Conformation of gemcitabine: An experimental NMR and theoretical DFT study

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KEYWORDS
Gemcitabine (Gemzar);
NMR;
Karplus;
DFT;
Conformation;
Solvent effect.

Abstract. The structural and conformational behavior of gemcitabine (2', 2'-difluorocytidine) was investigated by advanced NMR experiments and a computational quantum mechanical method (DFT) using Potential Energy Scanning (PES) in gas and solution phases in the Polarizable Continuum Model (PCM). Three stable conformers (G1, G2, and G3) were predicted from minimum points in a potential energy diagram. In order to measure coupling constant values, a set of 2D spectra (H-H COSY, H-C HM/QC, and H-C HMBC) was analyzed. Optimized structures and spin-spin coupling constant calculations in gas and solution phases were performed by B3LYP/6-311++G(d,p) method. Both energy and NMR parameters showed that G1-form is more stable than other conformers are. To analyze coupling constant, Karplus equations for $^1J_{C,H}$, $^2J_{C,H}$, and $^3J_{C,H}$ were derived. In addition, the investigation of solvent effect was carried out, and obtained results showed that both inter- and intra-molecular interactions affected the stability of G1 conformer.

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1. Introduction

Nucleosides and their derivatives are glycosylamines used in biotechnology and numerous biological processes [1-6]. They are also the most beneficial compounds for healing a majority of cancers [7-9]. As a deoxycytidine analogue, gemcitabine (2', 2'-difluorocytidine, dFdC), Scheme 1, is used as an effective treatment for many cancers including blood, pancreas, lung, biliary, etc. [10-16]. In recent years, a wide variety of investigations have been performed on linear synthesis of gemcitabine [17], its kinetic and diffusion studies [18], and its association with other pharmaceutical compounds to improve beneficial pharmaceutical effects [19,20].

Despite the fact that gemcitabine plays a key role in pharmaceutical and biotechnology fields, there is no detail found with regard to its 3D structure and stable conformers. As Scheme 1 shows, rotation around the N-glycosidic bond causes different conformations to the orientation of base ring rather than sugar ring. These conformers are determined by applying advanced NMR experiments along with DFT calculations [21-26]. In these methods, DFT calculations provide information about the available conformers by using the Potential Energy Scanning (PES). Then, NMR parameters, including chemical shifts and spin-spin coupling constants, are measured theoretically [27-29]. In the experimental section, structures are assigned, and values of coupling constants are obtained. To achieve this, a set of 1D- and 2D-NMR spectra is used including correlation spectroscopy (H-H COSY), Heteronuclear Multiple Quantum Coherence (HM/QC), and Heteronuclear Multiple Bond Coherence (HMBC) [30-31]. Finally, these experimental and theoretical data are used to interpret 3D structure and conformational study [32-39].
Coupling constant DFT studies have the best results for closely related systems, and this is the basic problem of these NMR parameters in the conformational studies [40]. In general, several parameters affect the spin-spin coupling constant. In this regard, many investigations were performed on coupling constants including bond length [41], solvent interaction [42], electronegativity of the substituent [43], etc. However, the dihedral angle dependency of coupling constant (Karplus equation) is the most important equation that considers NMR parameters in conformational studies. Accordingly, three-bond (vicinal) H-H coupling constant is the most important one in conformational investigations [44]. In addition, one- and two-bond (geminal) spin-spin coupling constants are often considered [45].

The purpose of the current paper is to determine the spatial structure and conformations of gemcitabine by two methods: 1) one- and two-dimensional NMR experiments and 2) density Functional Theory (DFT). In addition, in this work, the $^n$J ($n$: 1, 2, 3) Karplus equation is obtained for gemcitabine.

2. Experimental section
- **Material**: Gemcitabine (Gemzar) was purchased from Aburaihan Pharmaceutical Co. (Tehran, Iran) and was used without further purification.
- **NMR experiments**: $^1$H and $^{13}$CNMR spectra were recorded with a Bruker DRX 500 operating at 500.13 and 125.77 MHz for $^1$H and $^{13}$C, respectively.

The spectra were taken in D$_2$O solutions with a probe temperature at 298.0 K and referenced to solvent peak. The sample (8 mg) was dissolved in D$_2$O (0.5 mL), and 1D- and 2D-NMR experiments were performed by NQR technology and BBP probe, respectively.

NMR experiments were running at 90° (10.5 ms), 128 transients, and 32 k data points for $^1$H spectra and at 90° (15 ms), 512 transients, and 128 k data points for $^{13}$C spectra. $^1$H-$^1$H homonuclear correlation spectroscopy (COSY) spectra were collected using cosy2s pulse sequence with the following parameters: 90° pulse values with 1024 increments of 1 k data points for 12 ppm spectral width (f1 and f2) and 64 scans. The other 2D NMR spectra were acquired with 130 ppm (f1) and 12 ppm (f2) spectral width, relaxation delay, 2 s, 512 increments of 1 k and 64 scans for $^1$H-$^{13}$C Heteronuclear Multiple Quantum Coherence (HMQC). The chemical shifts were referenced to the methyl groups of a TMS internal standard (0.00 ppm for $^1$H and $^{13}$C).

All NMR spectra were analyzed using a professional software product, i.e., MesReNova 10.0.1.

3. Quantum chemical calculations
All the minimizations and calculations were carried out using the GAUSSIAN09 [46] program with the Density Functional Theory (DFT) by exchange-correlation hybrid functional B3LYP (three-parameter exchange functional of Becke B3 combined with the Lee-Yang-Parr correlation functional LYP) approach to polarization, diffuse functions, and 6-311++G(d,p) basis set [47-48]. The results were analyzed with Gaussview 5.0 visualization program.

This quantum chemical method and basis set often have a correct prediction geometry and structure parameters of medium-sized molecules [49]. Molecular geometries were optimized without any restriction. Chemical shifts were calculated with GIAO method, using corresponding TMS shielding calculated at the same theoretical levels as in the reference. The relative $^1$HNMR and $^{13}$CNMR shifts of gemcitabine were determined as follows:

$$\delta_{\text{calc}}(X_i) = \sigma(\text{TMS}) - \sigma(X_i),$$

where $\sigma(\text{TMS})$ and $\sigma(X_i)$ are the calculated isotropic magnetic shielding tensor of hydrogen and carbon of the reference (TMS) and gemcitabine, respectively. All of the calculations were performed in both gas and water solution phases.

4. Results and discussion
- **Geometry**: In the first section of computational analysis, geometrical structure was obtained (Figure 1) at 6-311++G(d,p) basis set of DFT method. Vibrational frequencies were calculated in an optimized structure, and imaginary frequency was not observed.

In addition, an optimization process was performed in a solution phase using the Polarizable
Continuum Model (PCM) [50] for aqueous solution, dimethyl sulfoxide (DMSO), chloroform and carbon tetrachloride (CCl₄) solution.

As Table 1 shows, there are significant differences between dihedral angles of gemcitabine in aqueous solution, compared to gas phase and other solvents. In addition, gemcitabine is more stable in the aqueous solution phase than others, showing 18.83 kcal mol⁻¹ solution energy. In fact, as will be shown, our impression is that the intermolecular hydrogen bonding with solvent molecules (Figure 2) would lead to special orientation of dihedral angles and greater stability.

Figure 3 shows the superposition of the lowest energy structure of gemcitabine in gas and aqueous solution phases. In aqueous media, the OH functional group at C9 is oriented toward the fluorine atom. This can be due to inter- or intra-molecular interactions that caused dihedral angles to become smaller than that in the gas phase. On the other hand, in the gas phase, space repulsion and space prevention can be the reason for the functional groups to stay away from each other.

More importantly in addition to the above theoretical prediction, H-H COSY NMR experiment (Figure 4) shows the weak correlation at solvent peak (4.75 ppm) and OH (at C9) peak (6.4 ppm). Therefore, it can be concluded that, in aqueous solution, gemcitabine is more stable than that in the gas phase and other solvents due to the performance of intermolecular hydrogen bonding, leading to special orientation of dihedral angles.

Table 1. The optimized ground state structural parameters of gemcitabine on DFT-B3LYP/6-311++G(d,p) level of theory in gas and solution phases.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Gas</th>
<th>Water</th>
<th>DMSO</th>
<th>CCl₄</th>
<th>Chloroform</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta F ) (kcal mol⁻¹) ( ^a )</td>
<td>18.83</td>
<td>-</td>
<td>0.63</td>
<td>11.30</td>
<td>6.28</td>
</tr>
<tr>
<td>Bond lengths (Å):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_7 - N_1 )</td>
<td>1.44</td>
<td>1.45</td>
<td>1.45</td>
<td>1.45</td>
<td>1.45</td>
</tr>
<tr>
<td>( C_{10} - C_{11} )</td>
<td>1.52</td>
<td>1.52</td>
<td>1.52</td>
<td>1.52</td>
<td>1.52</td>
</tr>
<tr>
<td>( C_7 - O_1 )</td>
<td>1.42</td>
<td>1.42</td>
<td>1.42</td>
<td>1.42</td>
<td>1.42</td>
</tr>
<tr>
<td>( C_8 - F )</td>
<td>1.38</td>
<td>1.37</td>
<td>1.38</td>
<td>1.38</td>
<td>1.38</td>
</tr>
<tr>
<td>( C_4 - N_4 )</td>
<td>1.36</td>
<td>1.35</td>
<td>1.35</td>
<td>1.35</td>
<td>1.35</td>
</tr>
<tr>
<td>Bond angles (°):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( O_1 - C_7 - C_8 )</td>
<td>102.93</td>
<td>103.36</td>
<td>103.36</td>
<td>103.00</td>
<td>103.30</td>
</tr>
<tr>
<td>( O_1 - C_7 - N_1 )</td>
<td>109.43</td>
<td>109.51</td>
<td>109.51</td>
<td>109.48</td>
<td>109.48</td>
</tr>
<tr>
<td>( C_8 - C_9 - C_{10} )</td>
<td>102.86</td>
<td>102.86</td>
<td>102.86</td>
<td>102.86</td>
<td>102.86</td>
</tr>
<tr>
<td>( C_{10} - C_{11} - O_{11} )</td>
<td>109.15</td>
<td>109.46</td>
<td>109.46</td>
<td>109.31</td>
<td>109.41</td>
</tr>
<tr>
<td>( N_{11} - C_{21} - O_{22} )</td>
<td>118.62</td>
<td>118.81</td>
<td>118.81</td>
<td>118.71</td>
<td>118.78</td>
</tr>
<tr>
<td>( N_1 - C_2 - N_3 )</td>
<td>116.79</td>
<td>117.87</td>
<td>117.85</td>
<td>117.22</td>
<td>117.51</td>
</tr>
<tr>
<td>Dihedral angles:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( O_1 - C_7 - N_1 - C_2 )</td>
<td>-132.18</td>
<td>-135.73</td>
<td>-135.59</td>
<td>-133.07</td>
<td>-133.76</td>
</tr>
<tr>
<td>( O_{11} - C_{11} - C_{10} - O_1 )</td>
<td>-68.43</td>
<td>-65.88</td>
<td>-65.95</td>
<td>-67.73</td>
<td>-66.96</td>
</tr>
</tbody>
</table>

\( ^a \) Energy differences related to the aqueous solution.
and coupling constants measurement. Figure 4 shows the gemcitabine H-H COSY NMR experiment in D$_2$O solvent. Figure 4 shows a weak correlation between solvent and sample signals. This correlation indicates intermolecular interaction which interprets the stability of Glconformer in aqueous media.

$^{1}J_{C_{C-H}}$ and $^{3}J_{C_{C-H}}$ heteronuclear coupling constants were obtained from HMQC and HMBC NMR spectra and are shown in Figures 5 and 6, respectively.

- **Computational analysis:** A significant rotational energy barrier is the main key in conformational study. Energy scanning calculations around $\beta$-dihedral angle ($N_1$-$C_4$-$C_7$-$O_7$) show significant energy barriers and, subsequently, stable conformers. A schematic diagram of energy as a function of $\beta$ is shown in Figure 7. On the base of potential energy scanning diagram, the minimum points in PES are defined as available conformers, and it is concluded that these conformers exist, which are more stable than others are.

As Figure 7 shows, gemcitabine has three minimum energy points named G1, G2, and G3. The most stable conformer (G1) corresponds to the deepest point of PES, and $\beta$ angle is -60 degree. In fact, this conformer is more stable than other conformers due to carbonyl group orientation associated with both oxygen and fluorine in a sugar ring. In this condition, gemcitabine can minimize space repulsion energy and provide conditions for intramolecular interactions. Figure 8 shows the 3-dimensional structure of gemcitabine conformers in aqueous solution. Therefore, it can be concluded that space prevention, repulsion energy, and most importantly, inter- and intra-molecular interactions are persistent factors for gemcitabine conformers. Table 2 shows the energy differences and $\beta$ angle values for G1 to G3.

By applying GIAO method, $^1$H and $^{13}$CNMR chemical shifts were measured for G1 to G3 in gas and solution phases at PCM solvent model and were compared to TMS shift. Tables 3 and 4 show the experimental and theoretical comparison of hydrogen and carbon chemical shifts for G1 to G3 conformers, respectively.

Table 2. Energy differences of conformations of gemcitabine; $\beta$ is in degree.

<table>
<thead>
<tr>
<th>Conformer</th>
<th>Beta</th>
<th>$\Delta \Delta$ (kcal mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>-68.43</td>
<td>-</td>
</tr>
<tr>
<td>G2</td>
<td>62.3</td>
<td>0.7</td>
</tr>
<tr>
<td>G3</td>
<td>175.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

$^\Delta = E_{\text{conf.}} - E_{G1}$.
From energy differences and chemical shifts, it can be concluded that G1 conformer has a higher natural population, compared to other conformers; therefore, the calculated chemical shifts for G1 are closer to experimental results. Nevertheless, spin-spin coupling constants are the NMR parameters related to structure parameters including dihedral angle. For this purpose, all $^3J$-coupling constants ($n=1, 2, 3$) of gemcitabine were experimentally obtained from 1-D and 2-D spectra in aqueous solution. In addition, spin-spin coupling constants were computed for G1 to G3 conformers using DFT/B3LYP/6-311++G* method in a PCM solvent model. The results showed good agreement to the most stable conformer, G1 (Table 5).

In order to distinguish different conformers, the Karplus equations have been developed from $^3J$-coupling constants ($n=1, 2, 3$). For this purpose,
Figure 6. 2D-HMBC NMR spectra of gencitabine in aqueous solution.

Figure 7. Diagram of Potential Energy Scanning (PES) of gencitabine molecule, scanned around \( \beta \) dihedral angle at DFT-B3LYP/6-311++G(d,p) level of theory.

Figure 8. Molecular structure of gencitabine’s conformers in aqueous solution. G1 is the most stable of all other conformers due to its intramolecular interaction.

- One-bond spin-spin coupling constant: In order to derive the \( ^nJ \) Karplus equations \((n=1, 2, 3)\),
dihedral angle \( (\beta) \) rotated from 180 to 150 with 30 increments, and 12 different modes were created. The spin-spin coupling constants were obtained and used to derive Karplus equation.

Table 3. Comparison of experimental (in D\(_2\)O solvent) and theoretical (6-311++G**\(^*\)) H chemical shifts (ppm).

<table>
<thead>
<tr>
<th>H-atom</th>
<th>Exp.</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>7.96</td>
<td>7.81</td>
<td>7.36</td>
<td>7.34</td>
</tr>
<tr>
<td>6</td>
<td>6.24</td>
<td>5.90</td>
<td>5.87</td>
<td>5.87</td>
</tr>
<tr>
<td>7</td>
<td>6.17</td>
<td>6.69</td>
<td>5.44</td>
<td>5.52</td>
</tr>
<tr>
<td>9</td>
<td>4.32</td>
<td>4.78</td>
<td>4.15</td>
<td>4.91</td>
</tr>
<tr>
<td>10</td>
<td>4.05</td>
<td>4.19</td>
<td>4.02</td>
<td>4.44</td>
</tr>
<tr>
<td>11a</td>
<td>3.81</td>
<td>4.38</td>
<td>4.11</td>
<td>4.09</td>
</tr>
<tr>
<td>11b</td>
<td>3.95</td>
<td>4.25</td>
<td>4.29</td>
<td>4.54</td>
</tr>
</tbody>
</table>

Table 4. Comparison of experimental (in D\(_2\)O solvent) and theoretical (6-311++G**\(^*\)) \(^{13}\)C chemical shifts (ppm).

<table>
<thead>
<tr>
<th>C-atom</th>
<th>Exp.</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>159.74</td>
<td>160.87</td>
<td>158.93</td>
<td>158.77</td>
</tr>
<tr>
<td>4</td>
<td>148.62</td>
<td>151.11</td>
<td>150.69</td>
<td>150.53</td>
</tr>
<tr>
<td>5</td>
<td>141.37</td>
<td>143.03</td>
<td>140.14</td>
<td>139.96</td>
</tr>
<tr>
<td>6</td>
<td>96.00</td>
<td>92.65</td>
<td>90.85</td>
<td>90.91</td>
</tr>
<tr>
<td>7</td>
<td>84.98</td>
<td>84.60</td>
<td>92.43</td>
<td>93.33</td>
</tr>
<tr>
<td>8</td>
<td>122.49</td>
<td>129.43</td>
<td>129.24</td>
<td>128.81</td>
</tr>
<tr>
<td>9</td>
<td>69.54</td>
<td>74.96</td>
<td>82.61</td>
<td>75.41</td>
</tr>
<tr>
<td>10</td>
<td>81.49</td>
<td>86.35</td>
<td>86.64</td>
<td>84.05</td>
</tr>
<tr>
<td>11</td>
<td>59.73</td>
<td>65.07</td>
<td>68.46</td>
<td>63.63</td>
</tr>
</tbody>
</table>

Table 5. Experimental and calculated scalar coupling constants (Hz) using DFT/B3LYP/6-311++G**\(^*\) method in a PCM solvent model for G1 conformer.

<table>
<thead>
<tr>
<th></th>
<th>Exp.</th>
<th>Gas cal.</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ^1)JC(C)(_9)-H(_9)</td>
<td>155.0</td>
<td>160.47</td>
<td>161.16</td>
</tr>
<tr>
<td>( ^1)JC(C)(<em>{10})-H(</em>{10})</td>
<td>185.01</td>
<td>156.70</td>
<td>156.24</td>
</tr>
<tr>
<td>( ^1)JC(C)(_7)-H(_7)</td>
<td>185.01</td>
<td>168.69</td>
<td>168.42</td>
</tr>
<tr>
<td>( ^1)JC(C)(_5)-H(_5)</td>
<td>196.55</td>
<td>152.07</td>
<td>157.52</td>
</tr>
<tr>
<td>( ^1)JC(C)(_6)-H(_6)</td>
<td>190.05</td>
<td>173.07</td>
<td>175.73</td>
</tr>
<tr>
<td>( ^1)JC(C)(<em>{11})-H(</em>{11a})</td>
<td>215.06</td>
<td>143.23</td>
<td>146.29</td>
</tr>
<tr>
<td>( ^2)J(_{H11a}-H11b)</td>
<td>-12.00</td>
<td>-10.65</td>
<td>-12.24</td>
</tr>
<tr>
<td>( ^2)J(_{F}-H9)</td>
<td>11.50</td>
<td>10.73</td>
<td>12.05</td>
</tr>
<tr>
<td>( ^3)J(_{H9}-H11)</td>
<td>4.05</td>
<td>2.23</td>
<td>2.11</td>
</tr>
<tr>
<td>( ^3)J(_{H9}-H9)</td>
<td>8.50</td>
<td>2.75</td>
<td>4.8</td>
</tr>
<tr>
<td>( ^3)J(_{H11}-H6)</td>
<td>8.00</td>
<td>7.58</td>
<td>7.71</td>
</tr>
</tbody>
</table>

the \( J \)-values of gencitabine at different \( \beta \) angles in gas and solution phases were calculated.

Orientation of \( C\_7-H\_7 \) bond toward carbonyl group leads to the exertion of maximum influence on \( ^1\)JC\(C\)\(_7\)-H\(_7\) value. In addition, \( ^1\)JC\(C\)\(_7\)-H\(_7\) is the only coupling constant directly related to \( \beta \) angle. One of the major practical advantages of the angular
dependences of $^1J_{C-H}$ values is the possibility of determination of the torsional angles. Therefore, $^1J_{C\overline{\gamma}-H_7}$ is chosen because, with the rotation of $\beta$ angles, $H_7$ has the maximum effect. Eq. (1) shows $^1J_{C\overline{\gamma}-H_7}$ Karplus equation in the gas phase:

$$
^1J_{C\overline{\gamma}-H_7} = 265.2 \sin (6 \times 10^{\gamma} + 2.5) \\
+ 6.3 \sin (0.03 \beta - 2.7).
$$

(1)

- **Geminal (two-bond) spin-spin coupling constant:** The two-bond coupling constant has important effect in a biomolecular structural study. $^2J_{C=H_7}$ Karplus equation as geminal coupling constant was obtained (Eq. (2)). Figure 9 shows the geminal coupling constants according to Eq. (2):

$$
^2J_{C=H_7} = & 5.69 \sin (0.003 + 2.04) \\
+ 2.04 \sin (0.03 - 4.34) \\
+ 0.43 \sin (0.05 + 0.37),
$$

(2)

$R^2 = 0.9904$.

- **Three-bond spin-spin coupling constant:** The most important Karplus equation is homo- and hetero-nuclear $^3J_{H-H}$. Since there is not any $^3J_{H-H}$ for gemcitabine around $C_7-N_0$ bond, the three-bond $^{13}C-^1H$ coupling constant was measured to obtain $^3J$ Karplus equation. Eq. (3) shows $^3J_{C\overline{\gamma}-H_8}$ Karplus equation in water solution. Figure 10 shows the three coupling constants according to Eq. (3):

$$
^3J_{C\overline{\gamma}-H_8} = 2.2 \sin (0.007\beta + 1.2) \\
+ 0.68 \sin (0.07\beta - 0.4) \\
+ 1.5 \sin (0.03 \beta - 0.35),
$$

(3)

$R^2 = 0.9883$.

5. Conclusion

This study considered conformational structure of gemcitabine by using 2D-NMR experiments and density functional theory. Molecular geometry, NMR parameters, and solvent effect were determined by using DFT/B3LYP/6-311++G(d,p) level of theory in gas and solution phases in a Polarizability Continuum Model (PCM). Based on these data, it can be concluded that gemcitabine is more stable in aqueous solution than other solvents are because of solvent-solute intermolecular interactions. In addition, solvent effect showed that stability of gemcitabine would be reduced from polar to non-polar solvents. In the gas phase, space repulsion results in instability compared to the solution phase as large as 18.83 kcal/mol.

Experimental analysis and geometry calculations showed that inter- and intra-molecular interactions played key roles in particular orientation of dihedral and bond angles in aqueous solution than in gas phase. To verify this claim, a correlation of solvent and gemcitabine signals in H-H COSY NMR experiment was shown. Conformational study using Potential Energy Scanning (PES) showed three stable conformers at a minimum point on PES. Spin-spin coupling constants were measured experimentally and theoretically to all conformers, and DFT calculations had good agreement with the 2D-NMR spectra. Based on the energy and NMR analysis, G1 conformer is more stable than others are.

References


**Biographies**

**Saeed Chashmniam** was born in 1989 in Eqlid, Iran. He received his BSc degree in Applied Chemistry from the University of Maragheh in 2012 and completed his MSc degree in the field of Physical Chemistry at the Sharif University of Technology in 2014. Now, he is a PhD Candidate in Sharif University of Technology on the topic of conformation of drug compounds using advanced NMR and DFT calculation methods under the supervision of Professor Mohsen Tafazzoli.

**Mohsen Tafazzoli** obtained his BSc degree from Shahid Beheshti University of Iran in 1981. In addition, he received his PhD degree in University of California, Davis in 1992 and, then, joined the Chemistry Department of the Sharif University of Technology. His research field involves the dynamic NMR spectroscopy (DNMR), structure elucidation of saccharides, \(^1\)H/\(^13\)C chemical shifts in the gas phase, calculation of chemical shielding, and nuclear quadrupole coupling constants (NQCC).