Reply to the Comment on "Structural and Vibrational Assignment of *p*-Methoxyphenethylamine Conformers"

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The identification of molecular conformers to optimized geometrical structures is commonly grounded on a set of theoretical and empirical correlations. Each test adds plausibility to the assignment, but it is the whole set that provides consistency and reliability to the identification. The choice of the tests is by no means standard, and sometimes the computed properties for these large molecules are not accurate enough to ascertain a single structure. In the case of the spectra of neurotransmitter molecules of the family of phenethylamine (PEA), the overlapping of the conformer bands added to the proximity of their origin bands makes the identification flimsy and delicate. Robertson et al.[1] (referred to henceforth as RSM) have recently questioned the choice of arguments used for our identification of the MPEA molecule[2] and have proposed a reassignment based on the three arguments that follow and which we analyze.

A. The correlation between the calculated relative stability of gauche and anti conformers and their origin bands intensities. We discuss this argument at two levels, one general and the other specific to MPEA. In a recent review, Rappé and Bernstein[3] conclude that calculations on gauche conformers are affected by a kind of basis set superposition error (BSSE) larger than for the anti ones; applied to MPEA, the calculations of gauche structures, with the NH_2 group close to the aromatic ring, benefit from the aromatic basis functions. In general, it may be stated that the more folded the structure the better the molecular basis functions describe the system, resulting in improved system energies. For the PEA molecule computed at the MP2/cc-pVDZ level,[3] the BSSE is around 8 kcal/mol (2.800 cm^{-1}) and the gauche-anti energy difference around 2 kcal/mol (700 cm^{-1}). Both the BSSE and the gauche-anti energy differences significantly decrease if computations are conducted at the B3LYP levels (instead of MP2), emphasizing the superior behavior of the DFT methods in this application. In addition, the intensity of the MPEA origin bands[2] is perturbed by changes in the transition oscillator strength, which in turn is affected by the relative orientation of the NH_2 group, an argument used by Simon's group in their identification of PEA conformers.[4] Keeping in mind the above-mentioned arguments, the assignment of MPEA conformer 1 to the strongest band is not surprising, particularly if the band intensity is explained in terms of population migration from the two anti conformers, which are less stable and assigned to bands F and G. Furthermore, if the correlation of band intensities to stabilities is strictly applied to the assignment, the identification of the weak band B to conformer 1 (ref 1, Figure 1), a mere 44 cm^{-1} less stable than the most stable conformer 8, is unjustified.

B. The overall appearance of the MPEA dispersed emission (DE) spectrum[1] prompts the grouping of the origin bands as {A, C, D, E} and {B, F, and G} (cf. Figure 8 of ref 1), and further to identify them as anti and gauche conformers, in contrast with our grouping as {A−D} and {E−G}.[2] We assume that the "overall appearance" refers to the vibrational activity with energies over 500 cm^{-1}, many of which are ring vibrations and of little use for identification purposes. However, there are alternative arguments that seem to be sounder. For example, the low energy vibrational activity of the ethylamino skeleton (within 100 cm^{-1}) groups features A, B, C, and F in the same set. To get a one-to-one identification we compared the calculated and experimental vibrational frequencies. However, despite the excellent matching of both set of data at the B3LYP calculations, the large number of bands and the close pattern of the conformer spectra hamper a reliable identification. There is only one set of vibrations, appearing in the spectrum of excitation (TOF) but not in emission, that may be applied to distinguish conformers, namely the torsion of the whole ethylamino group, ν_1, which is strongly affected by the presence of the $NH_2 \cdots \pi$ interaction. The characteristic bands appear in the excitation spectrum of all the conformers except for those associated to bands E and G (identified as anti conformers 1 and 3), probably due to the overlapping with other intense bands, and are used as the guideline to tentatively assign origins A to D to conformers 8, 5, 7, and 4. As stressed in the paper,[2] this was the weakest argument used for the identification purpose and it was looked on with suspicion because of the small difference of the vibrational energies.

C. (RSM argue[1] that) the spacing of our MPEA anti conformers origin bands do not match with those of PEA, amphetamine, and *p*-aminophenethylamine (APEA) conformers. The argument is emphasized by referring to the identification of APEA reported in a Ph. D. Thesis, whose grounds we cannot evaluate. In the past few weeks, we submitted a manuscript on the subject[5] to the *Journal of Chemical Physics*, where we compare the experimental and the computed ionization energies, study the change of the spectra with the stagnant pressure, and report the isomerization barriers between the APEA conformers, and as a result we identify the origin bands B and A to gauche conformers, feature C to structure V (the most stable one), and D to structure IV. The work also shows that the conformers' relative stabilities computed at the B3LYP/6-31++G** level (ZPE-corrected) are 0, 35, 31, and 86 cm^{-1}, for the equivalent to PEA V, II, III, and IV structures (cf. ref 1, Figure 1), and thereby support the identification of the most stable structure to an anti conformer.

In summary, we found that the three major arguments proposed by RSM to reassign the APEA conformers have alternative readings and counter-arguments, and we found our set more appealing and convincing. Obviously, the cascade-type identification of conformers suggested in ref 1, Figure 1 is not as safe and sound as a first approach may indicate.

In the above comments we have not discussed the structural identification of the conformers of tyramine, one of the keystone intermediate molecules in the identification series of RSM.[1] They overlook the pioneering assignment by Martínez et al.,[6] based on the comparison with 4-propylphenol, with which features A, B and D, E pairs share a spacing of 12 cm^{-1}. By contrast, they assume that the tyramine anti conformers are less stable and therefore their origin bands should be weaker. As we have discussed for APEA, it is hard to choose the most stable conformer. Further, the original assignment from Martinez et

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al. is consistent with the rule that anti conformers have red-shifted origin bands and gauche conformers have blue-shifted origin bands. In consequence, we prefer the assignment first proposed Levy et al.; in addition, Levy et al. assignments of MPEA and PEA, based on the spacing between bands, are identical to those proposed by us for MPEA[2] and by Simons et al. for PEA.[3,7]

In conclusion, the assignment of APEA and related molecules is difficult to rationalize, especially when no conclusive evidence exists and we have to play only with subtle hints and plausible arguments. We encourage the Oxford group to carry out IR−UV double resonance experiments of the systems presented in the Comment, to settle unequivocally the identification of the conformers, as already reported for tryptophan[8] and 2-methylamino-1-phenylethanol[9] molecules.

References and Notes

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