Supporting Information for:

Mimicking Anesthetic-Receptor Interactions in Jets: The Cluster Propofol-Isopropanol

By

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Dr. José A. Fernández Departamento de Química-Física, Facultad de Ciencia y Tecnología, Universidad del País Vasco-UPV/EHU. B° Sarriena s/n, Leioa 48940. SPAIN e-mail: josea.fernandez@ehu.es Fax: ++ 34 94 601 35 00. Phone ++ 34 94 601 5387 https://sites.google.com/site/gesemupv/ **Figure S1.** Calculated structures for propofol isopropanol at M06-2X/6-311++G(d,p) level, together with their relative stability in kJ/mol. ZPE correction was applied to all the energy values.



Figure S1. Cont.



29 [28.3]

Table S1. Calculated structures for propofol isopropanol at M06-2X/6-311++G(d,p) level, together with their relative stability in kJ/mol. ZPE correction was applied to all the energy values. ΔG column indicates the sum of the electronic and thermal Free Energies at 333.15K.

| Structure | ΔE (kJ/mol) | ΔE_{ZPE} (kJ/mol) | $\Delta G_{333.15K}$ (kJ/mol) | $D_{\theta}(kJ/mol)$ | BSSE (kJ/mol) |
|-----------|---------------------|---------------------------|-------------------------------|----------------------|---------------|
| 1 | 0.00 | 0.00 | 0.10 | -34.56 | 4.60 |
| 2 | 1.11 | 0.21 | 0.00 | -35.04 | 4.20 |
| 3 | 0.00 | 1.03 | 3.03 | -33.77 | 4.37 |
| 4 | 1.45 | 2.22 | 3.00 | -32.31 | 4.64 |
| 5 | 4.15 | 3.09 | 2.34 | -31.55 | 4.38 |
| 6 | 4.36 | 3.45 | 3.56 | -31.36 | 4.21 |
| 7 | 2.02 | 3.74 | 6.54 | -35.43 | 3.94 |
| 8 | 2.19 | 4.37 | 6.18 | -30.62 | 4.31 |
| 9 | 3.30 | 4.90 | 4.04 | -33.88 | 4.04 |
| 10 | 3.96 | 4.91 | 6.06 | -30.37 | 3.89 |
| 11 | 4.80 | 6.21 | 9.78 | -33.04 | 3.86 |
| 12 | 7.44 | 6.42 | 5.42 | -28.33 | 4.42 |
| 13 | 5.46 | 6.88 | 10.51 | -27.81 | 4.33 |
| 14 | 6.93 | 7.74 | 7.69 | -31.27 | 3.81 |
| 15 | 7.03 | 7.88 | 9.14 | -30.69 | 4.25 |
| 16 | 9.53 | 8.09 | 6.79 | -27.40 | 3.67 |
| 17 | 7.32 | 8.17 | 10.73 | -30.53 | 4.12 |
| 18 | 10.65 | 11.06 | 10.86 | -25.15 | 3.09 |
| 19 | 13.36 | 13.30 | 14.17 | -30.87 | 3.23 |
| 20 | 12.88 | 13.66 | 14.54 | -22.09 | 3.70 |
| 21 | 14.73 | 14.31 | 14.90 | -25.93 | 2.86 |
| 22 | 15.37 | 14.98 | 12.30 | -21.24 | 3.22 |
| 23 | 13.62 | 15.23 | 17.31 | -21.07 | 2.86 |
| 24 | 17.13 | 16.42 | 14.21 | -20.13 | 2.90 |
| 25 | 17.44 | 18.42 | 18.40 | -25.60 | 3.40 |
| 26 | 18.04 | 18.48 | 15.76 | -26.16 | 2.77 |
| 27 | 21.87 | 20.45 | 14.64 | -23.67 | 3.57 |
| 28 | 26.35 | 26.93 | 26.26 | -9.96 | 2.14 |
| 29 | 29.40 | 28.25 | 25.30 | -19.61 | 2.91 |

Figure S2. Experimental IDIRS for propofol isopropanol (upper trace) together with the predicted frequencies for each calculated structure at M06-2X/6-311++G(d,p) level. A correction factor of 0.935 was employed.





IR-IR-UV hole burning spectroscopy

Some molecules or clusters present overlapped electronic spectra and thus, when recording the IDIR spectrum, the transitions from each of the conformers cannot be resolved. In this case, a triple resonance technique, recently developed by Zwier's group,¹⁹ allows separating the IR spectra of the different isomers obtained via double resonance methods.

The technique is similar to that for the IR-UV method, but in this case, another IR laser is needed: a probe UV laser monitors the population of the overlapped electronic transition for two or more specific conformers in a supersonic jet, using a $S_1 \leftarrow S_0$ transition. An IR laser is introduced, at a repetition rate of 5 Hz, some micro-nanoseconds prior to the UV laser and it is fixed to a transition observed in the double resonance method. Then, a third laser is introduced temporally between them, at a repetition rate of 10 Hz. In this way, by scanning the second IR laser frequency while monitoring the 2c-REMPI signal, an ion-dip spectrum is obtained via active substraction, which corresponds to the IR ground state spectrum of the conformer selected by the first IR laser. The schematic and experimental setup is depicted in Figure S3.



Figure S3. Diagram of a triple resonance IR/IR/UV spectroscopy experiment. A prove UV laser monitors the population of two conformers whose electronic transitions are overlapped. A first IR laser is introduced at 5Hz, some ns/µs prior to the probe laser and fixed to a vibration on the IDIR spectrum while a second IR laser fired between the other two lasers is scanned. Each time the second IR laser is resonant with a vibrational transition of the selected conformer, a net effect is presented due to the gain at the selected transition's constant depletion produced by the first IR laser.

As the technique is considerably complicated, an example is offered for clarification: an aromatic molecule (X), which consist of carbons, hydrogens and a single OH group, is cooled under supersonic expansion conditions and only two conformers are formed: conformers A and B in a proportion of 4:1 (80% of conformer A and 20% of conformer B). These two conformers share common electronic transitions from the ground state to the excited state's vibrational levels and thus, they cannot be resolved. Consequently, when a IDIR experiment is done by fixing the UV laser in any of the electronic transitions, two OH stretching vibrations appear in the 3000-3800 cm⁻¹ region (for example at 3500 and 3600 cm⁻¹ for the conformers B and A respectively, Figure S4). For the sake of clarity, we will consider that both IR lasers have the same energy which does not fluctuate upon time, they have similar beam profiles and dimensions, and that the second IR laser exactly overlaps with the first IR laser and also with the UV laser. We also know that the UV laser is continually ionizing 100 molecules of our system, and therefore, 80 ions of conformer A and 20 ions of conformer B reach the detector in each of the UV pulses. In addition, the probability of both OH stretching modes is of 50%. If such conditions are fulfilled, when an IDIR experiment is done 40 molecules of conformer A are vibrationally excited at 3600 cm⁻¹ and 10 molecules of conformer B at 3500 cm⁻¹ (Figure S4a).

When doing the triple resonance method, the same result than in an IDIR experiment (Figure S4a) is achieved when the first laser is *off* (one must remember that it is fired at 5Hz while the other IR laser and the UV laser are fired at 10Hz). On the other hand, when it is *on* we will have three cases resulting in Figure S4b: 1) when the second IR laser is not resonant with any of the OH stretching vibrations, and as the first IR laser excites vibrationally 50% of the selected conformer A, a constant depletion of 40 molecules in the signal resulting in a baseline is obtained. 2) when the second IR laser is resonant with a stretching of conformer A, the first IR laser makes a dip of the 50% of the conformer A population, but the second laser depletes an additional 50% of the conformer A remaining population, resulting in a dip of 0.5*80=40 due to IR₁ and 0.5*(0.5*80)=20 due to the second, which amounts for a total dip of 60 molecules of the 100 ionized molecules. 3) when the second IR laser is resonant with a stretching of the conformer B, a depletion of 50% of the conformer A plus a 50% of conformer B is produced, which accounts for a total dip of 50 molecules. Thus, substraction of IR *on* from IR *off* signal results in the case shown in Figure S4c.

If fractions are used instead of molecules, the real case is achieved. When this technique is carried out using an active subtraction, a net effect is observed due to the gain in the selected transition's constant depletion caused by the first IR laser. Repeating the procedure for the rest of the OH stretching modes, an IR spectrum of each of the conformers is obtained.



Figure S4. Example of a triple resonance IR/IR/UV spectroscopy experiment. Case a: of the 100 ions reaching the detector, when the first IR laser is off and the second IR laser is resonant with the conformer A and B OH stretching modes, there is a depletion of the signal of 40% and 10% respectively. Case b: If the first IR laser is on and tuned into the OH stretching of conformer A there is a constant depletion, and when the second IR laser resonant with the conformer A and B OH stretching modes, there is a depletion in the remaining ions of 40% and 10% respectively. Case c: If an active substration of both signals is done, a net effect due to the gain in the selected transition's constant depletion is presented.