetamol at 298.15 K, 303.15 K and 308.15 K. The densities, viscosities and refractive indices of aqueous N-methyl glycine solutions at 298.15 K, 303.15 K and 308.15 K are reported in Table 1 and densities, viscosities and refractive indices of aqueous N-methyl glycine solutions in presence of paracetamol at 298.15 K, 303.15 K and 308.15 K are reported in Table 2. From the volumetric measurements we calculated limiting apparent molar volume (\(\phi_\ell\)), experimental slopes (\(\Delta\phi_\ell\)), transfer volume (\(\Delta\phi_\ell\)) and from the viscometric measurements we calculated viscosity A and B coefficients to analyse the nature of solute-solvent/ co-solute interactions. The refractive index data helps to find the molar refraction (\(R_M\)) which also helps to elucidate the interaction between solute and co-solute in aqueous medium.

2. Experimental Methods

2.1 Source and Purity Samples

The studied N-methyl glycine and co-solute paracetamol of purist grade was purchased from Sigma-Aldrich, Germany and was used as purchased. The mass purity of salts was ≥0.99. The salts were dried from moisture at 353.15 K for 48 h, and then they were cooled and store in a desiccator prior to use.

2.2 Apparatus and Procedure

The density (\(\rho\)) measurements were done by vibrating-tube Anton Paar Density-Meter (DMA 4500M) with an accuracy of 0.00001 x 10⁻³ (kg.m⁻³). The density meter was calibrated using by double-distilled water and dry air before taking the densities of our studied solutions [16]. The instrument has temperature monitoring system with the precision ±0.01 K.

The viscosity was determined using of Brookfield DV-III Ultra Programmable Rheometer having spindle size-42 fitted. The Rheometer was fitted with Digital Bath TC-500 which has a precision of ±0.0003 x 10\(^{-3}\) kg.

Mass measurements for preparation of stock solutions were done by Mettler AG-285 electronic balance with a precision of ±0.0001. The uncertainty in mass of solution is approximately ±0.0001 kg.

Acceptable precautions were followed to minimize evaporation losses during the measurements.

### Table 1

<table>
<thead>
<tr>
<th>Concentration of NCH (\Phi)</th>
<th>V(\phi_0)</th>
<th>(\Phi)</th>
<th>V(\phi_0)</th>
<th>(\Phi)</th>
</tr>
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<tbody>
<tr>
<td>298.15 K</td>
<td>303.15 K</td>
<td>303.15 K</td>
<td>303.15 K</td>
<td>303.15 K</td>
</tr>
<tr>
<td>0.01 M</td>
<td>0.997756</td>
<td>0.996216</td>
<td>0.994660</td>
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<tr>
<td>0.02 M</td>
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<td>0.996496</td>
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<tr>
<td>0.03 M</td>
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<td>0.996798</td>
<td>0.995155</td>
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### Table 2

<table>
<thead>
<tr>
<th>Molality (\mu)</th>
<th>(\phi)</th>
<th>(\eta/\phi)</th>
<th>(n_0)</th>
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<tbody>
<tr>
<td>298.15 K</td>
<td>303.15 K</td>
<td>303.15 K</td>
<td>303.15 K</td>
</tr>
<tr>
<td>0.01 M N-methyl glycine solution</td>
<td>0.9981</td>
<td>0.99664</td>
<td>0.99503</td>
</tr>
<tr>
<td>0.02 M N-methyl glycine solution</td>
<td>0.99836</td>
<td>0.99700</td>
<td>0.99538</td>
</tr>
<tr>
<td>0.03 M N-methyl glycine solution</td>
<td>0.99965</td>
<td>0.997725</td>
<td>0.99611</td>
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### Table 3

<table>
<thead>
<tr>
<th>Molality (\mu)</th>
<th>(\phi)</th>
<th>(\eta/\phi)</th>
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<tr>
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0.02 M N-methyl glycine

<table>
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<th>(\phi)</th>
<th>(\eta/\phi)</th>
<th>(n_0)</th>
</tr>
</thead>
<tbody>
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<td>303.15 K</td>
</tr>
<tr>
<td>0.013</td>
<td>0.9981</td>
<td>0.99664</td>
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<tr>
<td>0.023</td>
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</tr>
<tr>
<td>0.057</td>
<td>0.99944</td>
<td>0.99811</td>
</tr>
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</table>

### 3. Results and Discussion

#### 3.1 Density

Apparent molar volumes \(\phi\) of N-methyl glycine in aqueous paracetamol solution were determined from the densities of the solution using the following equation [18].

\[
\phi = \frac{M}{\rho} - 1000 (\rho - \rho_\text{l}) / (\rho_\text{l} \rho_0)
\]

where \(M\) is the molar mass of N-methyl glycine, \(\rho\) and \(\rho_\text{l}\) are the densities of solvent and solution respectively and \(M\) is the molarity of the solution. The \(\phi\) values of N-methyl glycine in aqueous paracetamol solution at 298.15 K, 303.15 K and 308.15 K are shown in Tables 3-5 respectively.

### 3.2 Viscosity

As the apparent molar volumes, \(\phi\), viscosity (\(\eta\)) and refractive index (\(n_0\)) of different molality of aqueous N-methyl glycine in aqueous paracetamol solution at 298.15 K, 303.15 K and 308.15 K are.

### 3.3 Interaction of \(\phi\)

The interaction of \(\phi\) values of N-methyl glycine in aqueous paracetamol solution at different temperatures are studied in Fig. 1. With increasing temperature the secondary solvation layer is released into the bulk solvent leading to the expansion of solution. As a result, the \(\phi\) values of N-methyl glycine in aqueous paracetamol solution increase with increase in temperature.

The parameter \(S_r\) defines the pair-wise interaction of solvated species in solution [20]. The \(S_r\) values of N-methyl glycine in aqueous paracetamol solution at different temperatures are reported in Table 4. The \(S_r\) value in our present study is least in 0.03 M N-methyl glycine at 308 K and highest in 0.01 M N-methyl glycine at 298.15 K. So, \(S_r\) values decrease with increasing temperature and molarity. This trend is exactly reverse than the \(\phi\) values explained earlier where \(\phi\) values increased.
with increasing concentrations of N-methyl glycine and temperatures. This weakening of \( \Phi \) values signify the presence of poor solute-solute interactions. The smaller \( \Phi \) values than the corresponding \( \Phi^0 \) signifies that the solute-solvent interaction is stronger than the solute-solute interaction.

<table>
<thead>
<tr>
<th>Temp. [K]</th>
<th>( \Phi^0 ) x 10^6</th>
<th>( \Delta \Phi^0 )</th>
<th>( S^0 ) x 10^13</th>
<th>B</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>303.15 K</td>
<td>6.103</td>
<td>0.6213</td>
<td>0.0013</td>
<td>0.0227</td>
<td></td>
</tr>
<tr>
<td>308.15 K</td>
<td>6.103</td>
<td>0.6213</td>
<td>0.0013</td>
<td>0.0227</td>
<td></td>
</tr>
</tbody>
</table>

The limiting apparent molar volumes of transfer of N-methyl glycine in paracetamol solution can be represented as follows [21].

\[ \Phi^0 = a_1 + a_2 T + a_3 T^2 \]  
(3)

The values of \( \Phi^0 \) of N-methyl glycine in paracetamol solution at 298.15 K, 303.15 K and 308.15 K are evaluated and reported in Table 5. The \( S^0 \) is not the only parameter for estimating the structure-making or breaking nature of any solute [30]. Hepler proposed a different technique to inspect the structure-making and breaking ability of the solute in aqueous solution from the following thermodynamic expression [23].

\[ \frac{\Delta \Phi^0}{\Delta T} = 2a_2 \]  
(5)

According to Hepler the structure making solutes should have positive \( \Delta \Phi^0/\Delta T \) values, whereas structure-breaking solutes should have negative values [24, 25]. The \( \Delta \Phi^0/\Delta T \) values of N-methyl glycine in paracetamol solution have been provided in Table 5. It is apparent that \( \Delta \Phi^0/\Delta T \) values are negative for N-methyl glycine in paracetamol solution which signifies that paracetamol perform as structure breaker in aqueous solution.

The limiting apparent molar volume of transfer, \( \Delta \Phi^0 \) for N-methyl glycine in paracetamol solution may be expressed as follows:

\[ \Delta \Phi^0 = \Phi^0 - \Phi^0(\text{N-methyl glycine in paracetamol}) = \Phi^0(\text{water}) \]  
(6)

The \( \Delta \Phi^0 \) value provide the idea about the nature solute-solvent interactions. The limiting apparent molar volume of transfer may be analyzed in the light of co-sphere overlap model given by Friedman and Krishnan [26]. According to the model positive \( \Delta \Phi^0 \) value signifies the existence of hydrophilic-hydrophilic, ion-ionic-hydrophilic and ion interactions, whereas the negative \( \Delta \Phi^0 \) value signifies the hydrophobic-hydrophobic interactions [27, 28]. The interactions between N-methyl glycine and paracetamol in aqueous medium may be of following categories.

\[ \text{i. Ionic-ionic interaction of the H- ion of water and N-methyl glycine with the -COOH ion of N-methyl glycine} \]
\[ \text{ii. H-bond between -COOH (N-methyl glycine) and -OH (paracetamol) and also with water.} \]
\[ \text{iii. Hydrophobic interaction of polar end of water with -COOH ion of N-methyl glycine and -OH group of paracetamol.} \]
\[ \text{iv. Ionic-hydrophilic interactions of -COOH (N-methyl glycine) and -OH (paracetamol) with the H_2O and OH ion of water.} \]
\[ \text{v. Hydrophobic-hydrophobic interaction of non-polar part of N-methyl glycine and paracetamol.} \]

The interactions of categories (i), (ii), (iii) and (iv) have positive contributions to \( \Phi^0 \) values while interaction of type (v) has negative contribution to \( \Phi^0 \) values [29-31]. The positive \( \Phi^0 \) value indicates that the hydrophilic-hydrophilic and ion-ion interactions are in domination over hydrophobic-hydrophobic and ionic-hydrophobic interactions. It is also seen that \( \Phi^0 \) values are increasing with increase in solubility of N-methyl glycine. The intermolecular distance between N-methyl glycine and paracetamol decreases with increasing concentration of N-methyl glycine as a result the hydrophobic-hydrophobic and ionic-hydrophobic interactions increase with solubility. Similar result can also be obtained from the following expression given by Franks et al [32].

\[ \Phi^0 = \Delta G + \Phi' - \Phi S \]  
(7)

where \( \Delta G \) is correlated with Van Der Waals volume, \( \Phi' \) is the volume correlated with wids or empty space and \( \Phi S \) is correlated with shrinkage volume due to electrostriction. The value \( \Phi' \) and \( \Phi S \) will remain same for the same class of solutes in aqueous solutions and only the volume due to electrostriction will vary. The hydrophilic-hydrophilic, ion-ionic and ion-hydrophilic interactions will increase with increasing solubility of N-methyl glycine and as a result \( \Phi S \) value will decrease [33]. For this reason, \( \Phi^0 \) values increase with increasing molality of N-methyl glycine.

The volumetric pair wise and triple ion interaction may be estimated from the following equation given by McMillen–Mayer [34].

\[ \Delta \Phi^0 = 2Y_{\text{svm}} + 3Y_{\text{svm}}^2 \]  
(8)

where \( Y_{\text{svm}} \) and \( Y_{\text{svm}}^2 \) are pair and triple ion interaction coefficients, limiting apparent molar volume of transfer respectively and \( Y_{\text{svm}} \) and \( Y_{\text{svm}}^2 \) represent N-methyl glycine and paracetamol respectively. The coefficients \( Y_{\text{svm}} \) and \( Y_{\text{svm}}^2 \) are estimated by putting the \( \Delta \Phi^0 \) values at different molalities of N-methyl glycine in presence of paracetamol in the above expression and mentioned in Table 6. It is observed that \( Y_{\text{svm}} \) values are positive whereas \( Y_{\text{svm}}^2 \) values are negative for N-methyl glycine in presence of paracetamol in aqueous medium at different temperatures. The positive values of \( Y_{\text{svm}} \) suggest that existing interactions in our studied solutions are mostly pair wise which arises from hydrophilic-hydrophilic and ion-ion interactions between solute and co-solute in aqueous medium [35].

\[ \text{Table 6 Pair, } Y_{\text{svm}}, \text{ and Triple, } Y_{\text{svm}}^2, \text{ interaction coefficients of N-methyl glycine in aqueous solution of paracetamol at 298.15 K, 303.15 K and 308.15 K temperatures} \]

<table>
<thead>
<tr>
<th>Temperature [K]</th>
<th>( Y_{\text{svm}} )</th>
<th>( Y_{\text{svm}}^2 )</th>
<th>( Y_{\text{svm}} )</th>
<th>( Y_{\text{svm}}^2 )</th>
<th>( Y_{\text{svm}} )</th>
<th>( Y_{\text{svm}}^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>298.15 K</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.001</td>
<td>-0.001</td>
</tr>
<tr>
<td>303.15 K</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.001</td>
<td>-0.001</td>
</tr>
<tr>
<td>308.15 K</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.001</td>
<td>-0.001</td>
<td>0.001</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

3.2 Viscosity Calculation

The viscosity data were fit into Jones–Dole equation [36],

\[ \eta = \eta_0 \left( 1 + \frac{n}{m} \right) \]  
(9)

where, \( \eta_0 \) and \( n \) are the viscosities of the solvent and solution respectively. A plot of \( (\eta_0 / m) / \eta \) against \( \eta_0 \) gives a straight line with an intercept \( A \) and a slope of \( B \). The \( (\eta_0 / m) / \eta \) values of N-methyl glycine of different molalities in aqueous solution are reported in Table 3. The viscosity coefficients \( A \) and \( B \) are reported in Table 4 and the variation of B with temperature of FN-methyl glycoline is shown in Fig 4. The viscosity B-coefficient signifies solute-solute interaction and provides valuable information concerning the solvation of the solute in solution [37, 38]. A close inspection reveals that \( B \) value is higher for 0.03 M N-methyl glycoline solution at 308.15 K and lowest at 0.01 M solution at 298.15 K. So, solute-solute interactions increase with increasing molarity and temperature. Viscosity A coefficient denotes solute-solute interaction. It is reflected from the Table 4 that the values of A coefficient decrease with the increase in molarity and temperature of N-methyl glycine in aqueous solution of paracetamol. Hence solute-solute interaction diminishes with molarity of N-methyl glycoline and also with temperature in K.
3.3 Refractive Index Calculation

The molar refraction, $R_m$ for any compound in its aqueous solution may be determined from the Lorentz–Lorenz relation [39]:

$$R_m = \left(\frac{n^2 - 1}{n^2 + 2}\right) \frac{M}{\rho}$$  \hspace{1cm} (10)

where, $R_m$, $\rho$, $M$ and $n_0$ are the molar refraction, density of solution, molar mass and refractive index, respectively. The refractive index of a material is defined as $c/c_0$, where $c$ is the speed of light in any medium and $c_0$ the speed of light in vacuum. The light is refracted more for the substance of higher refractive index [40]. According to Deetlefs et al. [41] the molar refraction of a substance will be higher when the molecules in any solution are more tightly packed. The values of $R_m$ are shown in Table 3. The increase in molar refraction values with increase in molarity of $N$-methyl glycine in aqueous paracetamol solution indicates close packing of molecules in the mixture resulting in maximum solute–solvent interactions.

3.4 $^1$H NMR Spectroscopy

Various spectroscopy may be employed to examine the diverse interaction playing in solution of any compound [42–46]. $^1$H NMR Spectroscopy of pure $N$-methyl glycine, paracetamol and their solution are recorded in D2O at 298.15 K and shown in Fig. 5.

![Fig. 5](image-url)  
**Fig. 5** $^1$H NMR spectra of N-methyl glycine, paracetamol and their solution in D2O

Up field chemical shift of protons of methyl group and methylene group of glycine in aqueous solution of paracetamol from its pure form may be regarded due to the involvement of adjacent -NH and -COOH groups in H-bonding with the -OH group of paracetamol. However higher $\Delta\delta$ for $N$-methyl glycine than the methyl group indicates that -COOH form stronger H-bond with -OH group of paracetamol than the -NH group. Similar up field chemical shift of protons adjacent to -OH group of paracetamol takes place which may also be considered due to its involvement in H-bonding with favorable groups of N-methyl glycine. The extend of $\Delta\delta$ for protons at p-position of -OH group is larger than the protons at p-position which indicates that -OH is more favorable in forming H-bond than the -NH group of paracetamol.

$^1$H NMR data: $N$-methyl glycine: [H NMR (300 MHz, D2O)]; $\delta$ 1.827 (3H, s), 3.754 (2H, s) paracetamol: [H NMR (300 MHz, D2O)]; $\delta$ 1.887 (3H, s), 6.566 (2H, d), 6.988 (2H, d) solution of $N$-methyl glycine and paracetamol [H NMR (300 MHz, D2O)]; $\delta$ 1.817 (3H, s), 1.874 (3H, s), 3.729 (2H, s), 6.634 (2H, d), 6.901 (2H, d).

4. Conclusion

The limiting apparent molar volume ($\phi$) and viscosity $B$-coefficient and molar refraction ($R_0$) values indicate the existence of strong solute–solvent interactions between $N$-methyl glycine and paracetamol in aqueous medium. The solute–solvent interactions enhances with increasing molarity of $N$-methyl glycine and temperature. On the other hand, the solute-solute interactions diminish with increasing molarity of $N$-methyl glycine and temperature. The nature of solute–solute interactions was evaluated from the limiting apparent molar volume of transfer ($\phi$) values. It was also observed that the interaction between our studied solute and co-solute in aqueous medium was mostly pair wise. $^1$H NMR Spectroscopy concretely support our findings obtained from volumetric, viscometric and refractive index study.

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References

sical mixtures of dichloromethane + N, ‐ N‐
M cylodextrins with M binaries solvation behavior of an ionic liquid (tetrabutylphosphonium D dimethylformamide probed by a conductometric study A B M interactions of resorcinol in mixed 1, 4
B M V coefficients of carbohydrates in aqueous cetrimonium bromide solutions at W Wang N N N R Ekka Gopal Ekka, M
Sindhu Roy Roy Deck Plechkova (48),
Habibur Rahaman, Kalipada Sarkar, Debasmita Das, Mahendra Nath Roy, Diverse interactions of N
industry.

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