Published in final edited form as:

Angew Chem Int Ed Engl. 2017 March 27; 56(14): 3872–3875. doi:10.1002/anie.201612231.

Borderline between Reactivity and Prereactivity of Binary Mixtures of Gaseous Carboxylic Acids and Alcohols

Luca Evangelisti^[a], Lorenzo Spada^{[a],[b]}, Weixing Li^[a], Fanny Vazart^[b], Vincenzo Barone^{[b],*}, and Walther Caminati^{[a],*}

^[a]Dipartimento di Chimica “G. Ciamician”, University of Bologna, Via Selmi 2, I-40126 Bologna, Italy

^[b]Scuola Normale Superiore t, Piazza dei Cavalieri 7, I-50126 Pisa, Italy

Abstract

By mixing primary and secondary alcohols with carboxylic acids just before the supersonic expansion within pulsed Fourier transform microwave experiments, only the rotational spectrum of the ester has been observed. However, when formic acid was mixed with tertiary alcohols, adducts have been formed and their rotational spectra have been easily measured. Quantum mechanical calculations have been performed to interpret the experimental evidence.

Keywords

Esterification; Molecular complexes; Rotational Spectroscopy; Chemical Dynamics Calculations; Hydrogen bonding

One of the most important reactions in organic synthesis is esterification, see Scheme 1:[1]

Scheme 1.

In the present study esterification takes place without catalyst.

To attain a satisfactory conversion a catalyst is generally needed, and yet the employment of one of the reactants in excess is necessary.[2] We discovered a very simple method to obtain esters from a gas phase 1:1 mixture of carboxylic acids and primary and secondary alcohols without need of catalyst. The details are reported below.

Several molecular complexes involving carboxylic acids[3–12] have been investigated by rotational spectroscopy, in order to understand the nature of their non-covalent interactions and to have information on their internal dynamics and on their conformational equilibria. Most attention has been paid to the complexes of carboxylic acids, mainly to their dimers[3] and to their adducts with water.[4] Plenty of data have been obtained on the dimers, concerning proton tunneling,[3a] Ubbelohde effect[3b] and conformational equilibria.[3c]

HCOOH (FA) is the prototype of the carboxylic acids family and for this reason it is involved in most of the investigations of carboxylic acids with molecules containing other functional groups, such as its adducts with H₂O,[4a] N(CH₃)₃,[5] anhydrides,[6] the simplest aldehyde (CH₂O),[7] the simplest amide (CH(CO)NH₂),[8] ethers (dimethylether), [9] ketones (cyclobutanone),[10] esters (isopropylformate)[11] and azines (pyridine).[12]

However, no MW studies of complexes between carboxylic acids and alcohols are reported. For this reason, we thought to investigate the prototype of this kind of complex, that is formic acid-methyl alcohol. Unexpectedly, we were not able to assign its rotational spectrum. Such a failure could be due, among to other reasons, to the complications related to the low V_3 barrier underlying the barrier to internal rotation of the methyl group, as well to the inversion of the methyl group from above to below the formic acid plane. In order to understand what was going on, we decided to start the investigation of the adducts carboxylic acids-alcohols from the adduct formic acid with a series of primary, secondary and tertiary alcohols. In details, we made supersonic expansions, with ca. 1% of carboxylic acid and 1% of alcohol in He for the following combinations: HCOOH-CH₃OH, HCOOH-C₂H₅OH, HCOOH-(CH₃)₂CHOH and HCOOH-(CH₃)₃COH, that is formic acid mixed with methyl alcohol and with primary, secondary and tertiary alcohols, respectively.

In all cases but the last one, it was not possible to observe the spectra of the adducts, but strong rotational transitions that we discovered to belong to the esters. Then we replaced linear alcohols with cyclic alcohols, like cyclohexanol (secondary) and 1-methyl-cyclopropanol (tertiary). Again, for the secondary alcohol we could observe only the rotational spectrum of the ester, and for the tertiary alcohol only that of the adduct. Finally, we exploited the replacement of HCOOH with carboxylic acids with stronger (CF₃COOH) and weaker (pivalic acid) acidity. In the first case we observed only the ester, while in the second case the experiment did not succeed, because pivalic acid was rapidly obstructing our nozzle and causing serious problems to the operation of the pulsed valve.

In Figure 1 we show, as an analysis example, the case of the mixture of FA with isopropanol. In the upper part of the graphic, the expected spectrum of the ester is drawn in blue, while the calculated spectrum of the adduct is indicated in red, negative values.

Only strong transitions of the ester have been identified in the rotational spectrum, according to the upper spectrum. In Table 1 we summarize the experimental evidence for the observed esters and adducts, respectively. In Table S1 of the Supporting Information we report the values of the largest dipole moment component (generally μ_a) for the adducts and for the esters, and the measured signal to noise (S/N) ratios of the strongest measured transitions of the observed species. The values of the S/N ratios are in the range 30-400. Up to now we assigned the rotational spectra of about 50 complexes of carboxylic acids and collected a considerable expertise regarding required empirical corrections to the *ab initio* data. For this reason we believe that, after scanning $2^*(B+C)$ frequency ranges, we would have been able to detect transitions of the competitive forms with a S/N ratio larger than 2/1. As a result we can state that the esterification reaction is largely shifted to the right when primary and secondary alcohols are involved, and vice versa in the case of tertiary alcohols.

As usually happens, we observed some unassigned lines (in the broadband spectra there are even more unassigned lines due to spurious signals), but they do not have patterns which can match the expected spectra.

The rotational spectra of methylformate and ethyl formate are available in the literature.[13, 14]

In all cases the rotational transitions of the monomers (acid and alcohol) were present in the spectra. Their intensities decreased considerably, however, when we observed the ester.

We tried to interpret the different behaviour of tertiary alcohols with chemical dynamics calculations. All calculations have been performed with a locally modified version of the Gaussian suite of programs.[15] The computations were carried out with the double-hybrid B2PLYP functional, in conjunction with the mAug-cc-pVTZ basis set[16] where *d*-functions on hydrogens have been removed. Semiempirical dispersion contributions were also included into DFT computations by means of the D3 model of Grimme, leading to B2PLYP-D3 functional.[17] Full geometry optimizations have been performed for all minima and transition states checking the nature of the obtained structures by diagonalizing their Hessians. In the case of complexes, the basis set superposition error (BSSE) has been corrected using the Counterpoise method.[18]

Energies of complexation and esterification have been obtained for the most significant examples listed above, including zero point corrections and, for the complexes, basis set superposition errors.[18] In addition, also the free energy changes at 298 K have been evaluated. The obtained results are shown graphically in Scheme 2 for FA – methanol, FA – ethanol, FA – isopropanol and FA – *tert*-butanol mixtures, and in the Supporting Information for the four additional mixtures mentioned previously. The starting point, with the acid and alcohol molecules separated from each other, is assumed to be the zero point energy (of free energy) value. The complete set of data obtained with the above mentioned calculations is reported in Tables S2-S17 in the Supporting Information. It seems that the G values are the most significant ones in interpreting the experimental evidence. Their changes (G^0) in going from the adducts to the ester are close to zero for the tertiary alcohols, but ca. -3 to -5 kcal/mol for the primary and secondary alcohols. In addition, the transition state values ($G^{0\dagger}$) for the esterification process is about 3 kcal/mol higher in the case of tertiary alcohols. We have to outline that the formation of the dimer during the supersonic expansion is not a simple and linear process. For example, when more than one conformation is possible, the constituting molecules can reach the thermal quasi-equilibrium as a result of repeated dissociation and reformation of the dimers in the low-temperature molecular expansion. Then, the conformational enrichments can be different with respect to the values corresponding to the thermodynamic equilibrium. The same argumentations can be applied to the quasi-equilibrium conditions for the esterification reaction. So, even a small free energy difference between different esterification reactions can turn out in completely different reaction advancements.

We have to mention, in addition, that organic chemists pay much attention to the fact that in tertiary alcohols steric effects makes the OH group less accessible than in the alcohols of the

other classes, which results in a reduced propensity to undergo the esterification reaction. However, the first step is the formation of the adduct, and we detect it only in the case of tertiary alcohols.

Finally, we have to take into account that a third component, the carrier gas (He in our case), is constituting our mixtures, in a concentration of about 99%. Its function is to convert the internal energy of the molecules into its own translational kinetic energy, up to reach a supersonic speed. Often it has the effect, especially when it has a high atomic mass, to cause a conformational relaxation. When the inter-conversion barrier is smaller than $2kT$, the less stable conformer disappears.[19] Will this factor influence our esterification processes? Probably yes, but not enough data are available to rationalize this effect. However, this experimental investigation outlines a sharp cut-off of the esterification reaction in going from primary and secondary to tertiary alcohols. Theoretical molecular dynamics calculations supply an indication in support of the experimental evidence.

Finally, we have to outline that the use of fast-mixing nozzles[20] would probably allow the observation of the rotational spectra of the prereactive adducts also for primary and secondary alcohols.

Experimental Section

In the experiments all samples were obtained from Aldrich and used without further purification. The rotational spectra in the 6-18.5 GHz frequency region were measured on a COBRA-type[21] pulsed supersonic-jet Fourier-transform microwave (FTMW) spectrometer,[22] described elsewhere.[23] Helium at a total pressure of 0.3 MPa was streamed over the various samples, in such a way to have ca. 1% concentration of the species of interest. The obtained mixtures were expanded through the solenoid valve (General Valve, Series 9, nozzle diameter 0.5 mm) into the Fabry-Pérot-type cavity. We tried several setups of the samples in the pre-expansion: He passing over the mixture, or first over the acid and then over the alcohol and vice versa, or using a Y-type set up. We also put some drops of sample inside the pulsed valve. We worked either at room temperature or cooled the samples, but the results did not qualitatively change.

The rest frequency was calculated as the arithmetic mean of the frequencies of the two Doppler components. The estimated accuracy of the frequency measurements is better than 3 kHz, resolution is better than 7 kHz.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the Italian MIUR (PRIN project 2010ERFKXL_001) and the University of Bologna (RFO) for financial support. L.E. was supported by Marie Curie fellowship POF-GA-2012-328405. W. L. thanks the China Scholarships Council (CSC) for financial support. The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement n. [320951]. We also thank Professors Claudio Trombini and Pier Giorgio Cozzi for helpful discussions.

References

- [1]. See, for example, Otera J. *Angew Chem Int Ed*. 2001; 40:2044–2045. and ref.s therein.
- [2]. See, for example, Lee AS-Y, Yang H-C, Su F-Y. *Tetrahedron Lett*. 2001; 42:301. and ref.s therein.
- [3]. Feng G, Favero LB, Maris A, Vigorito A, Caminati W, Meyer R. *J Am Chem Soc*. 2012; 134:19281–19286. [PubMed: 23127170] see for example, Feng G, Gou Q, Evangelisti L, Caminati W. *Angew Chem Int Ed*. 2014; 53:530–534. and ref.s therein. see for example, Feng G, Gou Q, Evangelisti L, Xia Z, Caminati W. *Phys Chem Chem Phys*. 2013; 15:2917–2922. and ref.s therein. [PubMed: 23340490]
- [4]. Priem D, Ha T-K, Bauder A. *J Chem Phys*. 2000; 113:169–175. see for example, Ouyang B, Howard BJ. *Phys Chem Chem Phys*. 2009; 11:366–373. and ref.s therein. [PubMed: 19088993] see for example, Schnitzler EG, Zenchyzen BLM, Jager W. *Phys Chem Chem Phys*. 2016; 18:448–457. and ref.s therein. [PubMed: 26616640] see for example, Feng G, Gou Q, Evangelisti L, Spada L, Blanco S, Caminati W. *Phys Chem Chem Phys*. 2016; 18:23651–23656. and ref.s therein. [PubMed: 27509832]
- [5]. Mackenzie RB, Dewberry CT, Leopold KR. *J Phys Chem A*. 2016; 120:2268–2273. [PubMed: 27023479]
- [6]. Vigorito A, Gou Q, Calabrese C, Melandri S, Maris A, Caminati W. *ChemPhysChem*. 2015; 16:2961–2967. [PubMed: 26247850] Mackenzie RB, Dewberry CT, Leopold KR. *Science*. 2015; 349:58–61. [PubMed: 26138972]
- [7]. Gou Q, Favero LB, Bahamyirou SS, Xia Z, Caminati W. *J Phys Chem A*. 2014; 118:10738–10741. [PubMed: 25329531]
- [8]. Daly AM, Sargus BA, Kukolich SG. *J Chem Phys*. 2010; 133:174304. [PubMed: 21054029]
- [9]. Evangelisti L, Spada L, Li W, Ciurlini A, Grabow J-U, Caminati W. *J Phys Chem A*. 2016; 120:2863–2867. [PubMed: 27102727]
- [10]. Evangelisti L, Spada L, Li W, Blanco S, Lopez JC, Lesarri A, Caminati W, Grabow J-U. *Phys Chem Chem Phys*. Accepted Manuscript 16 nov 2016.
- [11]. W. Caminati et al., manuscript in preparation.
- [12]. Spada L, Gou Q, Giuliano BM, Caminati W. *J Phys Chem A*. 2016; 120:5094–5098. [PubMed: 26886392]
- [13]. See, for example, Duan C, Carvajal M, Yu S, Pearson JC, Drouin BJ, Kleiner I. *A&A*. 2015; 576:A39. 1-7, and references therein.
- [14]. See, for example, Medvedev IR, De Lucia FC, Herbst E. *Astrophys J Suppl Series*. 2009; 181:433–438. and references there-in.
- [15]. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, et al. *Gaussian09 GDVI03*. 2015
- [16]. a) Grimme S. *J Chem Phys*. 2006; 124:34108. b) Papajak E, Leverentz HR, Zheng J, Truhlar DG. *J Chem Theory Comput*. 2009; 5:1197–1202. [PubMed: 26609710] c) Dunning TH. *J Chem Phys*. 1989; 90:1007.
- [17]. a) Goerigk L, Grimme S. *J Chem Theory Comput*. 2011; 7:291–309. [PubMed: 26596152] b) Grimme S, Ehrlich S, Goerigk L. *J Comput Chem*. 2011; 32:1456–1465. [PubMed: 21370243]
- [18]. a) Boys SF, Bernardi F. *Mol Phys*. 1970; 19:553–566. b) Simon S, Duran M, Dannenberg JJ. *J Chem Phys*. 1996; 105:11024–11031.
- [19]. Ruoff RS, Klots TD, Emilson T, Gutowski HS. *J Chem Phys*. 1990; 93:3142–3150.
- [20]. Legon AC. *Chem Commun*. 1996; 109 and ref.s therein.
- [21]. Balle TJ, Flygare WH. *Rev Sci Instrum*. 1981; 52:33–45.
- [22]. Grabow J-U, Stahl W, Dreizler H. *Rev Sci Instrum*. 1996; 67:4072–4084.
- [23]. Caminati W, Millemaggi A, Alonso JL, Lesarri A, López JC, Mata S. *Chem Phys Lett*. 2004; 392:1–6.

Figure 1.

The rotational spectra expected for the mixture FA-isopropyl alcohol in the case of esterification (blue, positive values) and of formation of the adduct (red, negative values) are extremely different from each other. The experimental observation of one or the other spectrum shows unambiguously if the adduct or the ester is formed.

Scheme 2.

Energy profiles of the multiple chemical process paths for the FA – methanol, FA – ethanol, FA – isopropanol and FA – *tert*-butanol mixtures. The observed species are indicated with a rectangular frame.

Table 1

Details (one transition example) of the spectra of the esters (first 5 columns) and of the adducts (last two columns) which have been formed in a supersonic expansion of binary mixture of carboxylic acids with primary and secondary alcohols, and with tertiary alcohols, respectively. All spectra cover a range of 0.4 MHz. The central frequency (ν_c) and the number of accumulation cycles (N_c) of each spectrum are given.

Esters					Adducts	
HCOOH + CH ₃ OH → Methylformate	HCOOH + CH ₃ CH ₂ OH → Ethylformate	HCOOH + (CH ₃) ₂ CHOH → Isopropylformate	HCOOH + cy-C ₆ H ₁₁ OH → Cyclohexylformate	CF ₃ COOH + CH ₃ OH → Methyl-Trifluoroacetate	HCOOH + (CH ₃) ₃ COH → FA- <i>tert</i> Butanol	HCOOH + cy-C ₃ H ₄ CH ₃ OH → FA-1-Methyl-Cyclopropanol

4 ₁₃ ←4 ₁₄ transition of the “E” species. ν_c = 16037.30 MHz; N_c = 200.	2 ₀₂ ←1 ₀₁ transitions of <i>gauche</i> (upper, ν_c = 14059.25 MHz; N_c = 1000) and <i>trans</i> (lower, ν_c = 10962.45 MHz; N_c = 1000) species	2 ₂₀ ←2 ₁₁ transition. It is split into two tunneling components. ν_c = 11836.55 MHz; N_c = 50.	7 ₀₇ ←6 ₀₆ transition. ν_c = 12942.45 MHz; N_c = 385.	5 ₀₅ ←4 ₀₄ transition. It is split into “A” and “E” species. ν_c = 14036.80 MHz; N_c = 50.	4 ₁₃ ←3 ₁₂ transition ν_c = 7645.00 MHz; N_c = 1113.	5 ₁₄ ←4 ₁₃ transition ν_c = 8961.95 MHz; N_c = 504.