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ARTICLE *in* JOURNAL OF PHYSICAL CHEMISTRY LETTERS · OCTOBER 2014

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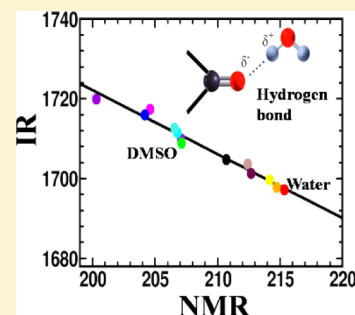
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S Supporting Information

ABSTRACT: Hydrogen-bonding plays a fundamental role in the structure, function, and dynamics of various chemical and biological systems. Understanding the physical nature of interactions and the role of electrostatics in hydrogen-bonding has been the focus of several theoretical and computational research. We present an experimental approach involving IR–¹³C NMR correlations to determine the electrostatic nature of carbonyl hydrogen-bonding interactions. This report provides a direct experimental evidence of the classical nature of hydrogen-bonding interaction in carbonyls, independent of any theoretical approximation. These results have important implications in chemistry and biology and can be applied to probe the reaction mechanisms involving carbonyl activation/stabilization by hydrogen bonds using spectroscopic techniques.

SECTION: Spectroscopy, Photochemistry, and Excited States



Hydrogen bond is ubiquitous in nature and plays a fundamental role in determining the structure, function, and dynamics in several chemical and biological systems.^{1–6} The chemical concept of hydrogen bond was introduced in the 1920s;^{7,8} to date the literature contains several discussions on the nature of the physical interactions that contribute to the hydrogen bonds.⁵ Several factors like electrostatics,^{9–13} polarization and dispersion effects,¹⁴ as well as contribution from the covalent character^{15,16} have been discussed since the inception of the concept to understand the physical nature of hydrogen-bonding and to classify hydrogen bonds. The role of classical interactions in hydrogen-bonding has been the focus of several theoretical and computational reports.^{17,18} Recently, the infrared (IR) frequencies of the carbonyl (C=O) vibrational probes were shown to have a linear correlation with the electrostatic fields calculated using molecular dynamics (MD) simulations.^{19,20} To the best of our knowledge, the electrostatic contribution to hydrogen-bonding was never interrogated from the experimental viewpoint independent of any theoretical approximation.

Carbonyl stretching mode serves as a great choice for vibrational probe because it is local and highly intense. Recent computational results have shown that the C=O stretching frequencies are linearly sensitive to the electrostatic field in hydrogen-bonded environments.²¹ Moreover, vibrational Stark effect (VSE) spectroscopy has predicted that the sensitivity of a C=O probe to electrostatic field is independent of its hydrogen-bonding status.¹⁹ Carbonyl vibrational probes are intrinsic to biological macromolecules as well as several small molecule ligands. Moreover, hydrogen-bond-mediated C=O activation by catalysts is assumed to play an important role in organocatalysis.²² Understanding the physical nature of hydrogen-bonding interactions to carbonyls can provide a pathway to estimate the electrostatic field exerted on a carbonyl within the

protein interior in a quantitative manner and to experimentally probe the reaction mechanisms and design novel catalysts for organocatalysis.

Experimental detection of hydrogen bonds in chemical and biological systems commonly utilizes the techniques of either IR or nuclear magnetic resonance (NMR) spectroscopy.²³ A single experimental technique is not sufficient to underpin the nature of physical interactions responsible for the spectral shifts, as similar shifts can be obtained both from electrostatic effects and specific chemical interactions. A correlation of two independent spectroscopic techniques that are sensitive to the changes in the local electrostatic field can provide insight into the role of electrostatics in hydrogen-bonding. For carbonyls, IR and ¹³C NMR are found to be sensitive to the polarity of the surrounding medium (electrostatics).^{19,24–27} While the observables from these two different experimental techniques respond to electrostatic field, the sensitivity of the IR frequency to field is the difference dipole (VSE), and that for ¹³C NMR chemical shift is the shielding polarizability.²⁸

In the present work, we have studied the correlation between the IR frequencies and the ¹³C NMR chemical shifts for hydrogen-bonded and non-hydrogen-bonded carbonyls to elucidate the electrostatic nature of interactions in carbonyl hydrogen bonds. Our analysis is based on the solvatochromic trends of model ketones and esters, a trend that can be largely attributed to the effective electric field created by the polarization of the solvent. The infinite miscibility of DMSO with water at room temperature makes water/DMSO solutions useful for gaining information about a wide range of hydrogen-

Received: August 1, 2014

Accepted: September 2, 2014

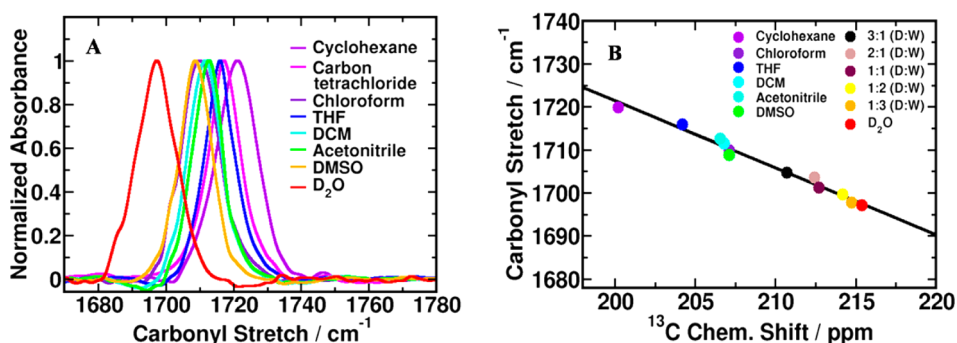


Figure 1. (A) Representative FTIR spectra of the C=O stretch band of acetone dissolved in a number of organic solvents and water. (B) Acetone carbonyl (C=O) stretching frequencies versus ¹³C NMR chemical shifts of the carbonyl carbon dissolved in aprotic solvents of varying polarity, water/DMSO solutions, and water. Water/DMSO points shown in Figure correspond to DMSO:water (D:W) ratios of 3:1, 2:1, 1:1, 1:2, and 1:3. The black line denotes the best-fit line, $R^2 = 0.98$.

bonding environments.²⁹ The IR–NMR correlation of these varying hydrogen-bonding environments was compared with that obtained from the non-hydrogen-bonding aprotic solvents. A combination of the results obtained from two independent spectroscopic techniques was utilized to determine the electrostatic nature of the carbonyl hydrogen-bonding interactions.

Acetone, the simplest organic ketone compound whose C=O stretching mode has been extensively characterized and studied in different solvents,^{24,27} is chosen as the model ketone, and solvatochromic IR experiments are performed in a wide range of aprotic solvents of varying polarity. As previously reported,^{19,24,27} we observe a gradual increase in red shift in the C=O stretching frequencies ($\bar{\nu}_{\text{C=O}}$) of acetone with the increasing polarity of the aprotic solvents (Figure 1A). $\bar{\nu}_{\text{C=O}}$ of acetone vary from 1719.9 cm⁻¹ in the nonpolar solvent (cyclohexane) to 1708.9 cm⁻¹ in the polar aprotic solvent (DMSO), with an overall frequency dispersion of 11.0 cm⁻¹. When acetone is dissolved in water (water refers to D₂O), due to the formation of hydrogen bonds, $\bar{\nu}_{\text{C=O}}$ shows a further red shift of ~11.8 cm⁻¹ as compared with that in DMSO. ¹³C NMR chemical shifts for C=O ($\delta_{\text{C=O}}^{13}$) have also been studied previously in various solvents^{25,26} and found to be sensitive to the polarity of the solvent. We observe a similar sensitivity for $\delta_{\text{C=O}}^{13}$ of acetone in aprotic solvents. When acetone C=O is hydrogen-bonded to water molecules, a further downfield shift is observed; $\delta_{\text{C=O}}^{13}$ increases from 207.1 ppm in DMSO to 215.4 ppm in water.

The solvatochromic shifts of $\bar{\nu}_{\text{C=O}}$ in non-hydrogen-bonding environments originate from the differences in the local electrostatic field that affect the vibrational frequencies of C=O. Different approaches have been reported for the calculation of the electrostatic field exerted on the vibrational probes.^{19,30–32} A semiempirical model like Onsager reaction field model³³ was extensively used for nitriles,^{30,34} and MD simulations were used to estimate the ensemble average electric fields for the carbonyls.^{19,35} It has been mentioned that the Onsager model fails to accommodate any specific chemical interaction like hydrogen-bonding,³⁰ making the electric field predictions using MD simulations a more potent approach. Although MD simulations are well-equipped to predict electric fields when the vibrational probe is hydrogen-bonded, it is still an approximate theoretical approach and might not be useful for cases where the nature of the interaction is not known a priori. An exclusive experimental approach is preferred to determine the physical nature of carbonyl hydrogen-bonding

interactions. Because $\bar{\nu}_{\text{C=O}}$ and $\delta_{\text{C=O}}^{13}$ are both sensitive to electrostatics, a tandem use of the experimental observables of IR and ¹³C NMR should recapitulate the linear sensitivity of both of the variables to electrostatic field but will be independent of any theoretical model to calculate it. This approach was previously used for non-hydrogen-bonded nitrile probes in aprotic solvents, and a linear correlation between IR frequencies and ¹³C NMR chemical shifts was observed, emphasizing on the electrostatic nature of interaction between the nitriles and the aprotic solvent molecules.^{30,34} Acetone C=O shows a similar linear correlation when dissolved in aprotic solvents (non-hydrogen-bonding). More interestingly, the ($\delta_{\text{C=O}}^{13}$, $\bar{\nu}_{\text{C=O}}$) ordered pair corresponding to water, where the protic solvent can form hydrogen bonds to the acetone C=O, also maintains the correlation seen for the non-hydrogen-bonding solvents (Figure 1B). The extendibility of the IR–NMR correlation, obtained for non-hydrogen-bonded solvents to a protic solvent (water) capable of hydrogen-bonding, shows that hydrogen-bonding in carbonyls is purely electrostatic in nature.

To further understand the nature of interaction in carbonyls in different hydrogen-bonding environments, we have scanned the polarity range between DMSO and water by using different water/DMSO solutions, where the volume ratio of DMSO:water is varied from 3:1, 2:1, 1:1, 1:2, to 1:3. $\bar{\nu}_{\text{C=O}}$ of acetone in these different water/DMSO solutions maintain the same linear correlation with the corresponding $\delta_{\text{C=O}}^{13}$ (Figure 1B), as seen for the aprotic solvents and water. The best-fit line obtained using all hydrogen-bonded and non-hydrogen-bonded points shows an excellent regression value (R^2) of 0.98. The ($\delta_{\text{C=O}}^{13}$, $\bar{\nu}_{\text{C=O}}$) points obtained from two independent experiments always fall on the *electrostatic line*,³⁰ thereby proving that the interactions in carbonyls are electrostatic in nature irrespective of their hydrogen-bonding status.

A recently published work on ester carbonyls (ester C=O), involving a similar approach of electrostatic field calculation using MD simulations, shows linear sensitivity of the ester C=O frequencies with electrostatic fields irrespective of the hydrogen-bonding status.³⁵ This intriguing result inspired us to apply our experimental correlation approach on esters to verify the electrostatic nature of ester C=O hydrogen bonds. The sensitivity of ¹³C NMR chemical shifts for ester C=O in different solvents has also been previously reported.²⁵ Ethyl acetate, whose carbonyl stretching frequencies have been well-characterized in different solvents,³⁶ is used as a model ester compound for the solvatochromic IR and ¹³C NMR experiments. The ester C=O frequencies ($\bar{\nu}_{\text{C=O,ester}}$) of ethyl acetate

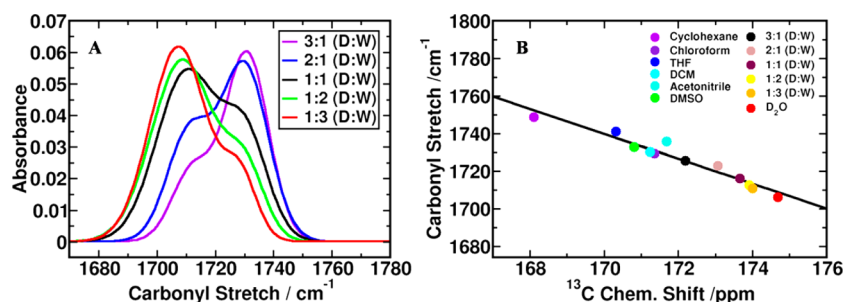


Figure 2. (A) FTIR spectra of the ester C=O stretch of ethyl acetate dissolved in water/DMSO solutions such that the DMSO:water (D:W) ratios are 3:1, 2:1, 1:1, 1:2, and 1:3. (B) First moment of the FTIR spectra of the ester C=O versus ^{13}C NMR chemical shifts of ethyl acetate dissolved in aprotic solvents, water/DMSO solutions, and water. The black line denotes the best-fit line, $R^2 = 0.97$.

vary from 1749.0 cm^{-1} in cyclohexane to 1732.8 cm^{-1} in DMSO with an overall frequency dispersion of 16.2 cm^{-1} and show a further red shift of 31.3 cm^{-1} in water from that in DMSO. The solvatochromic red shift in ester C=O of ethyl acetate (31.3 cm^{-1}) from DMSO to water is larger compared with that of acetone C=O (11.8 cm^{-1}). This shows that the ester carbonyl is more sensitive to the change in the environment, as compared with the ketone carbonyl. Similar to acetone ($\delta_{\text{C=O,ester}}^{13}\bar{\nu}_{\text{C=O,ester}}$), ordered pairs of ethyl acetate in the aprotic solvents as well as in water show a linear correlation (Figure S1, Supporting Information). Because the aprotic solvents can only interact with the ester C=O electrostatically, the ($\delta_{\text{C=O,ester}}^{13}\bar{\nu}_{\text{C=O,ester}}$) point for water reinforces the electrostatic nature of the hydrogen-bonding interactions in ester C=O probes.³⁵

Adopting an approach similar to that used for acetone C=O, we have examined the entire polarity range between DMSO and water using water/DMSO solutions for the ester C=O. In any composition of water/DMSO solutions, while the IR spectrum of acetone C=O gives a single peak, that of the ester C=O of ethyl acetate shows two peaks, indicating the existence of two populations. A bimodal distribution for acetone C=O in water/DMSO solution, if exists, will be overlapping and not distinguishable due to the small solvatochromic red shift of the C=O stretch from DMSO to water and the large spectral widths. For the ester C=O in water/DMSO solutions, the higher frequency peak ($\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$) is closer to $\bar{\nu}_{\text{C=O,ester}}$ in pure DMSO, and the lower frequency peak ($\bar{\nu}_{\text{C=O,ester}}^{\text{l}}$) is closer to $\bar{\nu}_{\text{C=O,ester}}$ in pure water. $\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$ shows a gradual red shift with increasing water concentration in the water/DMSO solution (Figure 2A). Because $\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$ in all water/DMSO solutions is close to $\bar{\nu}_{\text{C=O,ester}}$ in pure DMSO, one plausible assumption is that this peak arises from the population where the ester C=O is non-hydrogen-bonded ("DMSO-like environment"). $\bar{\nu}_{\text{C=O,ester}}^{\text{l}}$ being always close to that in pure water must be experiencing a hydrogen-bonded environment due to preferential solvation by the water molecules. If the assumption is correct, the two populations will interchange over time due to making and breaking of the hydrogen bonds owing to the intrinsic fluctuation dynamics of the solvent molecules. A direct experimental verification of hydrogen-bond dynamics is obtained using multidimensional spectroscopy (2D-IR), as discussed later.

Although two peaks were obtained for the ester C=O stretch in any water/DMSO solution, the ^{13}C NMR spectrum of the corresponding solution shows only a single peak for the ester carbonyl carbon. When the ^{13}C NMR chemical shifts for the ester C=O in water/DMSO solutions are plotted against

any one of the corresponding peak frequencies ($\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$ or $\bar{\nu}_{\text{C=O,ester}}^{\text{l}}$), the points deviate from the linear correlation. The deviation of the points arising from the mixed solvents is surprising as the points corresponding to both pure DMSO and pure D_2O are included in the best-fit line shown in Figure S1 (Supporting Information). The first moments of the FTIR spectra of the ester C=O in all pure solvents as well as water/DMSO solutions (including both the components of the bimodal distributions) show an excellent linear correlation with the ^{13}C chemical shifts ($R^2 = 0.97$). This result is in accordance with the asymmetric two state fast chemical exchange model. 2D-IR experiments on ethyl acetate in 1:1 DMSO/water, capable of experimentally probing the ultrafast exchange process, show waiting-time-dependent evolution of the cross peak between $\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$ and $\bar{\nu}_{\text{C=O,ester}}^{\text{l}}$ thereby confirming the occurrence of ultrafast chemical exchange^{37–41} due to making and breaking of the hydrogen bonds owing to the intrinsic solvent dynamics (details of the 2D-IR results to be discussed in another manuscript).

2D-IR results confirm the ultrafast exchanged model, and the timescale of chemical exchange strongly correlates with that of hydrogen bond dynamics in water.^{42–44} More interestingly, similar to the red shift observed in $\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$, $\bar{\nu}_{\text{C=O,ester}}^{\text{l}}$ also shows a gradual red shift with increasing water concentration. The red shift in $\bar{\nu}_{\text{C=O,ester}}^{\text{h}}$ is expected as the overall solvent polarity increases with increasing water concentration for the non-hydrogen-bonded population, but a similar red shift in the corresponding $\bar{\nu}_{\text{C=O,ester}}^{\text{l}}$ implies that the hydrogen-bonded population behaves in the same manner as the non-hydrogen-bonded counterpart. As the interactions modifying $\bar{\nu}_{\text{C=O,ester}}$ in the non-hydrogen-bonded configurations are purely electrostatic, a similar red shift in $\bar{\nu}_{\text{C=O,ester}}$ for the hydrogen-bonded configurations with increasing water concentration provides strong experimental evidence of the electrostatic nature of the ester C=O hydrogen-bonding interactions.

In summary, we have provided direct experimental evidence regarding the electrostatic nature of carbonyl hydrogen bond interactions for both ketone and ester model compounds. The implications of these results are manifold. These results provide experimental evidence that quantitative electrostatic field exerted on carbonyls can be estimated using MD simulations on model carbonyl compounds. Because the carbonyl interactions are electrostatic, a calibration of the electric field with respect to $\bar{\nu}_{\text{C=O}}$ of the model carbonyl will allow us to predict the electrostatic field on carbonyls in complex chemical/biological systems. In proteins, the detection of $\bar{\nu}_{\text{C=O}}$ of a particular amino acid is extremely challenging as it is often buried within the densely populated amide I region.

Isotope editing ($^{13}\text{C}=\text{O}$) of the carbonyl has been extensively used to isolate $\bar{\nu}_{\text{C}=\text{O}}$ for a specific amino acid. As the current results show a linear correlation between $\bar{\nu}_{\text{C}=\text{O}}$ and $\delta_{\text{C}=\text{O}}^{13}$, calibrating electrostatic fields (using MD simulations) on model $\text{C}=\text{O}$ with respect to $\delta_{\text{C}=\text{O}}^{13}$ will provide a way to estimate the local electrostatic field experienced by the isotope-edited carbonyl in the protein environment using ^{13}C NMR. Moreover, it has been reported that DMSO, acting as a cosolvent to water, can play the role of a stabilizer, an activator, a denaturant, an inhibitor, and also a cryoprotectant in biological systems.⁴⁵ Our results show that the carbonyl interactions are purely electrostatic in water/DMSO solutions and can possibly provide further insight into the mechanistic role of DMSO as a cosolvent. Development of new catalyst scaffolds for metal-free organocatalysis involving hydrogen-bonding catalysts has seen tremendous growth in the past decade. Several organic reaction mechanisms are predicted to involve activation/stabilization of the carbonyls through hydrogen bonds.^{22,46} ^{13}C NMR chemical shift of the carbonyl carbon was reported to be directly proportional to the Diels–Alder reaction rate using diarylacetylenediol catalysts.²² Our results provide a direct experimental way to verify the mechanistic understanding of these reactions involving hydrogen-bonded carbonyls using spectroscopic techniques.

EXPERIMENTAL METHODS

Acetone (Sigma-Aldrich) and ethyl acetate (Sigma-Aldrich) were used without further purification. The organic solvents, namely, cyclohexane, chloroform (CHCl_3), tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile, and DMSO, for the IR studies and the corresponding deuterated solvents for the NMR experiments were obtained from Sigma-Aldrich and used as supplied. Acetone and ethyl acetate were separately dissolved in different organic solvents and water so that the final concentration of liquid sample was 50 mM for the IR studies and 2% (v/v) for the NMR experiments. The concentration was not explicitly determined for the solvents where the solute was not soluble up to 50 mM. Acetone and ethyl acetate solutions were made in water/DMSO solutions, where the ratio of DMSO/water was varied from 3:1, 2:1, 1:1, 1:2, to 1:3.

The Fourier transform infrared (FTIR) absorption spectra were recorded on a GX PerkinElmer FTIR spectrometer with 1 cm^{-1} resolution at room temperature. For each sample, $\sim 60\ \mu\text{L}$ of the sample solution was loaded into a demountable cell consisting of two windows (CaF_2 , 3 mm thickness, Shenzen Laser), separated by a mylar spacer of 56 μm thickness. For recording each spectrum, 16 scans were collected from 1500–2000 cm^{-1} at 1 cm^{-1} resolution. The ^{13}C NMR spectra were recorded on a 400 MHz JEOL ECX NMR spectrometer.

ASSOCIATED CONTENT

Supporting Information

Plot of ester $\text{C}=\text{O}$ stretching frequencies versus ^{13}C NMR chemical shifts of ethyl acetate in various aprotic solvents and water. Solvatochromic FTIR spectra of ester carbonyls of ethyl acetate. Tables showing $\bar{\nu}_{\text{C}=\text{O}}$ and $\delta_{\text{C}=\text{O}}^{13}$ for acetone and ethyl acetate. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by CSIR-NCL MLP Grant No. 028126. S.B. thanks the Department of Science and Technology (DST) for Ramanujan Fellowship. S.B. and S.M.K. thank Dr. Yung Sam Kim (UNIST, South Korea) for acquiring the 2D-IR spectra.

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