Competition between intra- and inter-molecular hydrogen bonding: *o*-anisic acid ··· formic acid heterodimer

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Abstract: Four conformers of the heterodimer *o*-anisic acid – formic acid, formed in a supersonic expansion, have been probed by Fourier transform microwave spectroscopy. Two of these forms have the typical double intermolecular hydrogen bond cyclic structure. The other two show the *o*-anisic acid moiety bearing a *trans*-COOH arrangement supported by an intramolecular O-H··O bond to the neighbour methoxy group. In these conformers, formic acid interacts with *o*-anisic acid mainly through an intermolecular O-H···O hydrogen bond either to the O-H or to the C=O moieties, reinforced by other weak interactions. Surprisingly, the most abundant conformer in the supersonic expansion is the complex in which the *o*-anisic acid is in *trans* arrangement with the formic acid interacting with the O-H group. Such a *trans*-COOH arrangement in which the intramolecular hydrogen bond dominates over the usually observed double intermolecular hydrogen bond interaction has never been observed previously in an acid-acid dimer.

Introduction

Hydrogen bonding (HB) is one of the main targets in the research of non-covalent interactions [1] because it confers specific functions and activities to biological systems and is ubiquitous in chemistry and biochemistry. The carboxyl group which exists abundantly in biomolecules is one of the simplest functional groups having double HB donor/acceptor character. It is capable of forming exceptionally strong cyclic double HB rings when interacting with another carboxylic group. These double HB cycles are reinforced by cooperativity,[1] in particular by the so-called resonance assisted hydrogen bond.[2] In addition, when carboxylic side-chains occur repeatedly at regular distances along a biological macromolecule, a double HB network structure similar to those in nucleic acids may occur. In this way, carboxyl dimers have been taken as prototypes of doubly hydrogen bonded DNA base pairs which govern the processes of transcription and translation of the genetic information.[3]

The double HB interaction of acid dimers is so strong that the first microwave (MW) spectroscopic detections of carboxylic acid dimers by Costain[4] and Bellot and Wilson[5] were done with

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samples at room temperature. The acid systems have been extensively studied using spectroscopic techniques in an effort to elucidate the nature of the non-covalent interactions and the dynamics of the conformational equilibria associated with acid homodimers/heterodimers. Most of the homodimers have been studied with high resolution spectroscopic techniques, for example, rotationally resolved laser induced fluorescence (LIF)[6] or femtosecond degenerate four-wave mixing and Raman spectroscopy. [7,8] In particular, jet-cooled Fourier transform microwave (FTMW) spectroscopy has been demonstrated as one of the most sensitive and powerful technique to obtain precise information about the structure and dynamics of molecular complexes.[9,10,11] For example, FTMW spectroscopy was utilized in the recent analysis of the formic acid dimer,[11] among a large list of acid-acid heterodimers.[12-20] Some of the reported work focuses on proton transfer[13-16] which is related to genetic mutations of DNA.[13,21,22] Other reports provide information on the conformational equilibria of heterodimers with two,[17,18] three[19] and four different conformations.[20] In the aforementioned cases, all the acid dimer conformers observed exhibit the typical cyclic double HB ring, which connects the two acid subunits in the *cis*-COOH arrangement, while the conformational diversity detected comes from the different chain orientations.

One further step in expanding our knowledge of acid-acid interaction would be the experimental detection of acid dimers where one of them takes on the *trans*-COOH arrangement. The stabilization of the *trans* form usually results from an intramolecular HB interaction with a close-by polar group in an acid. [23,24] An example acid molecule with a *trans*-COOH disposition is *o*-anisic acid (2-methoxybenzoic acid, *o*AA) which was recently studied by using FTMW spectroscopy.[24] It was identified in that study that the most stable conformer T1 (see Figure 1) observed contains an intramolecular OH$_{acid}$···O$_{methoxy}$ interaction which stabilizes the *trans*-COOH configuration. In addition, two conformers with the *cis*-COOH arrangement were observed. Moreover, in the corresponding monohydrates, the *trans*-COOH form is the most abundant monohydrate detected, while one weak *cis*-COOH monohydrate was observed. In the case of an acid dimer, one may anticipate a strong competition between keeping the *trans*-COOH configuration or switching to the *cis*-COOH form to facilitate the formation of the double cyclic HB structure. Such competition is essential in order to maximize the overall stability of the acid dimer under consideration, offering a valuable window to appreciate the delicate balanced act displayed by the complex.

In this paper, we have studied the interaction of *o*AA with formic acid (FA) to analyze the conformational panorama of the corresponding heterodimer in order to answer some important questions: how many conformers may exist? Would one be able to detect some acid dimers with *o*AA in the T1 form, i.e. the *trans*-COOH form? Which acid dimer structure will dominate the

observed spectrum: the *cis*-COOH with cyclic HB structure or the *trans*-COOH form? In addition, our study offers the opportunity to analyze the internal rotation of the carboxylic group and the proton transfer motion both interconverting two non-equivalent acid dimer conformers, a topic that has been discussed before for some other diacid complexes.[18-20]

Results and Discussion

Analysis of the rotational spectrum

The conformational landscape of the *o*AA – FA heterodimer has been theoretically investigated at the B3LYP-D3/6-311++G(d,p) level of theory.[25] The four more stable conformers out of a total of nine predicted conformations (see Table S1 and Figure S1 of ESI) are shown in Figure 1 and their predicted rotational parameters are collected in Table 1. A section of the broadband chirped-pulse (CP)-FTMW rotational spectrum of the *o*AA - FA heterodimers is shown in Figure 2. Once the rotational transitions of the *o*AA monomer and *o*AA-water complex[24] and of all the known complexes of FA[26] were removed, the weaker transition patterns of the four acid dimers became recognizable. The four low energy conformers (Figure 1) are predicted as asymmetric prolate rotors with κ [27] values ranging between -0.73 and -0.83, and relatively high values for the *a*- and *b*-electric dipole moment components (see Table 1). The assigned lines exhibit the typical μ_a-type R-branch pattern and the same transitions for each conformer appear in a narrow frequency window (Figure 2). This observation may correspond to conformers with very similar rotational constants as in the present case. All the spectra were analyzed with the *S*-reduced Watson´s semirigid Hamiltonian[28] in the I^r representation. The

rotational parameters determined are reported in Table 2. As it can be seen in Table 2, the T1-F-2 conformer has somewhat larger centrifugal distortion effects than the other conformers, indicating a less rigid behavior of T1-F-2. Overall, the experimental intensity obtained is too low to detect any rarer isotopologues in their natural abundance (Figure 2).

Table 1. Rotational parameters predicted at the B3LYP-D3/6-311++G(d,p) level of theory for the four most stable *o*AA – FA complexes.

Parameter [a]	C2-F-1	C1-F-1	T1-F-1	T1-F-2
A/MHz	1244.09	1228.16	1138.06	1133.40
B/MHz	356.73	363.38	418.32	380.43
C/MHz	278.84	282.41	307.71	285.35
κ	-0.84	-0.83	-0.73	-0.78
P_{cc}/uÅ^2	5.24	6.36	4.91	1.62
μ_a/D	3.2	3.2	2.2	7.0
μ_b/D	0.8	1.2	5.0	2.0
μ_c/D	0.0	0.0	0.3	0.0
$\Delta E_{B3LYP-D3}$/cm^{-1}	0.0 [b]	36.8	1276.1	1411.2

[a] *A*, *B* and *C* are the rotational constants. κ Ray asymmetry parameter κ=(2*B-A-C*)/(*A-C*). P_{cc} is the planar moment of inertia with respect to the *ab* inertial plane, P_{cc}=(I_a+I_b-I_c)/2. μ_a, μ_b and μ_c are the components of the electric dipole moment. ΔE is the energy relative to conformer C2-F-1. [b] Absolute energy is -725.369021 Hartree.
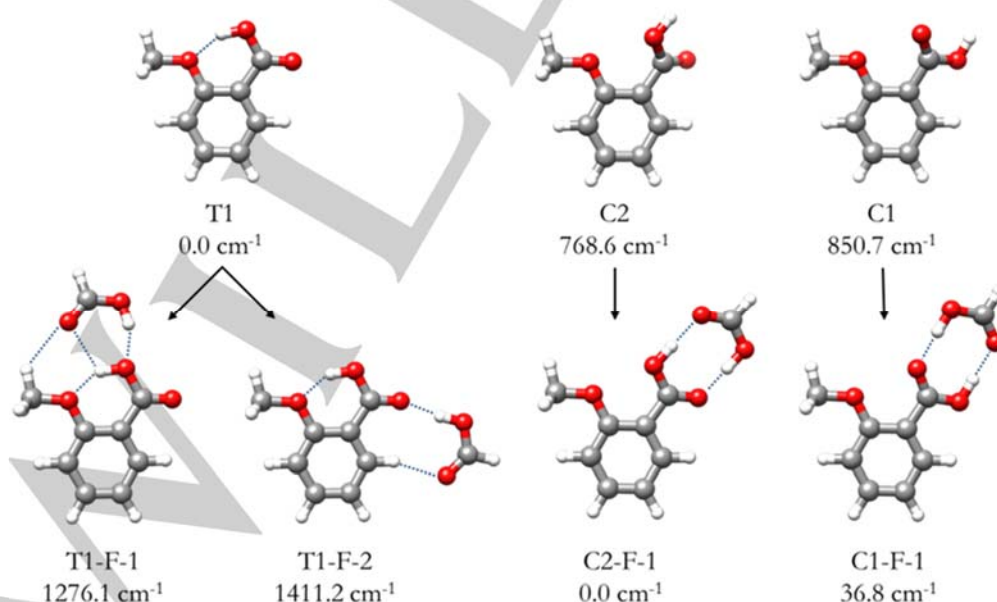

Figure 1. Conformational panorama of the *o*AA molecule and its heterodimer with FA. T and C refer to the *trans* or *cis*-COOH configurations of *o*AA, respectively. The B3LYP-D3/6-311++G(d,p) electronic energies listed are relative to that of T1 for *o*AA monomer, or that of C2-F-1 conformer for *o*AA-FA complex.
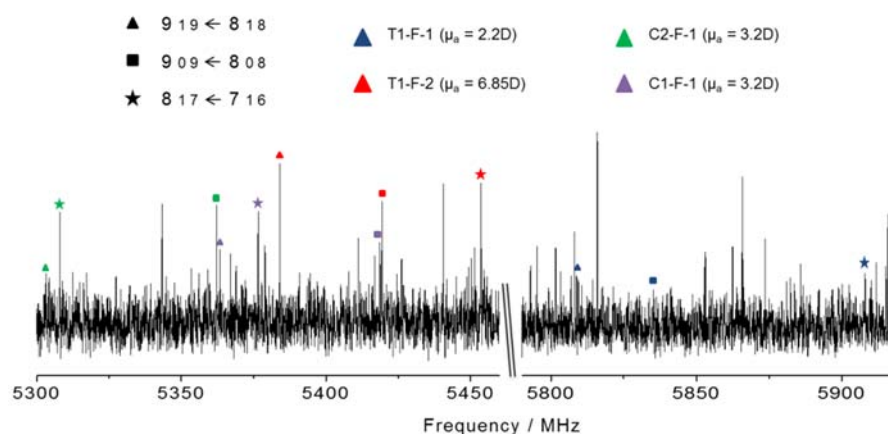
Figure 2. A section of the broadband CP-FTMW rotational spectrum of oAA - FA complex. Several assigned rotational transitions of the four oAA – FA heterodimers are indicated.

The comparison between the predicted and experimental rotational constants and the magnitude of electric dipole moment components revealed by the transition rules, allows corroborating without any doubt the identification of the four conformations of the dimer shown in Figure 1. The predicted rotational constants agree with the experimental values within less than 1%. Therefore, the r_e predicted structures could be taken as good estimations of the molecular geometries.

Relative intensity measurements were analyzed for the four conformers assigned to estimate their relative populations in the supersonic expansion assuming that the cooling in the jet brings all the molecular systems to the ground vibrational state of each observed conformer. [29] Using the squares of the predicted electric dipole moment components and assuming that all conformers have the same rotational temperature, the experimental relative populations of the acid dimer conformers in the jet are $N_{T1-F-1}/N_{C2-F-1}/N_{C1-F-1}/N_{T1-F-2}\sim100/95/85/30$ where the most abundant one is given the value of 100.

Structure

The T1-F-1 and T1-F-2 complexes are formed from the most stable conformer of oAA, T1 (see Figure 1).[24] In oAA T1 monomer form, the acid group exhibits a *trans*-COOH arrangement which is stabilized by a strong O-H···O hydrogen bond to the oxygen atom of the *ortho*-methoxy group. This oAA form has a planar skeleton with an experimental P_{cc} planar moment value of 1.97 u$Å^2$. In the T1-F-1 complex (see Figure 1), FA closes a six-membered ring-like sequential cycle with the oAA carboxyl O-H group intramolecularly bonded to the methoxy group. An additional, weak C-H···O=C hydrogen bond between the methyl group and FA seems to further stabilize the complex. In T1-F-2, the FA O-H group forms an OH···O=C hydrogen bond to the oAA carbonyl group. This is reinforced by an intermolecular C-H···O=C weak hydrogen bond. The P_{cc} values for the T1-F-1 and T1-F-2 complexes, ~2.85 u$Å^2$, suggest that

they have a nearly planar skeleton, with FA practically coplanar with oAA. The small deviations could be attributed to the out-of-plane contributions of intermolecular vibrations which would be more noticeable in the complex. This conclusion is in good agreement with the predicted structure of T1-F-2 form (P_{cc} =1.62 u$Å^2$, see Table 1), but not with the theoretical calculation for T1-F-1 (P_{cc} =4.91 u$Å^2$, see Table 1), which predicts FA lying out of the oAA skeleton plane in a slightly bent disposition.

Table 2. Experimental rotational parameters for the observed complexes of the oAA – FA.

Fitted Parameters[a]	C2-F-1	C1-F-1	T1-F-1	T1-F-2
A/MHz	1248.9820(55)[b]	1235.8085(40)	1144.35595(26)	1137.5868(13)
B/MHz	358.92561(17)	364.58912(13)	416.44449(18)	377.37898(37)
C/MHz	280.85647(21)	283.96781(18)	306.38489(13)	284.28358(24)
P_{cc}/u$Å^2$	6.6223(19)	7.7006(15)	2.84683(66)	2.8543(17)
D_J/kHz	0.00604(67)	0.00740(60)	0.0173(10)	0.0687(43)
D_{JK}/kHz	-	-	-0.0109(11)	-0.0982(70)
D_K/kHz	-	-	-	0.0367(41)
d_1/kHz	-	-	-	-0.0162(24)
$\mu_a/\mu_b/\mu_c$ [c]	+/-/-	+/-/-	+/+/-	+/+/-
N	41	36	76	61

[a] A, B and C are the rotational constants. P_{cc} is the planar moment of inertia with respect to the ab inertial plane, $P_{cc}=(I_a+I_b-I_c)/2$. D_J, D_{JK}, D_K and d_1 are the quartic centrifugal distortion constants. N is the number of rotational transitions fitted. σ is the rms deviation of the fit. [b] Standard error is given in parentheses in units of the last digits. [c] The + or – signs refer to whether the μ_i-type transitions were observed or not, respectively.

The conformers C1-F-1 and C2-F-1 are formed through the usual cooperative hydrogen-bonded eight-membered ring structure. In C1 (P_{cc} =5.07 uÅ^2) and C2 (P_{cc} =5.17 uÅ^2) conformers of oAA,[24] with the carboxylic group in a *cis* disposition, the *ortho* arrangement stimulates a repulsion between the methoxy and carboxyl oxygen atoms inducing a torsion of the –COOH group around the C-C bond which forces the carboxylic oxygen atoms to be out of the ring plane. The P_{cc} values observed for the C1-F-1 (P_{cc} =7.70 uÅ^2) and C2-F-1 (P_{cc} =6.62 uÅ^2) forms suggest that they inherit the structure of the original forms of oAA.[24] Using the DFT structure, the experimental values of P_{cc} are well reproduced for the torsional dihedral angle, ϕ between the benzene and COOH planes of oAA, being ±17.5°, for C1-F-1, and ±15.75° for C2-F-1. These values are very close to those obtained using the same approach for the monomer (±18.2° for C1 and ±18.0° for C2). (see Table 3).

Table 3. P_{cc} values and ϕ torsional angle between the benzene and COOH planes of o-anisic acid, for the isolated molecule and its complexes with water and formic acid.

		P_{cc}/uÅ^2	ϕ /° r_0[b]	ϕ /° DFT
oAA	T1	1.975701(39) [a]	0.0	0.0
	C2	5.17393(10)	18.0	15.25
	C1	5.07249(19)	18.2	17.7
oAA-w	T1-w-1	2.56390(12)	0.0	1.8
	C2-w-1	6.84282(46)	21.0	15.7
oAA-FA	T1-F-1	2.84683(66)	0.0	1.8
	T1-F-2	2.8543(17)	0.0	0.0
	C2-F-1	6.6223(19)	15.75	13.6
	C1-F-1	7.7006(15)	17.5	16.25

[a] Standard error is given in parentheses in units of the last digits. [b] pseudo r_0 values of the angles that reproduce the experimental P_{cc} values for the DFT structures.

Dissociation energy

The intermolecular stretching vibration is approximately coincident with the a-inertial axis in all the cases. The dissociation energy can then be experimentally estimated from the centrifugal distortion constant D_J, using a pseudo diatomic approximation to obtain the intermolecular stretching vibration force constant[30] and then assuming for this motion a Lennard-Jones potential function.[31] On the other hand, the dissociation energies corrected by basis set superposition error (BSSE) have been theoretically calculated at the B3LYP-D3/6-311++G(d,p) and MP2/6-311++G(d,p) levels using the counterpoise procedure.[32] The experimental and theoretical values listed in Table 4 are comparable for all the conformers, except in the case of T1-F-2. The centrifugal distortion effects are much

higher for this conformer as previously discussed (see Table 2). This indicates the existence of some kind of non-rigid effect which renders this pseudodiatomic model not applicable in this case. The dissociation energies for C1-F-1 and C2-F-1 have similar values to those obtained using the pseudo diatomic method for different FA clusters with similar structures. These energies are much higher than that for T1-F-1 indicating that the formation of the typical eight-membered HB ring, reinforced by cooperativity,[2] is stronger than the six-membered ring cycle formed in T1-F-1 complex.

Table 4. Dissociation energy (ED) (in kJ mol^{-1}) estimated from the pseudo diatomic approximation (ED exp) and predicted using the counterpoise procedure at the MP2/6-311++G(d,p) (ED(MP2)) and B3LYP-D3/6-311++G(d,p) (ED(B3LYP)) levels of theory for the oAA – FA dimers. These are compared with those of the related acid - FA clusters.

	R_{CM} / Å	E_D exp	E_D(MP2)	E_D(B3LYP)
T1-F-1	4.7763	30(2) [a]	40.4	53.1
T1-F-2	5.1301	7.1(4)	37.4	52.3
C2-F-1	5.2516	76(8)	63.5	86.0
C1-F-1	5.1875	62(5)	64.5	86.8
DFAA-FA *trans* [b]		61.7	49.0	
DFAA-FA *gauche*		63.3	50.5	
AA-FA *cis* [c]		64	51	
AA-FA *trans*		64	52	
BA-FA [d]		-	51.4	

[a] Standard error is given in parentheses in units of the last digits. It was derived from the standard error of D_J constant. [b] Difluoroacetic acid – formic acid cluster, reference 18. [c] Acrylic acid – formic acid cluster, reference 17. [d] Benzoic acid – formic acid cluster, reference 15.

Discussion

We have identified four conformers of the oAA – FA heterodimer. Two of them, T1-F-1 and T1-F-2, have oAA in the *trans*-COOH configuration, in contrast to the typical arrangement where the carboxylic groups take up the *cis*-COOH configuration in order to form the eight-membered cooperative HB ring. In fact, this is the first time that such kind of *trans*-COOH clusters are detected experimentally in the gas phase. The more stable one of the two, T1-F-1, is stabilized by three hydrogen bonds, some of them bifurcated, forming a complex HB web. The weaker complex, T1-F-2, reminds one of the typical *cis-cis* configuration, but in this case the acidity of the benzene hydrogen atom is very weak in comparison to that of the carboxylic group, making the interaction less strong. The other two forms C1-F-1 and C2-F-1 are stabilized by double HB interactions, forming an eight-membered ring, an usual occurrence in the acid-acid complexes. In all the conformers observed, the structures inherit the

conformational properties of the *o*AA precursor conformers. The experimental rotational parameters show that T1-F-1 and T1-F-2 have planar skeleton structures, while C1-F-1 and C2-F-1 present non-planar skeleton structures, as derived by the analysis of P_{cc}. Analyzing the values collected in Table 3, it is possible to corroborate that the structure for the *o*AA almost remains unchanged upon complexation. Nevertheless, the non-planarity angle experiments little changes upon complexation that may indicate small differences in the balance of the interactions that stabilize the conformers.

The most abundant form in the supersonic jet is T1-F-1, as it is concluded from the relative intensity measurements. This experimental observation contrasts with the predicted theoretical stabilities (see Table 1) and with the estimated dissociation energies, which for the C2-F-1 and C1-F-1 heterodimers are *ca.* two times higher than the value estimated for the T1-F-1 form (see Table 4). This can be explained by the hypothesis, that the complexes are formed at the beginning of the expansion where the three-body collision rate is high enough to allow for complexation. At this stage, the complex formation is expected to be dominated by a kinetic mechanism with a rate proportional to the concentration of reacting species, with T1 being more abundant than the C1 or C2 forms of *o*AA. As the supersonic expansion progresses, the collisional rate decreases rapidly so that evolution to equilibrium is quenched. Furthermore, in this case the evolution from the predicted higher energy heterodimers, T1-F-1 or T1-F-2, to the more stable heterodimers, C1-F1 or C2-F-1, would require an activation energy high enough to break the intramolecular hydrogen bond. A similar situation was observed in the complexes of *o*AA with water where the most abundant hydration complex observed contains the T1 conformer with a *trans*-COOH form even though it was predicted to be less stable than the *cis*-COOH hydrate complexes.[24] In the limit of kinetic controlled mechanism, one would expect the relative populations of ($N_{T1-F-1}+N_{T1-F-2}$) / N_{C2-F-1} / N_{C1-F-1} ~ 100/73/65 similar to those experimentally stablished for the monomer N_{T1} / N_{C2} / N_{C1} ~ 100/60/20 in a jet expansion.[24] This is not entirely accurate in the present case as demonstrated by the similar intensity observed for both C1-F-1 and C2-F-1 conformers.

In the *o*AA-water complex, the C2-water conformer was detected, but the C1-water form, predicted to be slightly higher in energy, was not observed, while both monomer forms C1 and C2 were also detected in the presence of water in the sample system. Therefore, it was estimated that the population ratios for *o*AA-water complexes remain as in the monomer, taking into account that the C1-water conformer has a low population below the detection limit. In the present case, neither C1 nor C2 monomer conformers were observed in the rotational spectra when FA was introduced in the sample flow. The above observation suggests that the *cis*-COOH *o*AA forms were exhausted by complex formation with FA, indicating that the double HB interactions are much stronger in the acid-acid heterodimer in comparison to the acid-water complex. On the other hand, it could be expected that the intensity ratio observed for the monomer would remain in the acid-acid complexes as in the case of the complexes with water, C2-W/C1-W ~ 3/1.

However, we have experimentally determined that C2-F-1 and C1-F-1 have almost similar abundances. To understand why the N_{C2-F-1} / N_{C1-F-1} ratio differs from the N_{C2} / N_{C1} ratio, i.e. not strictly following the kinetic control outcome, one may look into the possible conformational conversion paths. In some previously reported cases where the acid complexes are not symmetric, the double proton transfer motion gives rise to two different conformers, as occur in the present case for C2-F-1 and C1-F-1. For example, in the fluoroacetic acid – acrylic acid complex,[19] the presence of a less stable acid-acid conformer, where one subunit conformer was not detected in the acid monomer, was in part explained by conformational conversion in terms of the proton transfer motion. Also for 3,3,3-trifluoro-2-(trifluoromethyl) propanoic acid (TTPA)-FA,[33] the non-observation of the slightly less stable acid-acid conformer was attributed to the efficient incoherent double proton tunneling. Here we have evaluated at the B3LYP-D3/6-311++G(d,p) level the barrier for the double proton transfer as 2400 cm^{-1}, an usual value for other similar complexes.[15,16] In this way, the comparable experimental population of C2-F-1 and C1-F-1 could be explained as arising from a concerted double proton transfer motion that connects the two unequal conformers.[19] We therefore considered other possible pathways to interconvert these two conformers, for example the rotation around the C-COOH bond. The barrier for the rotation around the C-COOH bond is predicted to be about 800 cm^{-1} at the same level of theory used for the prediction in the proton transfer barrier. The comparable experimental population of C2-F-1 and C1-F-1 could be a consequence of both proton transfer and internal rotation.

Conclusions

In summary, we have detected a considerable number of conformers which reveals the richness and variety of interactions that can take part between two acid molecules, beyond the usual cyclic HB configuration with two *cis*-COOH configurations. In addition, this study demonstrates the first experimental observation of a model carboxyl acid-acid dimer in which one of the acids has the *trans*-COOH configuration. This adds a new kind of interaction between two acid groups, which would be of interest in biological macromolecules when the usual acid double HB interactions may be in competition with intramolecular HB interactions formed with other polar groups nearby.

Experimental Section

Commercial samples of *o*AA and FA were used without further purification. *o*AA, b.p. of 99-100ºC, was heated over his boiling point at. about 110ºC in a heatable nozzle. FA was placed in a reservoir located in the gas line just before the nozzle. The pressure vapour of the FA was enough to form a gas solution with the carrier gas. The mixture of FA with the Ne was used as carrier gas at a stagnation pressure of 2-3 bar. The resulting mixture of *o*AA and FA in Ne was expanded through a pulsed

nozzle of 0.8 mm inside the chamber forming a supersonic jet where the molecular clusters were formed.

The rotational spectrum of the *o*AA – FA molecular clusters has been recorded using two different CP-FTMW[34] spectrometers, one at the University of Alberta[35, 36] (7-18 GHz) and another located at the University of Valladolid[37] (2-8 GHz).

The different conformers formed in the supersonic expansion were explored by the polarization of the jet with a microwave chirp pulse of 5 μs (*ca.* 20 W), both in perpendicular directions. The following free induction decay radiation emitted was captured through a horn antenna, filtered and finally amplified with a low noise amplifier prior to its detection in the time domain.

The estimated accuracy of the measurements is better than 15 kHz.

Computational methods

Ab initio calculations were performed in order to predict and analyse the potential energy surface (PES) of *o*AA-FA complex. Taking into account the results obtained in the previous study of *o*AA monomer and *o*AA-W complexes[24] we have investigated the possible interactions between the three detected *o*AA conformers (T1, C1, C2) and FA. The nine lowest energy conformers found were optimized at B3LYP-D3/6-311++G(d,p) level of theory (Figure S1 and Table S1). Free energies, obtained by supplement the vibrational and thermal (418 K, 2.5 bar) entropic contributions to the electronic energy terms, were used to rank the conformers.

Examining the four lowest energy complexes (under 1000 cm^{-1}) it is possible to observe that the complexes which come from the *cis-o*AA conformers the rotational parameters, as rotational constants and electric dipole moments, have similar values since the mass distributions is similar for all of them. While for complexes that come from the *trans-o*AA conformer the values are slightly different. Frequency calculations were performed for all the conformers in order to establish that they were true minima. BSSE calculations[32] were made at B3LYP-D3/6-311++G(d,p) and also at MP2/6-311++G(d,p) level of theory with the aim to compare the results with the dissociation energies gave in the bibliography for similar acid-FA complexes.

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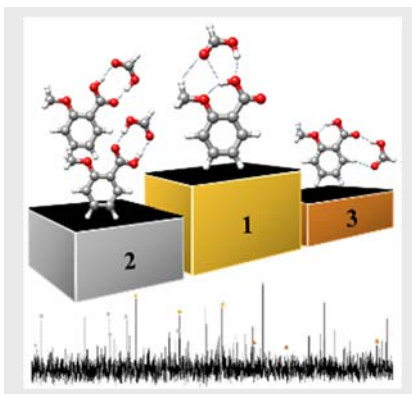
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