

Reply to "Comment on 'Arresting an Unusual Amide Tautomer Using Divalent Cations'"

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J. Phys. Chem. B 2019, 123 (40), 8419–8424. DOI: 10.1021/acs.jpcc.9b08463*J. Phys. Chem. B* 2021, 125. DOI: 10.1021/acs.jpcc.0c04272Cite This: *J. Phys. Chem. B* 2021, 125, 479–483

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In our publication, we assigned the blue-shifted shoulder of *N*-methylacetamide (NMA) in the infrared (IR) spectrum ($\sim 1645\text{ cm}^{-1}$) to an iminol tautomer stabilized in the presence of divalent metal cations (e.g., 5 M Ca^{2+}).¹ Cremer and co-workers comment that this shoulder arises from the dehydration of the amide oxygen upon interaction with the metal cations.^{2,3} Their assignment is based on three interesting experimental observations: (1) the IR spectrum of ^{15}N -isotope-labeled NMA does not show any considerable red-shift compared to that of NMA; (2) a new peak appears for NMA at 1680 cm^{-1} in the presence of 1 M DCl , which shows a 17 cm^{-1} red-shift for ^{15}N -labeled NMA; and (3) the IR spectrum of acetone C=O stretch also demonstrates a blue-shifted shoulder in the presence of a high concentration of CaCl_2 .

As seen in the presence of 1 M DCl , ^{15}N -labeling induces a $\sim 17\text{ cm}^{-1}$ red-shift. Apparently, in the presence of CaCl_2 , a similar red-shift in the higher-frequency shoulder will have a formidable overlap with the amide I band. Deconvolution of the overlapping transitions solely on the basis of peak positions in the IR absorption spectra can be challenging at times. 2D IR spectroscopy, which spreads the signal in two dimensions, has proven to be useful under such circumstances. We performed a 2D IR experiment on NMA in D_2O in the presence of 1 M DCl (Figures 1 and 2). If the iminol tautomer only contributes to the peak at $\sim 1680\text{ cm}^{-1}$, the amide I band at $\sim 1620\text{ cm}^{-1}$ should be the same as that in the absence of DCl. Interestingly, a modest change can be observed in the difference spectrum (Figure 2C) obtained by subtracting the 2D IR spectrum of NMA in neat D_2O (Figure 2B) from that in the presence of 1 M DCl (Figure 2A). In the presence of 1 M DCl , the peak magnitude at the high-frequency end of the amide I band of NMA increases, whereas that of the low-frequency end decreases. The frequency range for this increase in peak intensity is in agreement with the blue-shifted shoulder.

Cremer and co-workers have reported a peak at 1645 cm^{-1} for both ^{15}N -labeled NMA and unlabeled NMA. As the amide I resonance is not purely C=O in character, it is surprising that no red-shift was observed by Cremer for the blue-shifted shoulder for ^{15}N -labeled NMA. A dehydrated amide I band is expected to show a small red-shift upon isotope labeling. A small red-shift was indeed observed for the band at $\sim 1620\text{ cm}^{-1}$. We

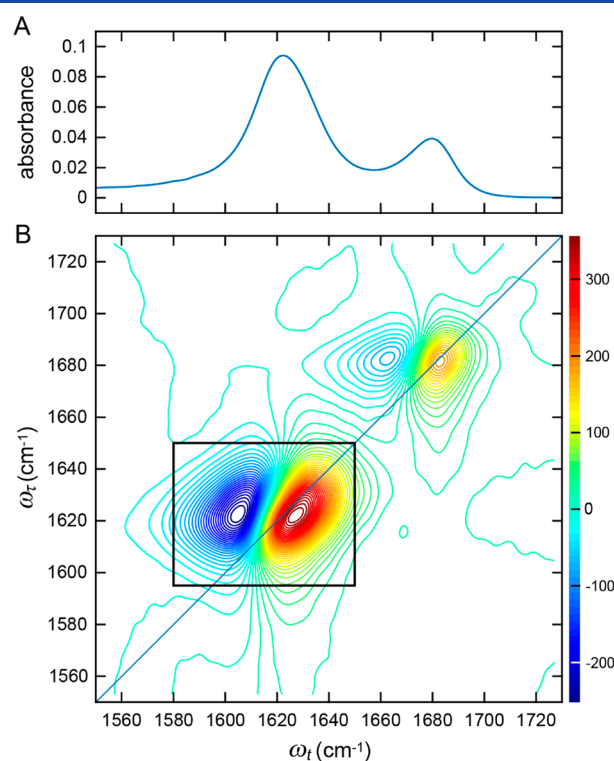


Figure 1. (A) FTIR and (B) 2D IR spectra (at $T = 0$) of aqueous solution of NMA in the presence of 1 M DCl . An enlarged view of the rectangular region is shown in Figure 2A. The concentration of NMA is 50 mM , and the thickness of the sample is $25\text{ }\mu\text{m}$.

believe that the blue-shifted shoulder can have a contribution from both dehydration of the amide oxygen upon interactions with Ca^{2+} cations and the iminol tautomer. The relative

Received: July 1, 2020

Revised: November 23, 2020

Published: December 10, 2020



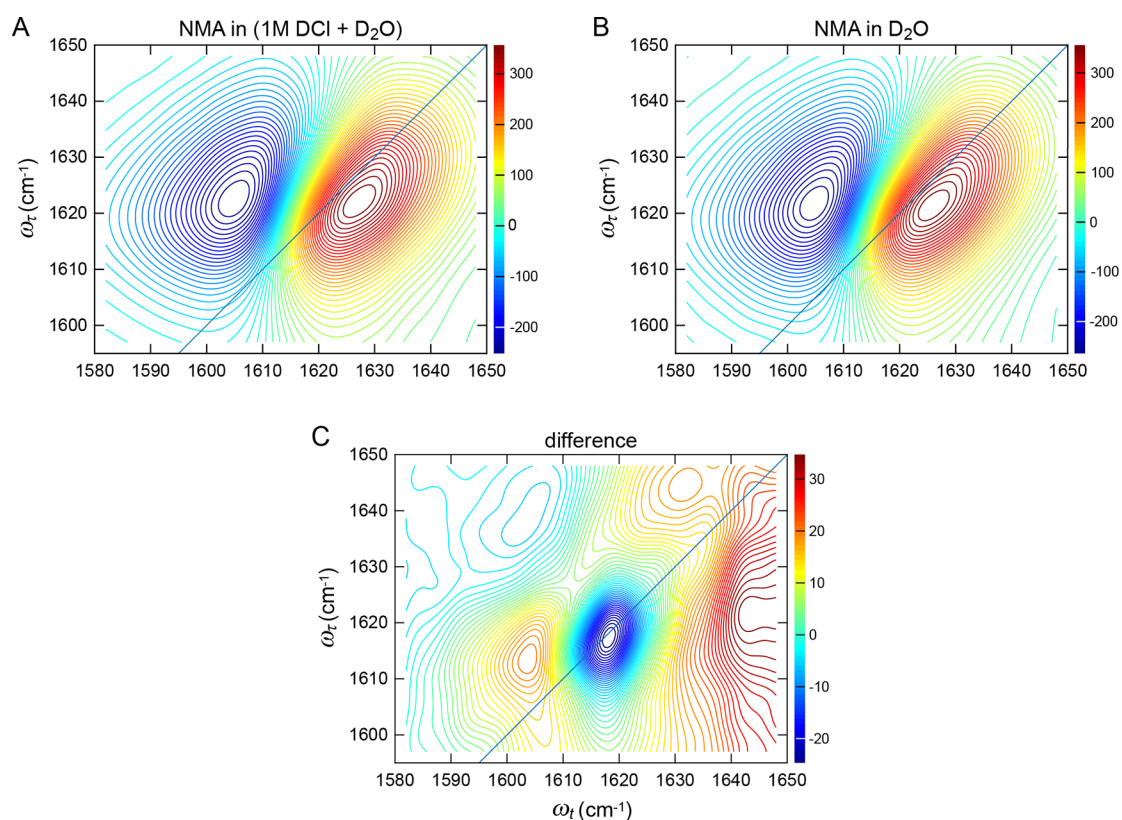


Figure 2. (A, B) 2D IR spectra of an aqueous NMA solution (A) in the presence of 1 M DCl and (B) in neat D₂O. (C) Difference spectrum between the spectra shown in parts A and B. The spectra in parts A and B were normalized to have the same integrated area. The spectra were collected at $T = 0$.

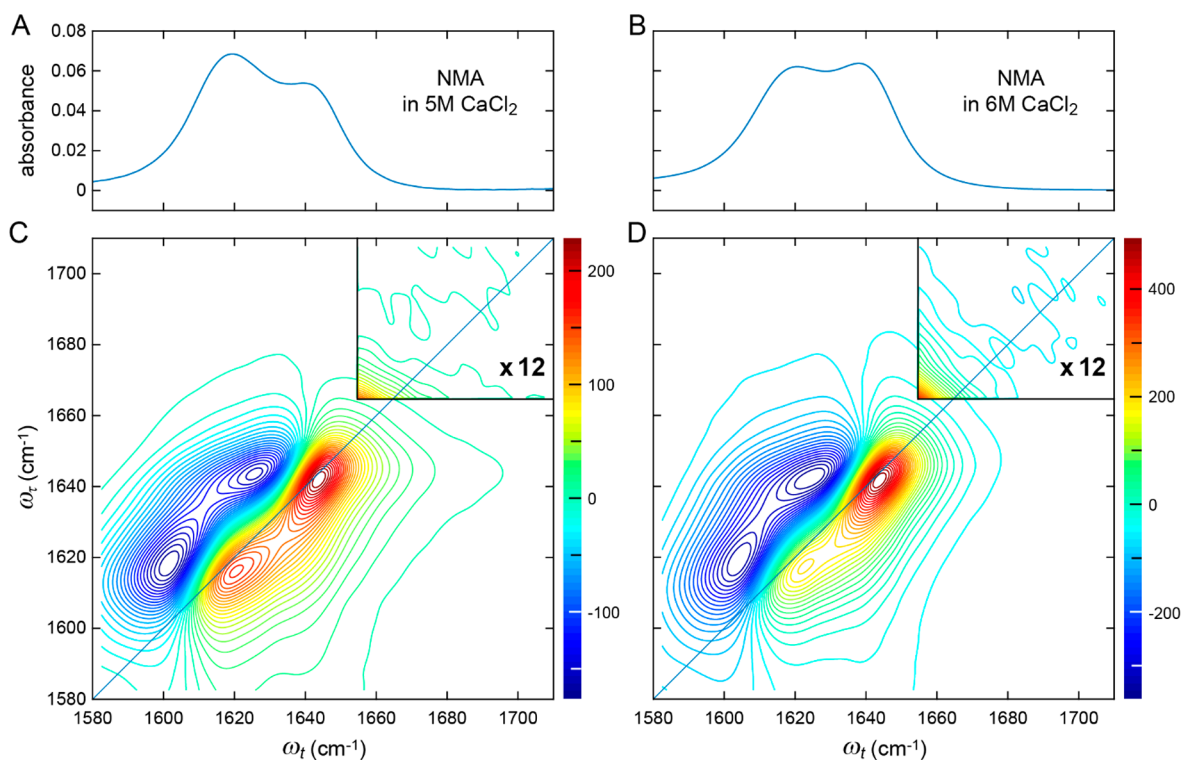


Figure 3. FTIR spectra and 2D IR spectra of aqueous solutions of NMA in the presence of 5 M (A, C) and 6 M (B, D) of CaCl₂. The concentration of NMA is 50 mM, and the thickness of the sample is 25 μ m. In each spectrum, the spectral magnitude inside the small rectangle was multiplied by 12 times.

contribution arising from each phenomenon is difficult to decipher at this point. Cremer's results on ¹⁵N-labeled NMA

definitely demonstrates that imimolate is not the sole contributor to the blue-shifted peak. However, as described

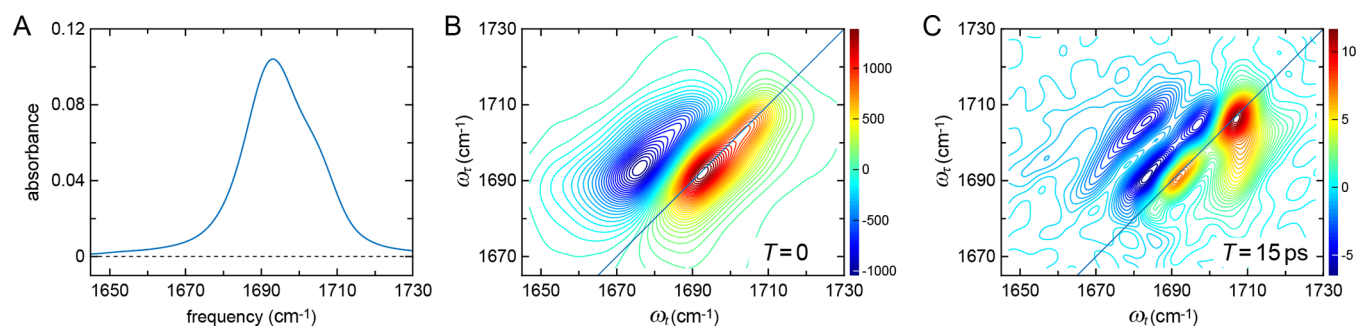


Figure 4. (A) FTIR spectrum of aqueous acetone in the presence of 4 M CaCl_2 , (B, C) 2D IR spectra at (A) $T = 0$ and (B) $T = 15$ ps. The concentration of acetone is 100 mM, and the thickness of the sample is 25 μm .

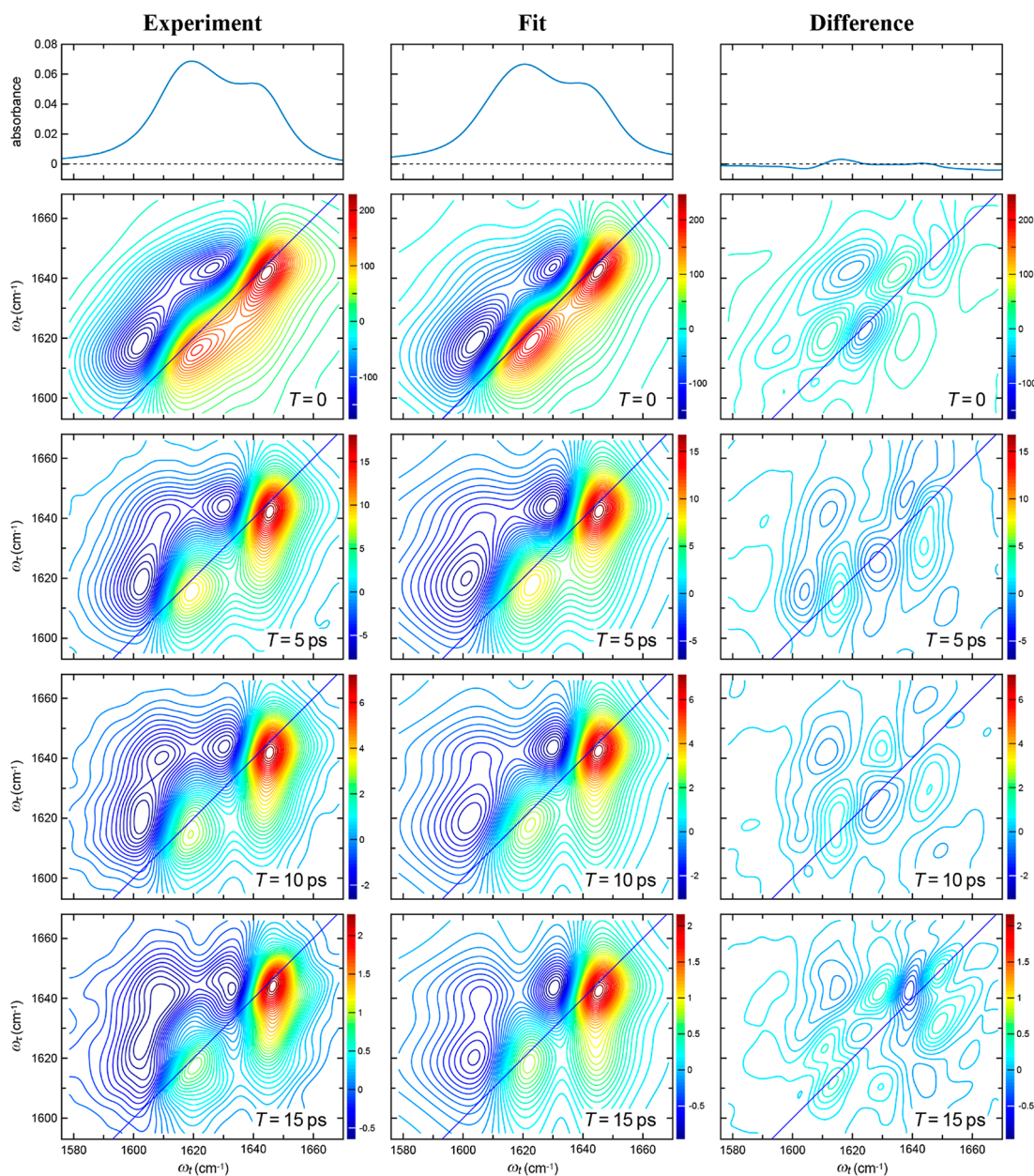


Figure 5. Experimental and simulated FTIR and T -dependent 2D IR spectra of an aqueous sample of NMA in the presence of 5 M CaCl_2 . Left column: experimental FTIR (top) and 2D IR spectra at $T = 0, 5, 10,$ and 15 ps. Middle column: experimental FTIR (top) and simulated 2D IR spectra at $T = 0, 5, 10,$ and 15 ps. Right column: difference between the left and middle columns. The simulated spectra were based on the model reported previously.^{5–7}

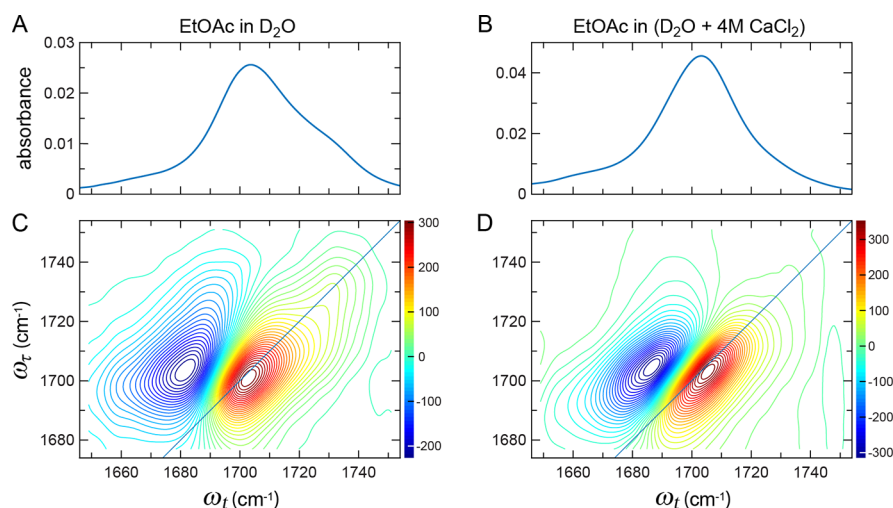


Figure 6. (A, C) (A) FTIR and (C) 2D IR spectra of ethyl acetate (EtOAc) in neat D_2O . (B, D) (B) FTIR and (D) 2D IR spectra of an aqueous solution of EtOAc in the presence of 4 M $CaCl_2$. The spectra in parts A and C have been reproduced from an earlier study.⁷ The 2D IR spectra were collected at $T = 0$. The concentration of EtOAc is 40 mM, and the sample thickness is 25 μm .

above, a partial contribution from the tautomer cannot be ruled out. A recent study by Cracchiolo et al. reported a peak at ~ 1680 cm^{-1} for aqueous NMA in the presence of a high concentration (6 M) of $CaCl_2$.⁴ However, we did not observe the reported peak in our 2D IR spectra of aqueous NMA in the presence of 5 and 6 M of $CaCl_2$ (Figure 3).

A similar blue-shifted shoulder is indeed seen for the acetone $C=O$ stretch in the presence of a high concentration (4 M) of $CaCl_2$. We performed 2D IR spectroscopy and estimated an exchange time scale of ~ 5 ps for acetone in the presence of 4 M $CaCl_2$ (Figure 4). We have also performed extensive numerical simulations, based on earlier reported protocols,^{5–7} to extract the exchange time scale in the case of NMA in the presence of 5 M $CaCl_2$ (Figure 5). A much slower exchange of ~ 17 ps is estimated for NMA in the presence of 5 M $CaCl_2$, plausibly arising from the partial contribution of Ca^{2+} attachment–detachment dynamics. Another distinct difference is in the intensities of the blue-shifted shoulders of acetone and NMA 2D IR spectra in the presence of $CaCl_2$. For NMA, the blue-shifted peak is more intense than that arising from amide I, whereas the reverse is true for acetone. A similar low-intensity blue-shifted peak arising from dehydration has been previously reported for ethyl acetate in D_2O .^{7,8} The reported hydration–dehydration dynamics time scale for ethyl acetate was 1.3 ps.⁷ The ~ 5 ps exchange time scale, along with the previous report of such a peak for ethyl acetate, indicates that the blue-shifted shoulder for acetone arises from dehydration. Our theoretical calculations predict that the $C=N$ mode has a higher extinction coefficient than that of the amide I mode. The slower exchange time scale in NMA when combined with the theoretical prediction hints at an additional phenomenon in NMA, which is absent for acetone. Interestingly, the blue-shifted shoulder in ethyl acetate completely vanishes in the presence of $CaCl_2$ (Figure 6). This shows that the shoulder peak is not a general phenomenon for carbonyls.

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<https://pubs.acs.org/10.1021/acs.jpcc.0c06005>

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Authors acknowledge SERB India (EMR/2016/001069 and EMR/2016/000576) and NRF of Korea (2017R1D1A1B03032623) for funding. R.K.S. thanks UGC for fellowship.

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