n→π* Interaction

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Direct Spectroscopic Evidence for an n→π* Interaction

*Santosh K. Singh, Kamal K. Mishra, Neha Sharma, and Aloke Das**

Abstract: *The n→π* interaction is an extremely weak but very important noncovalent interaction. Although this interaction is widely present in biomolecules and materials, its existence is counterintuitive and so has been debated extensively. Herein, we have reported direct spectroscopic evidence for an n→π* interaction for the first time by probing the carbonyl stretching frequency in phenyl formate using isolated gas-phase IR spectroscopy. This result also demonstrates that the conformational preference for the cis conformer of phenyl formate compared to the trans conformer arises due to the presence of the n→π* interaction in the former. The direct proof reported herein for this controversial but important noncovalent interaction should stimulate further experimental and theoretical investigation on this intriguing research topic.*

The relatively newly discovered noncovalent n→π* interaction has attracted growing research interest over the last decade.[1] This interaction is extremely weak in strength (0.2–1 kcal mol^{-1}) and its existence is considered to be counterintuitive.[1h] This noncovalent interaction is analogous to the well-known and relatively stronger hydrogen-bonding interaction (5–10 kcal mol^{-1}) in terms of electron delocalization.[2] The n→π* interaction involves delocalization of lone-pair electrons (*n*) on electronegative atoms into a π* orbital of generally an aromatic ring or a carbonyl group,[1c] whereas the hydrogen-bonding interaction involves delocalization of lone-pair electrons (*n*) on electronegative atoms into a σ* orbital of a X–H group, where X is conventionally an electronegative atom.[2c] Thus following the nomenclature employed for the n→π* interaction, the hydrogen-bonding interaction could also be classified as an n→σ* interaction.

Although the n→π* interaction is much weaker than the hydrogen-bonding interaction, the n→π* interaction, like any other noncovalent interaction, is widely present in materials, bio-macromolecules (proteins, DNA), amino acids, neurotransmitters, and drugs.[1b,f,3] The n→π* interaction was first discovered in Z-DNA in 1995 through analysis of its crystal structure.[3a] In 1999, Dougherty and Gallivan reported the first computational study on the n→π* interaction by studying the $C_6F_6\cdots H_2O$ complex.[4] The n→π* interaction (X···C=O or X···$\pi_{aromatic}$; X = N,O atoms) between an electronegative atom and a carbonyl group or an aromatic ring follows the Burgi–Dunitz trajectory of approach of a nucleophile towards an electrophile (for example, the C=O group) for an addition reaction.[1c,5]

Generally, the hydrogen-bonding interaction (X–H···Y) in a molecular system can easily be quantitatively characterized by measuring the red-shift in the X–H stretching frequency using IR spectroscopy.[6] Herein, we investigate whether the existence of the n→π* interaction can be proven by probing the stretching frequency of the C=O group involved in this interaction using a similar IR spectroscopic technique. Given that the n→π* interaction is very weak, it is not easy to identify the presence of this interaction from solution-phase IR spectroscopy because the spectroscopic signature of this weak interaction could be masked by the presence of various other interactions. Instead, IR spectroscopy carried out in an isolated collision-free environment, that is, in a supersonic jet, could be an ideal means to study this weak interaction quantitatively. In fact, a recent report on the experimental characterization of the n→π* interaction by measuring the O–H stretching frequency in the $C_6F_6\cdots H_2O$ complex used matrix-isolation IR spectroscopy.[7] However, there has been no report of the use of IR spectroscopy to measure quantitatively the strength of the n→π* interaction in an isolated gas phase.

The existence of the n→π* interaction has been demonstrated in the literature mostly from the analysis of X-ray crystal structures of biomolecules and materials in the RSCB Protein Data Bank (PDB) and Cambridge Structural Database (CSD), respectively, by identifying the close contact between an electronegative atom and a carbonyl group or an aromatic ring.[1a,b,f,k] However, the question arises as to whether this close contact between two electron-rich moieties occurs just because of optimization of the arrangement of other molecular units in the macromolecular systems. Preferential stabilization of the conformers of various organic molecules (such as small peptides or peptoids) having n→π* interactions over the ones without this interaction has been also studied by measuring the equilibrium constants from NMR spectroscopy.[1c,d] However, no direct spectroscopic evidence or quantitative information on the n→π* interaction has been established from NMR spectroscopy.

There are a few reported examples of microwave spectroscopic studies on the conformations of amino acids (β-alanine and γ-aminobutyric acid) as well as of the drug aspirin stabilized by n→π* interactions.[3c–e] Recently, Caminati and co-workers reported the structure of a complex of chlorotrifluoroacetylene and water stabilized by an n→π* interaction.[8] In this work, we have studied phenyl formate as the model compound in the isolated gas phase using electronic, vibrational, and UV–UV hole-burning spectroscopic techniques combined with ab initio calculations to prove the existence of the n→π* interaction.

[*] S. K. Singh, K. K. Mishra, N. Sharma, Dr. A. Das
Department of Chemistry
Indian Institute of Science Education and Research
Dr. Homi Bhabha Road, Pune-411008, Maharashtra (India)
E-mail: a.das@iiserpune.ac.in

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Figure 1a shows the electronic spectrum of phenyl formate measured by one-color resonant 2-photon ionization (1C-R2PI) spectroscopy. The spectrum contains many sharp bands, making the assignment non-trivial. As phenyl formate is a flexible molecule, it can exist as *cis* and *trans* conformers depending on the orientation of the carbonyl group with respect to the phenyl group. Figure 2 shows the structures of the *cis* and *trans* conformers of phenyl formate optimized at the M05-2X/aug-cc-pVDZ level of theory.

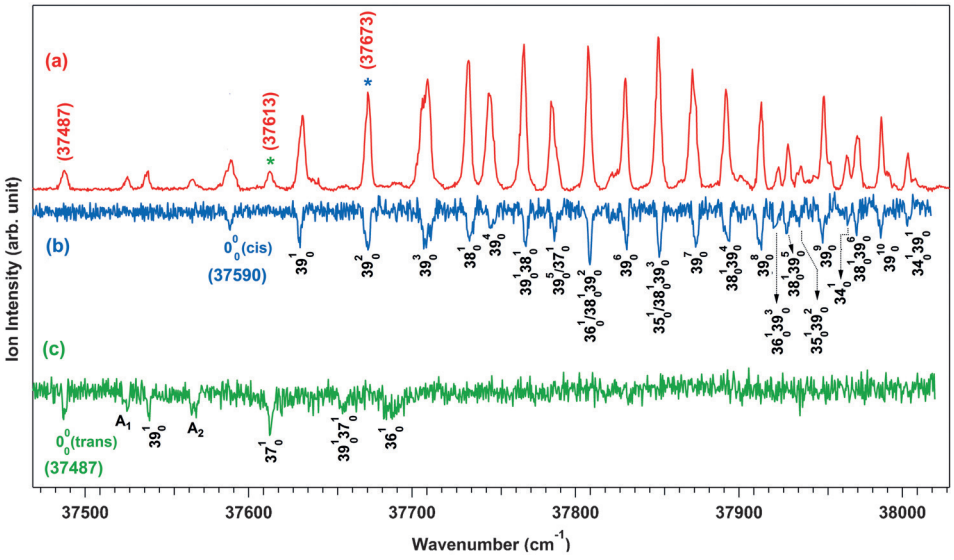

Figure 1. a) Electronic spectrum of phenyl formate measured using 1C-R2PI spectroscopy. b, c) UV–UV hole-burning spectra of phenyl formate measured by probing the bands at 37673 (b) and 37613 cm^{-1} (c), respectively (marked by asterisks in (a)). Tentative assignment of the bands in the electronic spectrum is done based on the calculated vibrational frequencies in the excited electronic state at the CIS/6-31+G(d) level of theory (see the text and Table S1 for detailed assignment). The bands marked as A_1 and A_2 are attributable to the *trans* conformer only but could not be assigned to the $S_1 \leftarrow S_0$ transition.

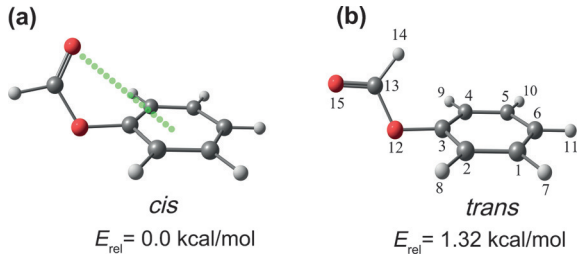

Figure 2. Optimized structures of the a) *cis* and b) *trans* conformers of phenyl formate obtained at the M05-2X/aug-cc-pVDZ level of theory. The atom numbering scheme is shown in the structure of the *trans* conformer. Atom colors: O = red; C = gray; H = white.

Zero point energy (ZPE) corrected relative energies of the two conformers are provided in Figure 2. The *cis* conformer is more stable than the *trans* conformer by 1.32 kcal mol^{-1}. The lowest energy transition at 37487 cm^{-1} displayed in the electronic spectrum (Figure 1a) could be assigned to the origin band resulting from the $S_1 \leftarrow S_0$ electronic excitation of one of the conformers of phenyl formate. However, the question arises as to whether multiple bands present in the spectrum are due to electronic excitation of a single conformer or both of the conformers.

Figure 1b and 1c show UV–UV hole-burning spectra, obtained by probing the bands at 37673 and 37613 cm^{-1}, respectively (marked by asterisks in the R2PI electronic spectrum; Figure 1a). The hole-burning spectra displayed in Figure 1b,c clearly indicate the presence of the two conformers of phenyl formate in the experiment. This is evident through the depletion of the ion signal of the set of transitions originating from the ground electronic state of each individual conformer. The electronic transitions corresponding to the hole-burning spectrum in Figure 1c are much weaker compared to those corresponding to the hole-burning spectrum in Figure 1b. A comparison of the relative intensities of the bands in Figure 1b and 1c indicates that the bands in Figure 1b are due to electronic excitation of the most stable conformer, that is, the *cis* conformer, and the bands in Figure 1c originate from excitation of the *trans* conformer of phenyl formate. The structural assignment of the two detected conformers has been confirmed by IR spectroscopy (see below for discussion).

It is apparent from Figure 1 that the electronic spectrum of the *cis* conformer of phenyl formate is richer in vibronic structure than that of the *trans* conformer. The vibronic bands of the two conformers (Figure 1b,c) have been tentatively assigned by calculating their structures and vibrational frequencies in the excited electronic state at the CIS/6-31+G(d) level of theory. The assignment of the bands has been provided in Figure 1b,c. For detailed assignment of the bands and a description of the modes of the *cis* and *trans* conformers of phenyl formate, see Table S1 in the Supporting Information.

The band at 37590 cm^{-1} in the spectrum shown in Figure 1b is assigned to the 0_0^0 band for the $S_1 \leftarrow S_0$ electronic excitation of the *cis* conformer of phenyl formate. It is interesting to note that the origin band of the *cis* conformer is very weak in intensity compared to that of the vibronic bands present in the spectrum. The electronic spectrum of the *cis* conformer is dominated by a long progression of the Ph–O torsion (mode 39) of 43 cm^{-1} as well as combination bands of mode 39 with the ring-bending vibration (mode 38) of 145 cm^{-1} (Figure 1b). The observation of this strong Franck–Condon activity in the electronic spectrum demonstrates that the most significant change in the geometry of the *cis* conformer of phenyl formate occurs along the Ph–O torsional coordinate ($\measuredangle C_4$-C_3-O_{12}-C_{13}; see Table S2). The

comparison in Table S2 of a few important geometrical parameters of both conformers of phenyl formate indeed corroborates this observation.

The spectrum shown in Figure 1c shows the 0_0^0 band for the $S_1 \leftarrow S_0$ electronic excitation of the *trans* conformer of phenyl formate at 37487 cm^{-1}. A few low-frequency vibrational modes of the *trans* conformer of phenyl formate calculated at the S_1 state are provided in Table S1. Here the spectrum does not show any significant progression of any normal mode, rather single quantum excitations of a few vibrational modes (modes 39, 37, and 36) are detected in the experiment. The geometrical parameters listed in Table S2 support this observation. It has been found that the bands at $[0_0^0 + 39\ cm^{-1}]$ and $[0_0^0 + 79\ cm^{-1}]$, marked as A_1 and A_2 in the spectrum shown in Figure 1c, cannot be assigned from the S_1-state calculated vibrational frequencies of the *trans* conformer of phenyl formate. This is quite intriguing as both of these bands show depletion in the ion signal simultaneously with all other bands in the hole-burning spectrum of Figure 1c. Thus the A_1 and A_2 bands share the ground state of the *trans* conformer only. It could be speculated that these two bands could be due to the transition to the S_2 state of the *trans* conformer which is close to the S_1 state. Detection of a similar $S_2 \leftarrow S_0$ band at 123 cm^{-1} above the S_1 origin transition in the jet-cooled electronic spectrum of diphenylmethane has been reported by Zwier and co-workers.[9] As the focus of this work is to obtain spectroscopic evidence for the $n \rightarrow \pi^*$ interaction by determining the ground-state structures of the two conformers of phenyl formate, high-level ab initio calculations of the excited electronic states to confirm the assignment of these two bands (A_1 and A_2) was not pursued herein.

Figure 3a and 3c show IR spectra measured in the carbonyl stretching region by excitation of the $[0_0^0(cis) + 83\ cm^{-1}]$ and the $[0_0^0(trans) + 126\ cm^{-1}]$ bands, respectively, in the electronic spectrum of phenyl formate (Figure 1a) using resonant ion dip infrared (RIDIR) spectroscopy. Theoretical IR spectra calculated at the M05-2X/aug-cc-pVDZ level of theory displaying the carbonyl stretching frequency of the *cis* and *trans* conformers of phenyl formate are provided in Figure 3b and 3d, respectively. The calculated IR stretching frequency has been scaled using a factor (0.9577) obtained from the ratio of a reported experimental carbonyl stretching frequency (1746 cm^{-1}) and the M05-2X/aug-cc-pVDZ level calculated carbonyl stretching frequency (1823 cm^{-1}) of methyl lactate, a similar ester-like phenyl formate. The experimental carbonyl stretching frequency of methyl lactate reported in the literature was measured using matrix isolation FTIR spectroscopy.[10]

There is an excellent agreement between the experimental and theoretical IR spectra of the two conformers of phenyl formate (Figure 3). The IR band detected at 1766 cm^{-1} in the vibrational spectrum shown in Figure 3a is assigned to the carbonyl stretching frequency in the *cis* conformer of phenyl formate where the carbonyl group is pointed towards the phenyl ring. On the other hand, the IR band detected at 1797 cm^{-1} in the vibrational spectrum shown in Figure 3c is assigned to the carbonyl stretching frequency in the *trans* conformer of phenyl formate, where the carbonyl group is pointed away from the phenyl ring. The IR spectroscopic data clearly demonstrate that the detected red-shift of 31 cm^{-1} in the carbonyl stretching frequency of the *cis* conformer of phenyl formate compared to that of the *trans* conformer is due to an attractive interaction between the carbonyl group and the π-cloud of the phenyl ring in the *cis* conformer.

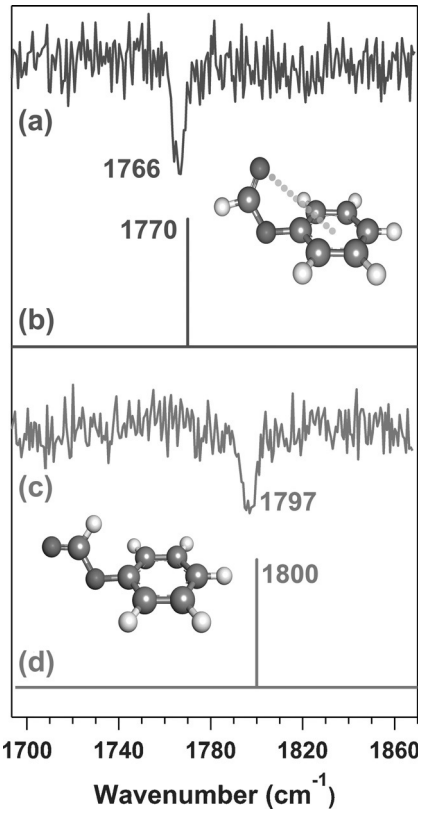

Figure 3. IR spectra obtained by probing the a) $[0_0^0(cis) + 83\ cm^{-1}]$ and c) $[0_0^0(trans) + 126\ cm^{-1}]$ bands in the electronic spectrum shown in Figure 1. Theoretical IR spectra of the *cis* and *trans* conformers of phenyl formate calculated at the M05-2X/aug-cc-pVDZ level of theory are shown as stick diagrams in (b) and (d), respectively. The calculated IR frequency has been scaled with respect to the reported experimental carbonyl stretching frequency of methyl lactate.[10]

Natural bond orbital (NBO) analysis performed at the M05-2X level shows that second-order perturbative energy $\left(E^{(2)}_{n\rightarrow\pi^*}\right)$ for the $n \rightarrow \pi^*$ interaction between the lone-pair electrons on the carbonyl oxygen and the π* orbitals of the phenyl ring in the *cis* conformer of phenyl formate is 1.03 kcal mol^{-1}. Figure 4 displays the NBOs showing the overlap between the carbonyl oxygen lone pair orbital and π* orbitals of the phenyl ring in the *cis* conformer. Further NBO analysis of both *cis* and *trans* conformers of phenyl formate has been carried out to look into all of the orbital interactions present and to determine the role of the $n \rightarrow \pi^*$ interaction to decrease the C=O stretching frequency in the *cis* conformer relative to the *trans*. Second-order perturbative energy values for interactions between various NBOs in the *cis* and *trans* conformers of phenyl formate and the NBO view for the overlap between corresponding orbitals are given in Table S3 and Figure S3–S5.

In phenyl formate, overlap between the lone-pair orbital on the ether oxygen (O_{12}) atom and the carbonyl π* orbital

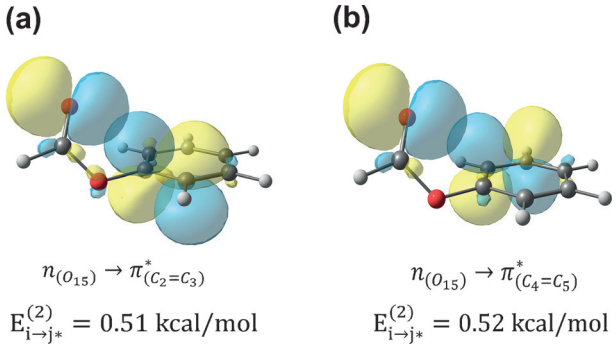

Figure 4. NBO view showing the overlaps between the carbonyl oxygen lone-pair orbital (i) and two different π* orbitals (j*) on the phenyl ring in the *cis* conformer of phenyl formate.

decreases the C=O stretching frequency whereas overlap between the lone-pair orbital on the carbonyl oxygen (O_{15}) atom and the C_{13}-O_{12} σ* orbital increases the C=O stretching frequency. It has been found that the red-shift in the C=O stretching frequency in the *cis* conformer of phenyl formate compared to that in the *trans* conformer is due to the presence of the n→π* interaction in the *cis* conformer, and that this noncovalent interaction favors neighboring orbital interactions which decreases the C=O stretching frequency. Detailed explanation on NBO analysis is provided in the Supporting Information.

Thus the present result provides, for the first time, direct spectroscopic evidence for the presence of the n→π* interaction by using IR spectroscopy. The most important point is the detection of conformers of phenyl formate, one with the n→π* interaction and the other without. It should be pointed out that the dispersion interaction between carbonyl and phenyl groups also contributes to the stability of the *cis* conformer of phenyl formate. The stability obtained through similar carbonyl···π dispersive interactions has been reported in systems such as the Phe-Gly-Gly tripeptide, 2-pyridone···benzene, and 2-pyridone···hexafluorobenzene.[11]

It is important to mention here that the IR spectra measured by excitation of the A_1 [0^0_0 (*trans*) + 39 cm^{-1}] and A_2 [0^0_0 (*trans*) + 79 cm^{-1}] bands in the electronic spectrum of phenyl formate (Figure 1c) reconfirms that these two bands originate from the *trans* conformer only (IR spectra shown in Figure S1).

In summary we have reported herein direct spectroscopic evidence of a weak noncovalent interaction, namely the n→π* interaction, for the first time by studying phenyl formate using IR–UV double-resonance spectroscopy in a supersonic jet. Two conformers of phenyl formate have been detected in the experiment. The *cis* conformer having the n→π* interaction between the carbonyl group and the phenyl group is more stable than the *trans* conformer which does not have any n→π* interaction. Detection of a significant degree of red-shift in the carbonyl stretching frequency of the *cis* conformer with respect to that of the *trans* conformer provides direct evidence for the favorable interaction between the carbonyl and the phenyl groups in the *cis* conformer. It is anticipated that this direct experimental proof for the presence of this weak and counterintuitive noncovalent interaction will stimulate further theoretical and experimental work on this subject given that the n→π* interaction is widely present in biomolecules and materials. It will be also quite intriguing for theoreticians to perform high-level quantum chemistry calculations of the excited electronic states (such as S_1, S_2) for accurate assignment of the proposed $S_2 \leftarrow S_0$ transitions in the electronic spectrum of the *trans* conformer of phenyl formate.

Experimental Section

To perform isolated gas-phase spectroscopy, phenyl formate vapor (heated at 60 °C) seeded in 70% Ne/30% He gas mixture was expanded into a high-vacuum chamber through a pulsed nozzle (diameter = 0.5 mm, 10 Hz) and ionized with tunable pulsed UV (10 Hz, 10 ns) and IR (10 Hz, 10 ns) lasers.[12] The spectroscopic techniques which were used in this experiment were one-color resonant two photon ionization (1C-R2PI), UV-UV hole-burning and resonant ion-dip infrared (RIDIR) spectroscopy.[12] Experimental results were analyzed with the help of ab initio calculations performed using the Gaussian 09 program.[13] The experimental techniques and computational methods have been described in detail in the Supporting Information.

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