Applied Catalysis A: General 516 (2016) 58–69

Contents lists available at ScienceDirect

Applied Catalysis A: General

journal homepage: www.elsevier.com/locate/apcata

Kinetics and mechanistic study of the Bamberger rearrangement of *N*-phenylhydroxylamine to 4-aminophenol in acetonitrile-trifluoroacetic acid: A substrate acid complex as *para* selectivity driver

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ARTICLE INFO

Article history:
Received 12 November 2015
Received in revised form 15 February 2016
Accepted 16 February 2016
Available online 21 February 2016

Keywords:
Bamberger rearrangement
Trifluoroacetic acid
4-aminophenol
Kinetics and mechanism

ABSTRACT

The paper deals with the kinetics of Bamberger rearrangement of *N*-phenylhydroxylamine to 4-aminophenol in acetonitrile as a solvent catalyzed by TFA. The influence of the water is also investigated being the rearranging moiety in the mechanism. It is evident that the presence of water depresses the rate of the rearrangement suggesting the rate-determining step does not involve water as the key reagent. In acetonitrile, at lower temperature than that of reaction, we evidence the formation of a PHA-TFA complex, and its equilibrium has been measured between 288 K and 298 K. We observe also the addition of water destroys this complex but the ternary equilibrium PHA, water and TFA cannot easily measured because of the complex solvent effect on the Uv–vis and NMR signals. Starting from this evidence, we have proposed a kinetic model, which takes into account all the equilibria, and the results of the fitting gives reliable thermodynamic and kinetic parameters of the entire process. Finally, we have suggested that the PHA-TFA complex is the key intermediate, which determines the regioselectivity of the rearrangement. In fact, preliminary quantum chemistry calculation have shown that the TFA interaction with the —NHOH group causes the hindering of the *ortho* position, thus favoring the attack of water to the *para* one.

1. Introduction

Aminophenols are important raw materials for several products in the field of dyes, polymer and pharmaceutics [1–3]. For instance, acetaminophen (*N*-acetyl-4-aminophenol, also known as paracetamol), benzoxazoles and substitutes compounds are drugs a widely employed as analgesic, antipyretic and intermediates whose production is in continuous growth [4–8]. More recently, a similar reaction path has been employed in the synthesis of heterocycles of industrial importance starting from nitrobenzene and glycerol via modified Skraup reaction [9].

Industrial synthesis of paracetamol is based on 4-aminophenol, which is obtained by different routes, however, the selective hydrogenation of nitrobenzene is likely the most convenient from both economic and environmental point of view [1,2,4–8]. The major concern of this process is, however, the presence of H_2SO_4, which is origin of corrosion, safety, environmental and separation problems. The reaction (see Scheme 1) is industrially carried out in Continuous Stirred Tank Reactor in which the biphasic reaction medium is used to accomplish simultaneously the Pt catalyzed hydrogenation of nitrobenzene and the acid catalyzed Bamberger rearrangement of the intermediate *N*-phenylhydroxylamine (PHA) [4,5,8]. The presence of the aqueous solution of H_2SO_4 is the key for obtaining high selectivity to the 4-aminophenol. The reason of such a behavior is due to the easy protonation of the phenyl hydroxylamine ($pK_a = 1.96$ [10]), which is extracted from the organic phase. In the acid solution (H_2SO_4 concentration 0.6–1 mol L^{-1}), the *N*-phenylhydroxylamonium salt is readily formed and it undergoes fast Bamberger rearrangement to the corresponding 4-hydroxyanilinium cation [11].

From environmental point of view, the major drawback of the process is the neutralization of the acidic phase, with the consequent by-production of sulfate salts, which are undesired low values products and/or wastes. In addition, diluted sulphuric acid causes huge corrosion concern, with the consequent increased costs of the hydrogenation plant [1,2,4,5,8].

Therefore, removal of H_2SO_4 from the reaction is likely the most important target for the improvement of the process. In this sense, several researchers have recently proposed the use of biphasic liquid system or gas phase reactions (water-nitrobenzene) employing

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http://dx.doi.org/10.1016/j.apcata.2016.02.020
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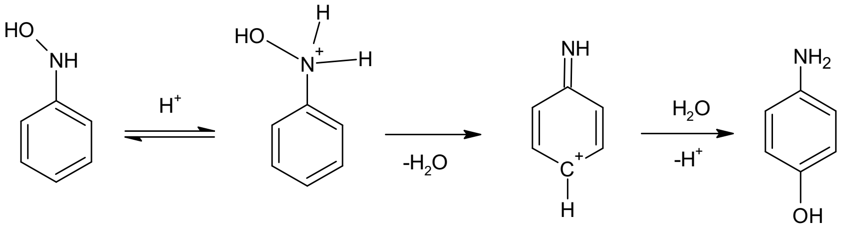


Scheme 1. Commonly accepted mechanism for Bamberger rearrangement.

bifunctional Pt supported on solid acid but quite unsatisfactorily results have been obtained for practical purposes [12–15]. Starting from these considerations, a single liquid phase process could be a catwalk to a more sustainable process by using solvent and catalyst easily reusable [16–19]. In fact, very recently we propose the selective hydrogenation of nitrobenzene in a single liquid phase reactions achieving 45% of aminophenol yield in one-step [16]. Bases of these researches have been the recent results in the Beckmann rearrangement of ketoximes in CH_3C N—CF_3COOH solvent catalytic system [17–19]. The analogy between Beckmann and Bamberger rearrangement originates from the idea that both oximes and PHA are nitrogen-containing compounds, whose interactions with TFA play the key roles in these reactions. Above all, the mechanism of the Bamberger rearrangement is well known from long time and it can be depicted as in Scheme 1, *via* a nitrenium ion intermediate followed by nucleophilic attack of a water molecule [11,20,21].

This mechanism does not explain, however, many features of the reaction, such as the regioselectivity of the hydroxylation in 4-position of the phenyl ring [11,20,21]. This evidence is confirmed also by using solid acid catalyst for which almost complete selectivity in 4-position has been observed [22]. Besides, the Bamberger rearrangement of PHA carried out in aqueous solution of carbon dioxide shows a complete selectivity to *para* position [23]. In fact, reactions whose selectivity toward the 4-position is not respected are those carried out in the presence of metal catalyst, in which the presence of a metal-organic intermediate determine a different reaction product [24].

To say the truth, nobody detects a free nitrenium ion in solution, thus suggesting that this ion is not an existent intermediate, but more likely, a hypothetical stage in concerted mechanisms [20,21,25]. Recently, DFT calculations suggest the absence of the nitrenium intermediate in the Bamberger rearrangement [26]. In this study, the stabilization of a dication intermediate occurs *via* the formation of a complex formed of four hydrogen-bonded molecule of water surrounding the anilinium intermediate, which favors the attack of the water in *para* position, for steric reasons. Actually, in the heterogeneous Pd catalyzed hydrogenation of nitrobenzenes, nitrenium ion is a likely intermediate, since its coordination with Pd may stabilize a surface nitrenium complex [16,27].

Starting from these bases, the study of the Bamberger rearrangement of PHA in non-aqueous solvent, in the presence of TFA, is interesting, not only for synthetic purposes, but also for mechanistic ones. In addition, new insight on the mechanism of the rearrangement may help to develop a more selective and sustainable one pot hydrogenation of nitrobenzene to 4-aminophenol.

Here we present a study on the kinetics of Bamberger rearrangements of PHA in acetonitrile catalyzed by TFA as a reusable homogeneous acid catalyst.

2. Experimental

2.1. Materials

Nitrobenzene, aniline, 4-aminophenol, 2-aminophenol, trifluoroacetic acid, trifluoroacetic anhydride, were all Aldrich products, their purity were checked by the usual methods (melting point, TLC, HPLC, GC and GC–MS) and employed without any purification, acetonitrile HPLC gradient grade was supplied by BDH, methanol, nitromethane, dimethylformamide and dimethyl sulfoxide are ACS reagent supplied by Aldrich. Phenylhydroxylamine was prepared by following the classic procedure proposed by Kamm, scaled down for gram amount synthesis [28].

2.2. Equipment

Products were identified by gas chromatography (GC), gas chromatography coupled mass spectrometry (GC–MS) and high performance liquid chromatography (HPLC). GC and GC–MS analyses were carried out with an Agilent 7890A, equipped with FID or MS detector Agilent 5975C. Separation was achieved by a HP 5 column (I.D. 320 μm 30 m long), using helium as the carrier under the following analysis conditions: injector 523 K, detector 543 K, flow 1 mL min^{-1}, oven 333 K for 3 min 523 K 15 K min^{-1} and 523 K for 15 min.

Due to the thermal instability of the products, routine analysis were carried out by HPLC (Perkin Elmer 250 pump, LC 235 diode array detector and a C 8, 5 μm, 4 mm i.d. 25 cm long column) analysis were carried out with CH_3C N—H_2O as mobile phase in isocratic 70% of CH_3CN at 1 mL min^{-1}. The response factors obtained by standard solutions of the pure products give conversion, yield and selectivity.

A Perkin Elmer lambda 3 Spectrophotometer were employed for the spectrophotometer measurements of the equilibria and of the kinetics.

A Bruker Avance 300 spectrometer operating at 300.13 MHz allows the recording of the ^1H Nuclear Magnetic Resonance (NMR) spectra of reagents and products.

Conductivity measurements were carried by using a Solartron 1260 gain phase analyzer at 2000 Hz with a standard platinized electrodes cell with 1 cm^{-1} of cell constant.

2.3. Equilibria of N-phenylhydroxylamine TFA in acetonitrile

The standard procedure to measure the interaction of PHA with TFA in acetonitrile has been carried out by using a conventional spectrophotometer in a 3 mL cuvette of 1 cm of optical length. The additions of a concentrated solution of TFA in acetonitrile by a micrometric micro-syringe in the cuvette gives the desired acid concentration.

Table 1
Results of equilibrium calculations by Koltof and Chantoony procedure. Run conditions: T 298 K, PHA 1×10^{-3} mol L^{-1}.

Water (mol L^{-1})	TFA (mol L^{-1})	H^+ (mol L^{-1})	$PHAH^+$ (mol L^{-1})	$pK_{PHA\text{-}H}$	pK_{TFA}
1.2	1×10^{-1}	2.49×10^{-7}	3.46×10^{-5}	5.16	10.06
6	1×10^{-1}	1.31×10^{-4}	2.31×10^{-4}	3.36	6.32
1.2	1×10^{-2}	7.78×10^{-8}	1.11×10^{-5}	5.16	10.06
6	1×10^{-2}	3.89×10^{-5}	8.18×10^{-5}	3.36	6.32

2.4. Reaction kinetics

The Bamberger rearrangement of the PHA were carried out under nitrogen (charged at atmospheric pressure) in a jacketed sealed glass reactor (40 mL) at several temperatures and autogenous pressure. These are typical run conditions of the reaction: temperatures 313–353 K, PHA concentrations $6 \times 10^{-4} - 1.2 \times 10^{-3}$ mol L^{-1}, TFA concentrations 1×10^{-2}–1×10^{-1} mol L^{-1}, water concentrations 0.3–6 mol L^{-1}, solvent acetonitrile, reaction volume 25 mL.

The course of reactions was checked by sampling the liquid phase at established intervals, and by diluting the samples at a suitable concentration for the analysis. The changes in the UV spectra of the solution are recorded in a thermostated spectrophotometric quartz cell (2 mL path-length 1 cm) at various temperatures. Since strong solvent effect is evident for all bands, the samples were analyzed by HPLC after dilution in the mixture of the HPLC eluent (acetonitrile-water 70%). The spectral behavior of the kinetics between 200 and 340 nm shows several wavelengths with a noticeable variation but the more reliable data has been obtained at 220 and 275 nm, where the characteristic bands of the 4-aminophenol are observed (see Supplementary materials).

The use of a computational software (Wolfram Mathematica) allows the implementation of the minimization procedure by using the built-in functions of the program. The procedure, for gaining the constancy of the "kinetic factor" (k_{mod}) by reagents concentrations, consists in a minimization of the variance of the k_{mod}. Such constant is proportional to the k_{obs} and to a power low equation in TFA and H_2O concentrations, where the exponents are the minimization variables of the variance (complete data set is in Supplementary materials).

2.5. NMR measurements

The measurements were carried out in a 300 MHz nuclear magnetic resonance spectrometer, at 298 K by using deuterated DMSO or deuterated chloroform at a concentration close to that of reactions. All the chemical shifts were referred to the internal standard tetramethylsilane.

3. Results and discussion

3.1. Some preliminary consideration on bamberger rearrangement

Bamberger rearrangement is one of those reactions whose mechanisms have been remained in a kind of limbo for long time because of the obscure nature of its regioselectivity, for which only very recently a plausible explanation has been given [25]. However, the reaction in the presence of non-aqueous solvent has not been studied yet, and a kinetic study, in this environment, may help to adding some new insight on this uncertain topic. As a matter of fact, the reaction has almost two steps since the interactions of the substrate with TFA is certainly occurring because of the quite high acidity and basicity of TFA and PHA, respectively (in aqueous solvent TFA $pK_a = 0.23$ and PHA $pK_a = 1.96$) [29,10]. After this step, the rearrangement may follow several pattern of reaction, but the role of the solvent will be not negligible, in any case [30]. For these reasons, a preliminary treatment on the equilibria in water, acetonitrile and TFA is of interest for discussing the kinetics of the rearrangement.

3.2. Equilibria of TFA and PHA, in acetonitrile

In order to model the reaction an approximate evaluation of the pK_a of PHA, TFA and the amount of the species in solution has been carried out by using the procedures of Koltoff and Chantooni applied to water acetonitrile mixtures [29,31]. Even though, the values of pK_a are an estimate, they allow an evaluation of the ionic species in solution and thus verifying, if it exists a correlation between these values and the kinetic parameters. Table 1 reports some results of these calculations (detail and complete calculations are in Supplementary materials). It is evident that increasing TFA and water concentration increase both the H^+ and the protonated PHA.

These calculations put in evidence that the concentrations of the ionic species are related both to solvation ability of the solvent and to the acid-base properties of TFA and PHA. Then the augmentation of the amount of water causes the increasing of the ionic species but reaction rates, as we will show extensively in Section 3.4, does not follow this trend.

On the basis of this calculation, the concentration of the ionic species are negligible, but the evident Uv–vis spectral variation of Fig. 1(A), as TFA concentration increases, at temperatures where the rearrangement does not occur, it cannot be ascribed to a simple solvent effect but more likely to a formation of a complex PHA-TFA. Such a compound is likely to be an ionic couple, in fact, acetonitrile is well known to be a solvent whose solvating power does not allow anion and cation separation but the formation of ionic couples is favored [30]. The spectral variation observed in Fig. 5(B) is due to addition of water on the adduct TFA-PHA previously formed. It is evident that the increase of PHA bands (the shoulder at 240 nm raises) is related to the increase of water concentration. Likely, the interaction between TFA and PHA decreases by adding water, but the band of neat PHA is not restored at least to 3.7 mol L^{-1} of water. In fact, the increase of the concentration of water causes not only the rises of PHA, but also a modification of the solvent itself, thus giving a different spectrum with respect to the starting PHA. It is noteworthy, the formation of a complex with TFA in the presence of two competing molecules, namely the PHA and the water, is a complex phenomenon. A complete treatment of the argument is beyond the scope of this work, but it will be took into account, as an equilibrium (in a first approximation) for the calculation of the kinetics (see Section 3.5) [30].This is in agreement with the results observed employing the same solvent-acid system in the Beckmann rearrangement of the cyclohexanone oxime [17,18]. In that case, at temperature where cyclohexanone oxime does not rearrange, quite strong interaction between cyclohexanone oxime and TFA exists, and this equilibrium has an enthalpy variation of -19 kJ mol^{-1}. This suggests the formation of a complex, which could be ascribed to the ionic couple complex (TFA-cyclohexanone oxime), rather than a real protonation equilibrium [17,18]. In the Beckmann rearrangement, after the formation of the complex, the reaction proceeds *via* an ester intermediate [17–19]. In the Bamberger

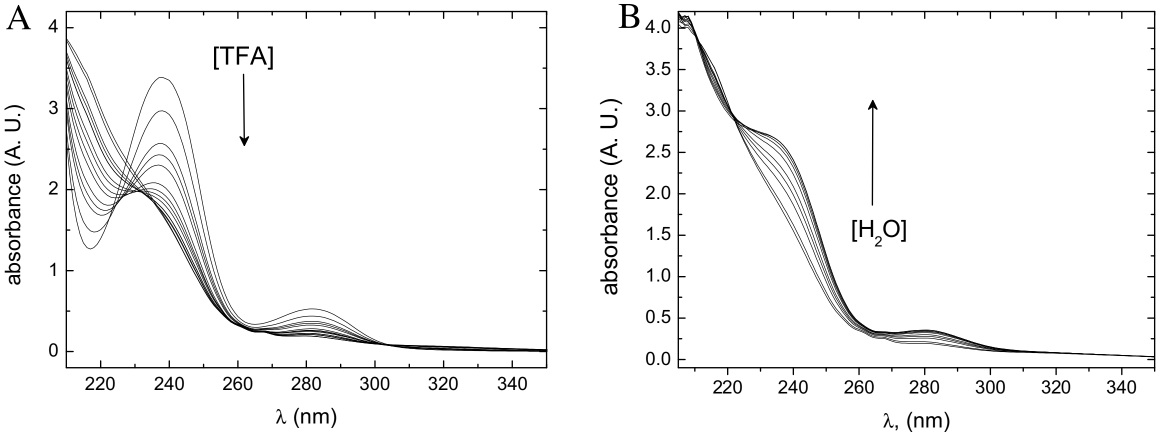


Fig. 1. A Spectral variation of PHA increasing TFA concentration (0–0.12 mol L^{-1}), B addition of water after TFA (3 10^{-3}–3.7 mol L^{-1}).

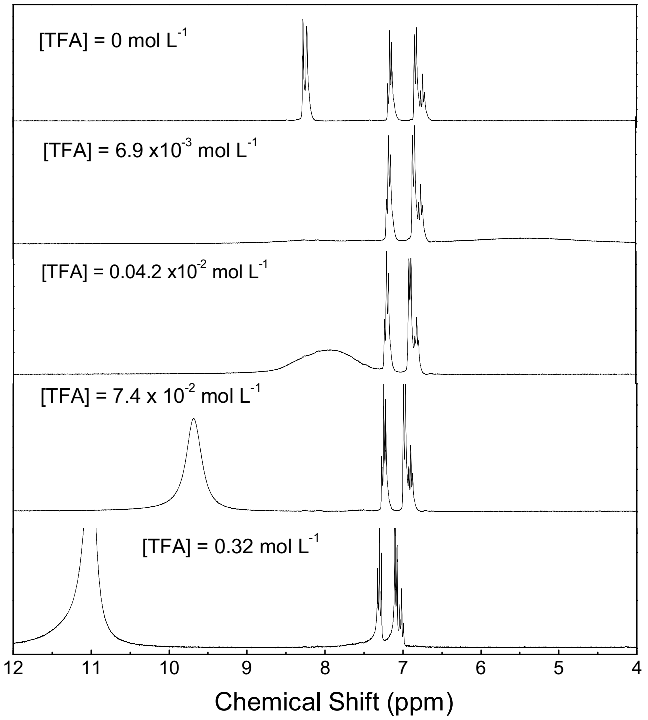


Fig. 2. ^{1}H NMR spectra of PHA in the presence of TFA. Run conditions: 300 MHz DMSO-d_6, T 298 K, PHA concentration of 5×10^{-2} mol L^{-1}. Chemical shift: TFA 0 mol L^{-1}, (t, δ 6.71 ppm *J* = 7 Hz; d, δ 6.83 ppm, *J* = 8 Hz, δ 7.17 ppm *J* = 7 Hz, δ = 8.23 ppm, δ = 8.28 ppm); TFA 0.0069 mol L^{-1}, (t, δ 6.76 ppm *J* = 7 Hz; d, δ 6.84 ppm, *J* = 8 Hz, δ 7.18 ppm *J* = 7 Hz, broad δ = 5.3 ppm); TFA 0.042 mol L^{-1}, (t, δ 6.82 ppm *J* = 7 Hz; d, δ 6.89 ppm, *J* = 8 Hz, δ 7.20 ppm *J* = 7 Hz, broad δ = 7.9 ppm); TFA 0.074 mol L^{-1}, (t, δ 6.90 ppm *J* = 7 Hz; d, δ 6.97 ppm, *J* = 8 Hz, δ 7.24 ppm *J* = 7 Hz, broad δ = 9.7 ppm); TFA 0.32 mol L^{-1}, (t, δ 7.02 ppm *J* = 7 Hz; d, δ 7.08 ppm, *J* = 8 Hz, δ 7.28 ppm *J* = 7 Hz, broad δ = 11 ppm).

rearrangement, such an ester intermediate has never observed in the reaction media. Furthermore, the NMR measurements (see Fig. 2) give poor information on the nature of the TFA-THA complex, because of the strong quenching of the signals due to the presence of TFA (Fig. 3).

It appears, however, that such a specie has the signals of the aromatic protons very close to those of the starting PHA. In fact, the addition of TFA does not noticeably modify the spectrum of the protons of the phenyl ring, except for a downfield shift, likely due to an interaction of TFA with the NHOH group. This strong interaction is in agreement with the absence of the NHOH at 8.25 ppm and 8.21 ppm assigned to the aminic proton and to the hydroxyl one, respectively. The addition of the TFA cause their disappearing because of the exchange with that of the TFA, whose signals at 6.9×10^{-3} mol L^{-1} is a very broad band centered at about 5.3 ppm. As a matter of fact, the quenching of the signal of the proton of TFA and those of the NHOH group, together with the directly related downfield of the phenyl protons with the amount of TFA, are further proofs of the strong interaction between the acid and the PHA, suggesting the formation of a stable complex (see Fig. 2).

In order to verify the reactivity of PHA with TFA, which does not give any product of esterification or amidation we study the reactivity of PHA with trifluoroacetic anhydride, which gives *N*-hydroxy-trifluoroacetanilide almost immediately, in agreement with literature data (see Supplementary materials) [32]. The spectrum of *N*-hydroxy-trifluoroacetanilide does not change by increasing the temperature to 343 K, after 1 h of reactions, in the presence of a stoichiometric amount of TFA, (see Fig. 2). This suggests *N*-hydroxy-trifluoroacetanilide is quite stable at 343 K and no rearrangement to 4-aminophenol or to its derivatives occurs. This

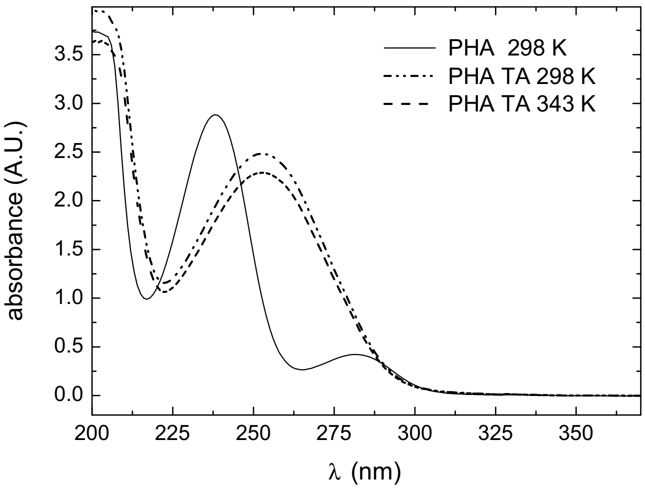


Fig. 3. Reactivity of PHA with trifluoroacetic anhydride (TA) at 298 K and at 343 K for 1 h. Run conditions: Uv–vis spectra at 5×10^{-4} mol L^{-1} solvent acetonitrile, optical length 1 cm.

evidence establishes that *N*-hydroxy-trifluoroacetanilide is not an intermediate of the Bamberger rearrangement.

Starting from these evidences the equilibrium intermediate is neither an amide nor an ester of the TFA but it could be ascribed to anionic couple or a kind of cluster complex. Apart, the spectroscopic evidence of NMR and UV Vis bands displacement, the only information on the nature of this compound come from conductivity measurements. In fact, the conductivity of the solution at0.3 mol $L^{-1}$of TFA in acetonitrile is 4 μS cm^{-1}, which suggests the presence of the TFA practically undissociated. This in agreement with the calculations reported in Table 1.The addition of PHA at a concentration of 10^{-3} mol L^{-1} raises the conductivity to 150 μS cm^{-1}, a value compatible with a conductivity in nonaqueous solvent of a highly associated ionic compound, but not with that of a free ion [33].

Until now the reflections on the nature of the specie detected by spectroscopic measurements, does not give an evaluation of the equilibrium of formation of such a complex, which is probably the key intermediate of the kinetics of reaction. For this reason, we measure the equilibrium constant (K_{eq}) by spectrophotometric measurements of the complex PHA-TFA at 298, 293 and 288 K in acetonitrile as a solvent (Scheme 2, Eq. (1)). At such temperatures the rearrangement practically does not occur, since its kinetics is very slow, thus allowing the measurement of the equilibrium of formation of the PHA-TFA specie. We consider in the equilibrium calculation the concentration of the species in solution and not the activity, since there are no charge separation and each activity coefficient is proportional to the specific Sechenov factor, which can be englobed in the K_{eq} [34].

$$\text{PHA} + \text{TFA} \rightleftharpoons \text{PHA-TFA} \qquad \text{Scheme 2}$$

$$K_{eq} = \frac{[PHA - TFA]}{[PHA]\,[TFA]} \tag{1}$$

The measurements at various temperature give a linear Van't Hoff plot (Fig. 4), thus allowing the extrapolation of the equilibrium constant at the temperatures of reaction. As expected, the equilibrium is moderately exothermic with an enthalpy of reaction of *c.a.* −12 kJ mol^{-1}. This value is in agreement with that measured for the system TFA with cyclohexanone oxime (*c.a.* −19 kJ mol^{-1}) [17]. Clearly, the concentration of the cluster decreases as the temperature increase and the negative entropy of formation suggests the formation of the cluster causes a reduction of the global number of molecules in solution.

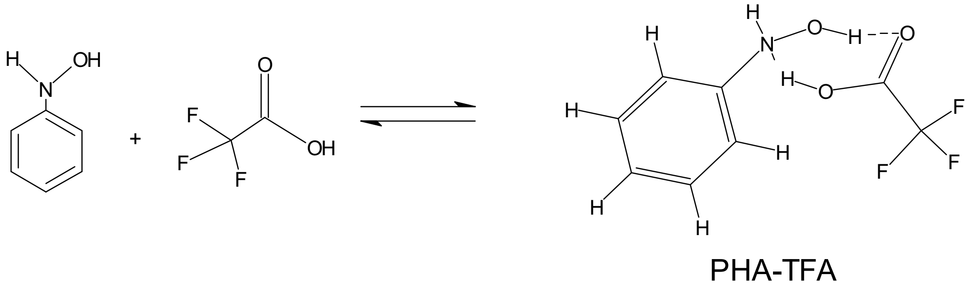
3.3. *Reaction rate: comparison of spectrophotometric and HPLC measurements*

The complex behavior of the UV–vis, spectra needs an independent measurement of the reaction rate in order to correctly choice the wavelength for measuring the kinetics of reaction. Actually, spectra of reagent and product change as the ratio of water and TFA is modified, because of the strong effect that has this parameter on the TFA-PHA complex equilibrium. The practical consequence of this solvent effect is the impossibility of having an unambiguous measurement of the kinetics simply by following the spectral change. For this reason a comparison of kinetics obtained by analysing with HPLC samples withdrawn at various time are useful to assess the reliability of the UV–vis measurements. Table 2 reports the pseudo first order kinetic constants determined by using both techniques. At 0.3 mol L^{-1} of water, the scarce variation of the bands in the UV–vis spectra does not allow a reliable evaluation of the kinetics by UV–vis measurements. However, the quite good correspondence of the kinetic constants, obtained by UV–vis and HPLC analysis at 1.2 and 6 mol L^{-1} of water, suggests that the kinetic constants measured with the two methods are comparable (see Table 2) and for our purposes the two methods are equivalent.

The evaluation of the observed first order kinetic constant (k_{obs}) allows the comparison of the reactions by varying the operative variables but this behavior does not allow any consideration on the reaction mechanism. In fact, the reaction is multi-step, since spectrophotometric measurements evidences the PHA-TFA intermediate. The formation of such a complex, however, is not evident on the time *vs*. product profile of the overall kinetics (see Fig. 5). This behavior is typical kinetics where the pre-equilibria are in stationary state influencing the k_{obs} but not the overall profile, which remain first order, apparently. In fact, k_{obs} is substantially constant doubling substrate concentration (Table 2). This kind of time *vs*. concentration profile (first order kinetics), without any evident intermediate, even though in agreement with previous literature data in mineral acids, gives poor information on the reaction mechanism [11,20,21].

3.4. *Influence of the operative variables on the reaction kinetics: temperature, PHA, TFA, and water concentration*

In order to take information on the reaction path, we investigate the role of some operative variable on the reaction kinetics. Of particular interest is the role of water, on the reaction kinetics



Scheme 2. Equilibrium of PHA, TFA and the complex PHA-TFA.

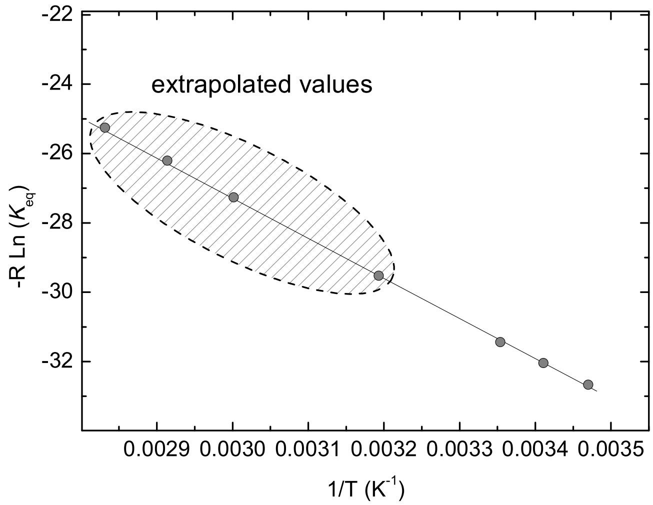


Fig. 4. Vant'Hoff plot of the equilibrium PHA-TFA: $\Delta H^\circ = -12.6\,\mathrm{kJ\,mol^{-1}}$, $\Delta S^\circ = -11.3.\,\mathrm{J\,K^{-1}\,mol^{-1}}$.

Table 2
Comparison of the k_{obs} obtained with UV–vis and HPLC at 343 K TFA 0.1 mol L^{-1} in CH_3CN as a solvent, reaction volume 25 mL.

Water	PHA	HPLC10^{5}xk_{obs}	UV–vis (220 nm)10^{5}xk_{obs}	UV–vis (275 nm)10^{5}xk_{obs}
(mol L^{-1})	(mol L^{-1})	(s^{-1})	(s^{-1})	(s^{-1})
0.3	1 × 10−3	61.0	/	/
1.2	1 × 10−3	48.1	49.0	49.0
6	1 × 10−3	18.4	22.9	23.0
6	1.2 × 10^{-3}	/	22.8	23.1
6	6 × 10^{-4}	/	23.0	22.9

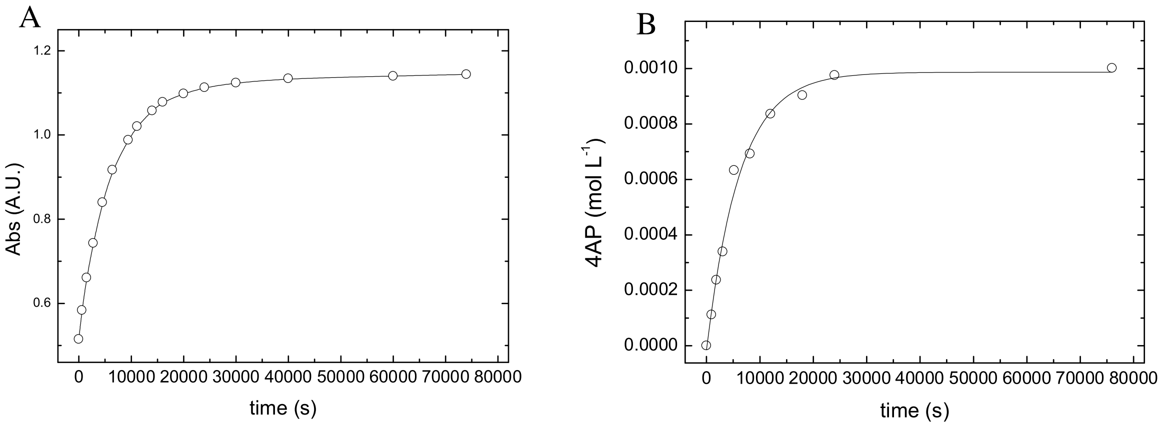


Fig. 5. Comparison of two fittings of first order equation on the kinetic profile 4-hydroxyaniline formation measured by both spectrophotometric UV–vis 220 nm (A) and HPLC (B) analysis. Run conditions: temperature (343 K), PHA (10^{-3} mol L^{-1}), TFA (10^{-1} mol L^{-1}), water (6 mol L^{-1}), solvent acetonitrile, reaction volume 25 mL.

being an active participating reagent on the mechanism [26]. On the basis of well-established literature data, water enters in the reaction pathway as an intermolecular reagent, in fact, the migration of the hydroxyl group is not specific but it comes from the

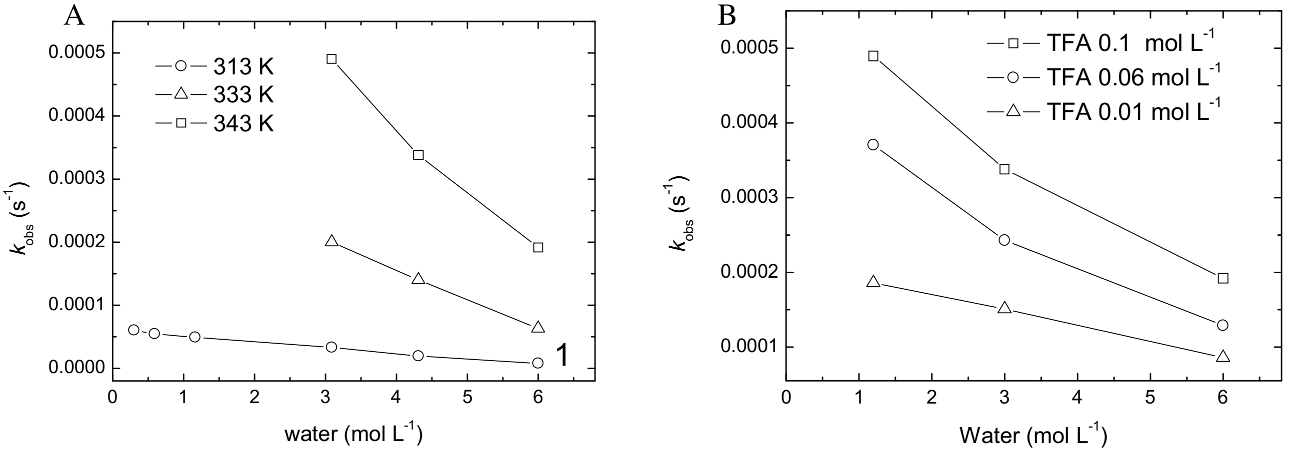


Fig. 6. Influence of water on the k_{obs} at various TFA concentrations and temperatures. Run conditions: PHA (10^{-3} mol L^{-1}), TFA (10^{-1} mol L^{-1}), solvent acetonitrile reaction volume 25 mL., point 1 extrapolated from Arrhenius plot.

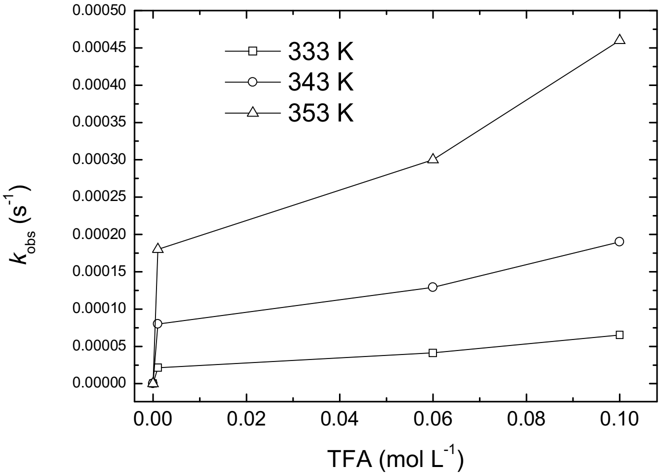


Fig. 7. Influence of the TFA concentration on the k_{obs} at various temperature. Run conditions: PHA (10^{-3} mol L^{-1}), water (150 mmol), solvent acetonitrile, reaction volume 25 mL.

solvent [11,20,21]. For this reason, water concentration is a fundamental parameter also for this study, even though, we use acetonitrile as a solvent. Fig. 6 shows the influence of water amount on the k_{obs}, there is a monotone decreasing of the k_{obs} as the amount of water raises. This behavior suggests that the limiting step is not the attack of the water as nucleophile, even though it has a clear influence on the overall kinetics.

The amount of acid, as expected, influences directly the k_{obs}, which increases monotonically as the TFA concentration rises. This behavior is expected since the rate of rearrangement to an electron-deficient nitrogen is generally directly related to the amount of acid (*e.g.* in the Beckmann rearrangement [35–37]). In this case, however, it is more probably related to the formation of an intermediate whose equilibrium is influenced by the simultaneous presence of TFA and PHA. On the contrary, as pointed out in Section 3.2, the PHA protonation depends directly to PHA, TFA and water concentrations but the amount of the latter is inversely proportional to the k_{obs}. This suggests that the catalysis is not due to proton exchange but likely *via* the formation of the PHA-TFA complex Fig 7.

The Arrhenius Plots (Fig. 8) at various TFA and water concentration show temperature factors (apparent activation energy) comprised between 79 kJ mol^{-1}and 104 kJ mol^{-1}.

This behavior suggests that both TFA and water concentration has a clear influence not only on the observed kinetic constant but also on the energy of the various steps of the process, thus suggesting the presence of temperature dependent equilibria. In any case, these behavior are in agreement with those measured in sulfuric acid by other authors, then it is likely that despite of, different solvent and reaction environment a similar reaction path may occurs [11,20,21].

3.5. The kinetics of reaction

As already pointed out in previous sections, the equation rate is first order, but the influence of the operative variables on the k_{obs} suggests the presence of equilibria affecting the rate constant. In fact, the effective kinetic constant depend from the temperature only. Starting from these considerations, we have to remember that in Section 3.2, we observed the formation of the PHA-TFA complex and we measured its equilibrium in acetonitrile as a solvent. In addition, the presence of water influences this equilibrium, but due to the shift of the bands, in the UV–vis region, the equilibrium of the system acetonitrile-TFA-PHA-water is not possible to measure reliably. Then, it is necessary to determine these equilibria by an indirect procedure. It appears from what reported in Section 3.4 that the k_{obs} depends from both TFA and water concentration. For this reason, we plot k_{obs} *vs* TFA/water mole fractions (Fig. 9A). Starting from this evidence, we define a k_{mod}, obtained by combination

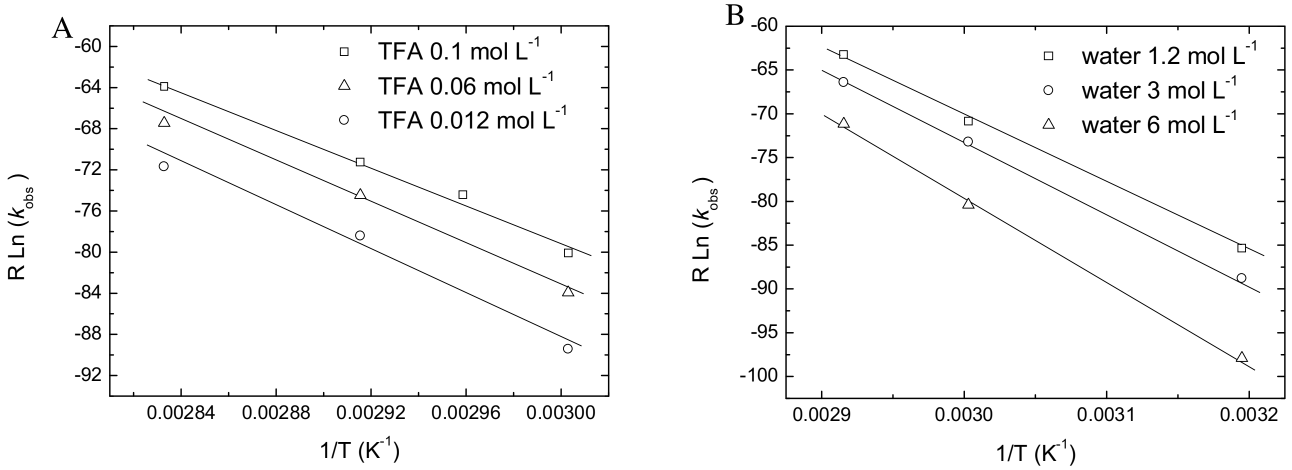


Fig. 8. Arrhenius Plot at various TFA concentrations (A) and water amount (B): (A) 92 kJ mol^{-1} in TFA 0.1 mol L^{-1}, 97 kJ mol^{-1} in TFA 6 × 10^{-2} mol L^{-1} and in TFA 10^{-2} mol L^{-1}; (B) 79 kJ mol^{-1} (water 1.2 mol L^{-1}), 81 kJ mol^{-1}(water 3 molL^{-1}), 92 kJ mol^{-1} (water 6 mol L^{-1}). Run conditions: PHA (10^{-3} mol L^{-1}), solvent acetonitrile, reaction volume 25 mL.

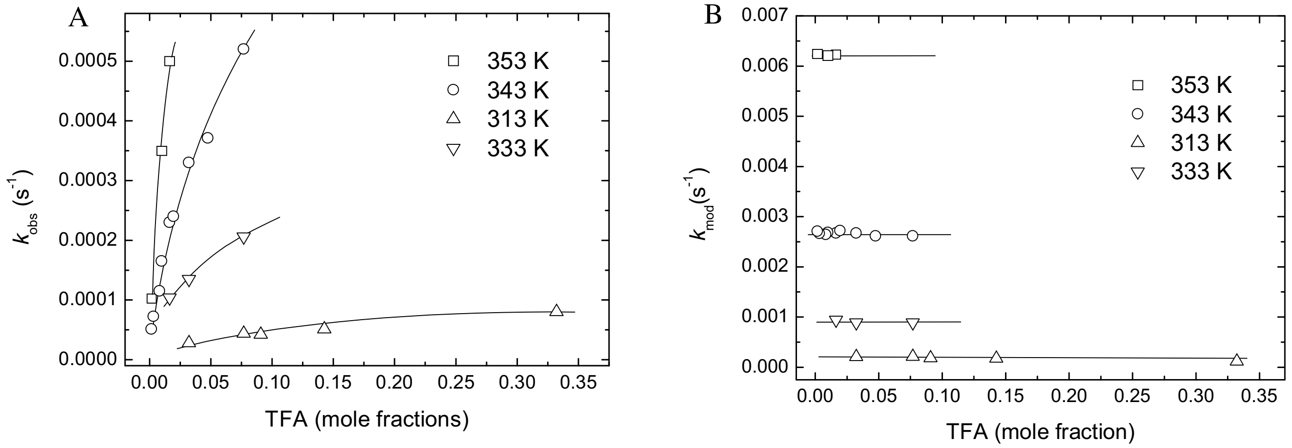


Fig. 9. Comparison of k_{obs} (a) and k_{mod} (B) at various temperatures in function of the TFA mole fraction.

of the k_{obs} with the initial water and TFA concentrations. Eq. (2) shows the dependence of the reaction rate from k_{obs}, as a pseudo first order kinetics and it defines the k_{mod} as a power low equation in water and TFA concentrations (details of the calculations are in Supplementary materials). It appears in Fig. 9 B that k_{mod} does not change with the mole fraction TFA/H_2O, thus suggesting its independence from the species present in solution.

$$r = k_{obs}[PHA] = k_{mod}[PHA]\frac{[TFA]^{0.69}}{[H_2O]^{0.5}}\text{thus}k_{mod} = k_{obs}\frac{[H_2O]^{0.5}}{[TFA]^{0.69}} \quad (2)$$

In Fig. 10 B, it is evident, that k_{mod} depends only by the temperature, and the Arrhenius plot is linear (Fig. 9). The power low expression $[PHA][TFA]^{0.69}[H_2O]^{-0.5}$ represents the equilibria in solution of TFA, water and PHA, from which derives the PHA-TFA complex, then, we suppose this is key intermediate, from which depends the kinetics of reaction.

This behavior of the k_{mod} suggests that these constant is strictly related to the actual kinetic of reaction. If we consider the activation parameter obtained by fitting the Eyring-Evans-Polanyi equation we obtain the enthalpy of the activated state of $\Delta H^{\ddagger} = 77.6$ kJ mol^{-1} and the positive entropy of activation (177 J mol^{-1} K^{-1}), which could be related to a dissociative mechanism for the activated state [30]. In agreement with a displacement of a molecule of water from PHA to the solvent.

On the light of these calculations, it appears a direct relationship between the rate of reaction with TFA and PHA and an inverse one with water concentration. This behavior is a further proof that TFA dissociation and PHA protonation are not the determining stages, since they depends directly by water and TFA concentrations and in acetonitrile these processes are negligible. Then, we could suppose that the PHA-TFA complex is the key intermediate in the reaction kinetics, and we suppose Eq. (3)is the rate of reaction, where k is the actual kinetic constant Fig. 11.

$$r = k[PHA - TFA] \quad (3)$$

Then, we obtain Eq. (4) by rearranging Eqs. (1) and (2), since k_{mod} has a behavior typical of a “true” kinetic constant, we reasonably suppose$k = k_{mod}$, then we calculate the equilibrium concentration of the PHA-TFA complex by Eq. (5).

$$r = k_{obs}[PHA] = k[PHA - TFA] = k_{mod}[PHA]\frac{[TFA]^{0.69}}{[H_2O]^{0.5}} \quad (4)$$

$$[\mathrm{PHA} - \mathrm{TFA}] = [PHA]\frac{[TFA]^{0.69}}{[H_2O]^{0.5}} \quad (5)$$

After these considerations, we try to calculate the equilibria in solution taking into account for the presence of water. Despite of the complexity of the three component system (water, TFA, acetonitrile), we suppose the equilibrium of the species in solution

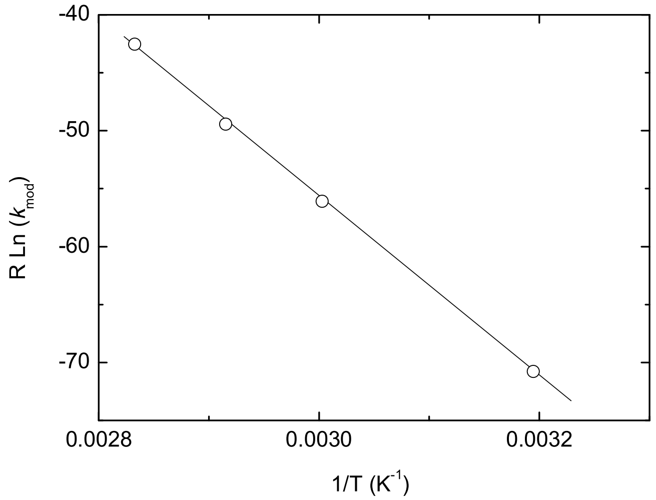


Fig. 10. Arrhenius plot of the modified kinetic constant k_{mod}. Eyring-Evans-Polanyi equation parameters: $\Delta H^{\ddagger} = 77.6\ \text{kJ mol}^{-1}$, $\Delta S^{\ddagger} = 177\ \text{J K}^{-1}\ \text{mol}^{-1}$.

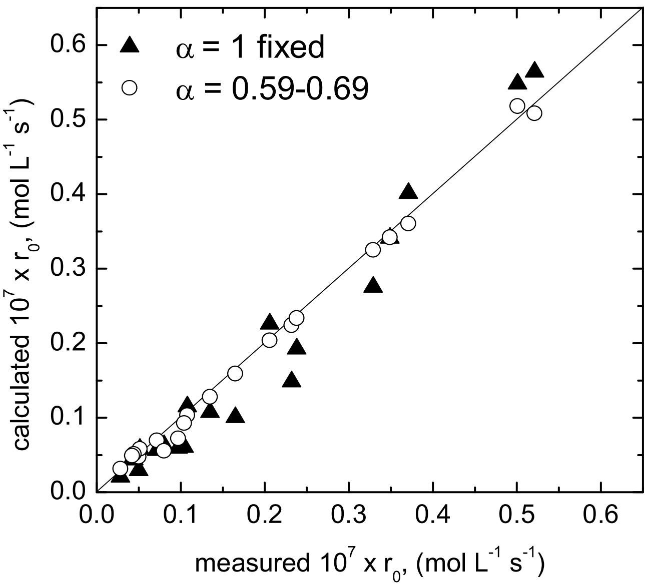
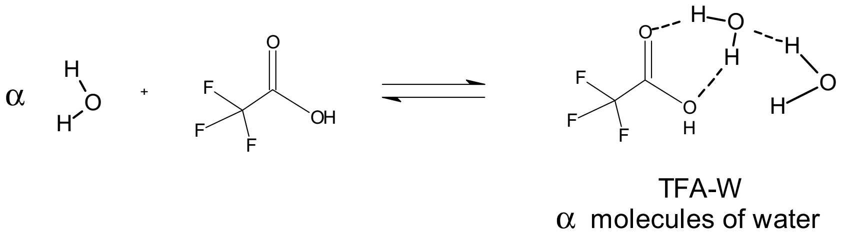


Fig. 11. Experimental vs calculated r_0 values.



Scheme 3. Equilibrium of TFA, H_2O and the complex TFA-W.

could be described by the equilibrium of formation the complex PHA-TFA (Scheme 2 and Eq. (1)) and the equilibrium of water with TFA (Scheme 3and Eq. (6)).

By reducing the simultaneous Eqs. (1), (6)–(8), where Eqs. (7) and (8) are the mass balance of TFA and PHA, respectively, we obtain an expression of the PHA-TFA concentration in function of the $[PHA]_0$, $[TFA]_0$, $[H_2O]$, concentrations at time 0, and of K_{eq}, K_S, α. As described in Section 3.1, Eq. (5) takes into accounts for the equilibrium between TFA, PHA and the complex PHA-TFA, while Eq. (6) describes the competing equilibrium of water with TFA on forming a TFA-W cluster. Besides, in Eq. (6), we assume the equilibrium of the TFA-W complex depends on a variable number of molecules of TFA and water and the exponentα of Eq. (6) takes into account for the stoichiometric ratio of the complex Fig. 12.

$\alpha H_2O + TFA \rightleftharpoons$ TFA-W Scheme 3

$$K_{eq} = \frac{[PHA-TFA]}{[PHA]\,[TFA]} \tag{1}$$

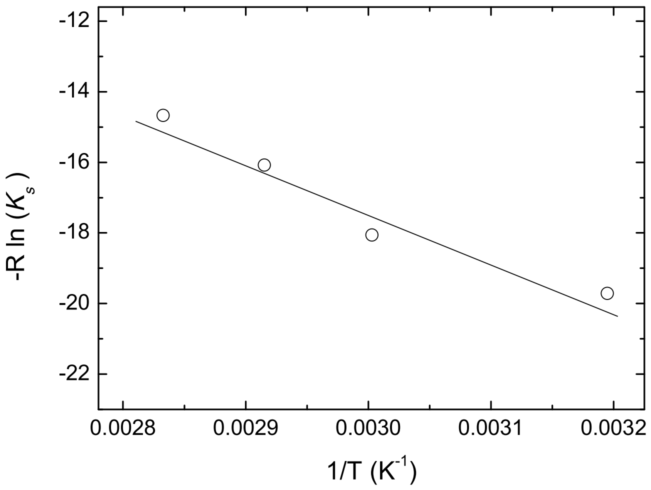


Fig. 12. Van't Hoff plot of the equilibrium TFA-W complex: $\Delta H^\circ = -13.5$ kJ mol^{-1}, $\Delta S^\circ = -23$ J K^{-1} mol^{-1}.

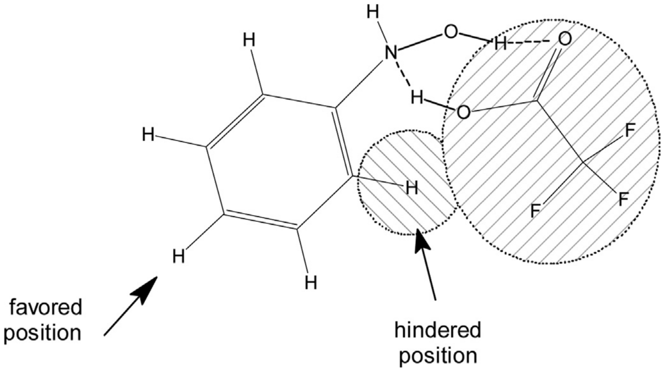


Fig. 13. Steric hindrance towards a nucleophilic attack to the para positions of the PHA-TFA complex.

$$K_s = \frac{[TFA - W]}{[TFA]\,[H_2O]^{\alpha}} \tag{6}$$

$$[TFA]_0 = [TFA] + [PHA - TFA] + [TFA - W] \tag{7}$$

$$[PHA]_0 = [PHA] + [PHA - TFA] \tag{8}$$

Then, simultaneous equations 1, 6–8 have as unknown parametersα and K_S. By the minimization of the square residuals between the calculated [PHA-TFA] (by solving the simultaneous Eqs. (1), (6)–(8)) and the values obtained from Eq. (5) (derived from the measured rate of reaction) we obtain the values of the two parameters (α and K_S). From a mathematical point of view, the solutions of the simultaneous equation is a bi-parametric approach for the calculation of the equilibria that takes into accounts the complexity of the system. It is noteworthy that at first attempt, we have tried a model, with one molecule of water and one of TFA in the equilibrium with the TFA-W complex (namely α = 1). In this case, the correspondence, between the calculated initial rate of reaction and those measured, was quite poor (see Fig. 13 black triangles, see also Supplementary materials). From a practical point of view, the necessity of a further parameter to describe these complex equilibria is reasonable, since the formation of a TFA-W complex is dependent on the solvent. In fact, water modify the characteristic of the solvent, for instance, favors charge separation. This procedure, however, is useful since it introduces a single parameter (α) directly related to the equilibrium of the solvent but having an evident physical meaning. Fig. 13 (open circles) shows the goodness of the model, being evident a good correspondence between calculated *vs.* the experimental initial reaction rates, additionally the points are well behaved around the middle of the line.

Table 3 shows some results of the fitting; it appears that the value of α is lower than 1 suggesting that the TFA-W complex is likely a cluster composed of more than one molecules of TFA and water. In any case, the interaction of TFA with water explains the depressive effect of water on the reaction kinetics, thus competing in the formation of the PHA-TFA complex. K_S is the equilibrium constant of TFA, water and the TFA-W complex, whose physical meaning can be related also with the modification of the solvent as water concentration increases. Also in this case, it seems that, despite of the indirect procedure for obtaining the equilibrium constants, the model holds, since the Van't Hoff plot is consistent and the value of the enthalpy of formation (moderately exothermic-13.5 kJ mol^{-1}) of the cluster is in agreement with the constant of formation of these kind of complex [38]. Entropy of formation is negative for 23 J K^{-1} mol^{-1} suggesting the involvement of lower number of molecules passing from the free state to the associated one. These results are physically consistent, and then it is a further proof of the goodness of the model. On these bases, we could attempt an explanation of the kinetics and of the regioselectivity of the reaction Fig. 12.

Until now, we have shown the role of the PHA-TFA complex as a stationary state specie, whose equilibrium influences the overall kinetics. This explanation on the kinetic mechanism, however, does not straightly elucidate the regioselectivity towards the *para* position. The complex PHA-TFA should be responsible also of the regioselectivity towards the *para* position if we consider the *ortho* position is sterically hindered. In fact, the –NHOH group interacts with the –COOH one of the TFA resulting in a hindered structure in *ortho* position. This is evidenced in Fig. 13, which shows a

Table 3
Table of the thermodynamic and of the kinetic constants. Run Conditions: PHA (1×10^{-3} mol L^{-1}), TFA (1×10^{-1} mol L^{-1}), solvent acetonitrile, reaction volume 25 mL.

TFA (mol L^{-1})	H_2O (mol L^{-1})	T (K)	10^5 x k_{obs} (s^{-1})	10^3 x k_{mod}	K_{eq}	K_s	α	10^5 x PHA-TFA (mol L^{-1})
1×10^{-1}	6	353	50.1	6.28	20	5.85	0.679	8.23
6×10^{-2}	6	353	34.9	6.32	20	5.85	0.679	5.43
1×10^{-2}	6	353	9.72	6.25	20	5.85	0.679	1.15
1×10^{-1}	1.2	343	52.1	2.73	22	7.69	0.623	18.6
1×10^{-1}	3	343	32.9	2.74	22	7.69	0.623	11.9
1×10^{-1}	6	343	23.2	2.70	22	7.69	0.623	8.24
6×10^{-2}	1.2	343	37.1	2.75	22	6.95	0.601	13.1
6×10^{-2}	3	343	23.8	2.82	22	6.95	0.601	8.36
6×10^{-2}	6	343	16.5	2.74	22	6.95	0.601	5.80
1×10^{-2}	1.2	343	10.8	2.89	22	4.08	0.592	3.80
1×10^{-2}	3	343	7.18	2.86	22	4.08	0.592	2.43
1×10^{-2}	6	343	4.99	2.86	22	4.08	0.592	1.69
1×10^{-1}	0.1	313	8.01	0.12	33	10.5	0.699	44.4
1×10^{-1}	1.2	313	4.43	0.24	33	10.5	0.699	21.4
1×10^{-1}	3	313	2.84	0.24	33	10.5	0.699	12.9
1×10^{-1}	1.2	333	20.6	1.09	25	8.8	0.618	18.6
1×10^{-1}	3	333	13.5	1.07	25	8.86	0.618	11.9
1×10^{-1}	6	333	10.4	1.12	25	8.86	0.618	8.24

by-dimensional representation (it is more clear with respect to the tridimensional one) of the PHA-TFA complex obtained by a preliminary energy minimization of the structure by SCF calculation of the couple PHA-TFA without charge separation (details in Supplementary materials). The real structure of the PHA-TFA specie, it is more likely to be a complex cluster of molecules, whose structure could be object of a theoretical study, but this is beyond the scope of this work. In this way, the attack of water, which is a quite weak nucleophile, toward the *para* position is more probable than the *ortho* one. Formation of cluster as intermediate for explaining the regioselectivity of the reaction has been already proposed in a computational study, where the formation of a cluster of molecule of water stabilizes a dication intermediate deriving from the protonated PHA in aqueous solution [25]. In acetonitrile, the charge separation does not significantly occur then the formation of the PHA-TFA complex plays the major role on activating the molecule for the rearrangement. Clearly, the presence of water, which competes with PHA on forming cluster with the acid, depresses the formation of the PHA-TFA complex, thus reducing the reaction rate of the rearrangement.

4. Conclusion

In this work, we found that the Bamberger rearrangement in acetonitrile catalyzed by TFA does not depend from the protonation of the PHA. In fact, it is strictly related to the formation of a PHA-TFA complex, which is responsible of the kinetics as well of the regioselectivity towards the para position on forming the aminophenol. The equilibrium of the PHA-TFA intermediate is measured spectrophotometrically and its value is employed in the determination of the kinetic parameters. The role of water on depressing the reaction rate is also connected with its equilibrium with TFA on forming a TFA-W adduct, which in turn causes a decreasing of the concentration of the PHA-TFA complex. The proposed kinetic model takes into accounts both equilibria, giving a good fitting of the experimental data and it allows the calculation of the equilibrium constant of TFA with water. In addition, the model permits the calculation of the enthalpy and entropy of all the steps of the reaction, suggesting a dissociative transition state for the kinetics.

Acknowledgements

Financial support by Ca' Foscari University of Venice is gratefully acknowledged (ADIR fund 2014).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.apcata.2016.02.020.

References

[1] S. Mitchell, R. Waring, Aminophenols, vol. 2, 4th edition, John Wiley & Sons, 1999.
[2] S.K. Tanielyan, J.J. Nair, N. Marin, G. Alvez, R.J. McNair, D. Wang, R.L. Augustine, Org. Process Res. Dev. 11 (2008) 681.
[3] K. Hunger, Industrial Dyes, 25, Wiley-VCH Verlag, Weinheim, 2003.
[4] C.V. Rode, M.J. Vaidya, R. Jaganathan, R.V. Chaudhari, Chem. Eng. Sci. 56 (2001) 1299–1304.
[5] http://www.dsir.gov.in/reports/techreps/tsr131.pdf.
[6] J.R. Fritch, O.S. Fruchney, T. Horlenko, D.A. Aguilar, C.B. Hilton, P.S. Snyder, W.J. Seelinger, U.S. Pat. 5,155,273 to Hoechst-Celanese Co. (1992).
[7] Y. Gao, F. Wang, S. Liao, D. Yu, React. Kinet. Catal. Lett. 64 (1998) 351–357.
[8] K. Min, J. Choi, Y. Chung, W. Ahn, R. Ryoo, P.K. Lim, Appl. Catal. A: Gen. 337 (2008) 97–104.
[9] H. Saggadi, D. Luart, N. Thiebault, I. Polaert, L. Estel, C. Len, Catal. Commun. 44 (2014) 15–18.
[10] I.M.C. Brighente, L.R. Vottero, A.J. Terezani, R.A. Yunes, J. Phys. Org. Chem. 4 (1991) 107–112.
[11] T. Sone, Y. Tokuda, T. Sakai, S. Shinkai, O. Manabe, J. Chem. Soc. Perkin Trans. 2 (1981) 298–301.
[12] S. Wang, Y. Ma, Y. Wang, W. Xue, X. Zhao, J. Chem. Technol. Biotechnol. 83 (2008) 1466–1471.
[13] A. Deshpande, F. Figueras, M.L. Kantam, K.J. Ratnam, R.S. Reddy, N.S. Sekhar, J. Catal. 275 (2010) 250–256.
[14] S. Wang, B. He, Y. Wang, X. Zhao, Catal. Commun. 24 (2012) 109–113.
[15] T. Komatsu, T. Hirose, Appl. Catal. A: Gen. 276 (2004) 95–102.
[16] G. Quartarone, L. Ronchin, A. Tosetto, A. Vavasori, Appl. Catal. A: Gen. 475 (2014) 169–178.
[17] L. Ronchin, A. Vavasori, M. Bortoluzzi, Catal. Comun. 10 (2008) 251–256.
[18] L. Ronchin, A. Vavasori, J. Mol. Catal. A: Chem. 313 (2009) 22–30.
[19] G. Quartarone, E. Rancan, L. Ronchin, A. Vavasori, Appl. Catal. A: Gen. 472 (2014) 167–177.
[20] G. Kohnstam, W.A. Petch, D.L.H. Williams, J. Chem. Soc. Perkin II (1984) 423–427.
[21] T. Sone, K. Hamamoto, Y. Siji, S. Shinkai, O. Manabe, J. Chem. Soc. Perkin II 159 (1984) 1596–1598.
[22] K.J. Ratnam, R.S. Reddya, N.S. Sekhara, M.L. Kantama, A. Deshpande, F. Figueras, Appl. Catal. A: Gen. 348 (2008) 26–29.
[23] S. Liu, Y. Hao, J. Jiang, Ind. Eng. Chem. Res. 53 (2014) 8372–8375.
[24] A. Vavasori, M. Capponi, L. Ronchin, Chem. List. 106 (2013) 1191.
[25] J.C. Fishbein, R.A. McClelland, Can. J. Chem. 74 (1996) 1321–1328.
[26] S. Yamabe, G. Zeng, W. Guan, S. Sakaki, Beil. J. Org. Chem. 9 (2013) 1073–1082.
[27] E.A. Gelder, S.D. Jackson, C.M. Lok, Chem. Commun. (2005) 522–524.
[28] O. Kamm, Org. Synt. Coll. 4 (1925) 57.
[29] S. Espinosa, E. Bosch, M. Roseís, J. Chromatogr. A 964 (2002) 55–66.
[30] C. Reichardt, Solvents and Solvent Effects in Organic Chemistry, 2nd ed., VCH, Weinheim, 1988, pp. 79.
[31] M.K. Chantooni, I.M. Kolthoff, Anal. Chem. 51 (1979) 133–140.

[32] P.S. Branco, S. Prabhakar, A.M. Lobo, D.J. Williams, Tetrahedron 30 (1992) 6335–6360.
[33] J. Barthel, H.J. Gores, G. Schmeer, R. Wachter, Non-Aqueous Electrolyte Solut. Chem. Modem Technol. 111 (1983) 33–144.
[34] A. Pietropolli Charmet, G. Quartarone, L. Ronchin, C. Tortato, A. Vavasori, J. Phys. Org. Chem. 27 (2014) 680–689.
[35] N.C. Marziano, L. Ronchin, C. Tortato, O. Tonon, R. Bertani, Int. J. Chem. Kin. 36 (2004) 419–426.
[36] N.C. Marziano, L. Ronchin, C. Tortato, A. Vavasori, C. Badetti, J. Mol. Catal. A: Chem. 277 (2007) 221–232.
[37] N.C. Marziano, L. Ronchin, C. Tortato, A. Vavasori, M. Bortoluzzi, J. Mol. Catal. A: Chem. 290 (2008) 79–87.
[38] M. Ilczyszyn, H. Ratajczak, J. Chem. Soc. Faraday Trans. 91 (1995) 1611–1618.