Received: 6 February 2014,

Revised: 14 March 2014,

(wileyonlinelibrary.com) DOI: 10.1002/poc.3319

Thermodynamics and kinetics of indole oligomerization in 0.5 mol L⁻¹ aqueous sulfuric acid: evaluation of some temperaturedependant parameters

Giuseppe Quartarone^a, Andrea Pietropolli Charmet^a, Lucio Ronchin^a*, Claudio Tortato^a and Andrea Vavasori^a

Indole is present in a wide variety of natural compounds with physiological activities, as well as it is a very important intermediate in medicinal and industrial chemistry. For this reason, the evaluation of indole protonation, oligomerization equilibria and the study of the kinetics of dimer and trimer formation in diluted sulfuric acid at various temperatures are of paramount importance because of their practical and scientific implications. Here, we calculate the protonation equilibria by using the literature titration data together with a quantum chemical computational approach, in order to obtain reliable pK_a value of indole from 288 to 313 K. Starting from these calculations, we are able to measure the oligomerization equilibrium constants of indole, their kinetic constants, whose values are dependent of indole pK_a , at different temperatures. Enthalpy and entropy of the reactions are calculated by means of Van't Hoff equation, while the activation parameters of Eyring–Evans–Polanyi equation are evaluated for the whole kinetic constants. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: activation parameters; Indole protonation; oligomerization equilibria; oligomerization kinetics

INTRODUCTION

The heterocyclic ring system of indole is present in a wide variety of natural compounds (for instance, tryptophan, serotonin, etc.); many of which have important physiological activities.^[1,2]

Indole derivatives play a very important role in the synthesis of several compounds with pharmacological activity such as diindolemethane, which is a well-known anticancer and antiviral agent.^[1,2] Indoles and heterocyclic compounds are, however, important chemicals in intermediates chemistry, on material sciences and, in general, in theoretical investigation.^[3–5] Besides, another important field of employment of indoles is the inhibition of corrosion, for instance, they are used as corrosion inhibitor for ferrous and nonferrous alloy, but the nature of the protective phenomenon is still not completely understood, and the role of the indole polymers is only faintly explored.^[6–9]

The behaviour of indoles in aqueous acid solution is strictly connected to their chemical nature, and the substituents play a crucial role in the equilibria of formation of the respective dimer and trimer.

Several studies on indole and derivatives, both experimental and computational, can be found in the literature.^[3–5] In a previous paper, we studied some aspects of indole dimerization and trimerization by evaluating some kinetic and thermodynamic parameters; however, this research has been intended as a preliminary step for more detailed evaluation of the whole process, which is also comprehensive of the protonation equilibria.^[10] Indole pK_a value is characterized by a large uncertainty because of the presence of these oligomerization equilibria, which cause large deviation on the activity coefficient function. This is clearly evidenced by the deviation of the linearity of the substituent effect on pK_a

of several indoles observed in aqueous acid solution.^[11,12] As a matter of fact, indole protonation equilibrium deviates from those of other indoles, and this is connected to the involvement of the molecule in other equilibria, such as that of dimerization. The evaluation of the protonation equilibrium by spectrophotometric measurements is, for these reasons, cumbersome and uncertain, and the values of the pK_a are not reliable especially at temperature higher than room temperature. For these reasons, a theoretical evaluation of the pK_a in conjunction with the more recent reinterpretation of the classical spectrophotometric measurements seems to be a better way for obtaining reliable values of equilibrium and kinetic constants of indole oligomerization.^[10-12]

The formation of dimer and trimer of indole, as well as the reversible nature of these molecules, is known from long time,^[13,14] but there are no data on the equilibrium constants of these reactions except those reported in our preliminary studies.^[10] Early studies on dimerization and trimerization of indoles pointed out that the oligomer formation is related both to indole and acid concentration, as well as to the nature of the acid itself.^[15,16]

The synthesis of indole polymers and of their reactions in different media has been carefully studied for long time, and several strategies have been reviewed.^[17,18] The early paper of

^{*} Correspondence to: L. Ronchin, Department of Molecular Science and Nanosystems, Università Ca' Foscari Venezia, Dorsoduro 2137, 30123, Venice, Italy. E-mail: ronchin@unive.it

a G. Quartarone, A. Pietropolli Charmet, L. Ronchin, C. Tortato, A. Vavasori Department of Molecular Science and Nanosystems, Università Ca' Foscari Venezia, Dorsoduro 2137, 30123, Venice, Italy

Schmitz-Dumont reports some data relating the repartition of indole, dimer and trimer in biphasic condition starting from indole dispersed in aqueous solution of acids at different concentrations: Anyway, no thermodynamics and/or kinetics data were given.^[16] The reactivity of indoles as nucleophile has been carefully investigated towards several electrophiles.^[19–22] The general behaviour of these reactions resembles the majority of aromatic substitutions in which the rate-determining step is the formation of a Wheland-like intermediate.^[19–21]

In our previous paper, we report some preliminary results on the thermodynamics and kinetics of indole oligomerization at 298 K, but because of the lack of information on indole protonation equilibria at various temperatures, the complete investigation on equilibria and kinetics has been delayed until now.^[10] Recently,^[23] high-level quantum chemical calculations suggested a revision of the experimental indole gas-phase basicity value, thus confirming the work of da Silva *et al.*^[24] The computed values of pK_a were found in good agreement with the most recent data.^[10] In this paper, together with the thermodynamics and kinetics behaviours of dimerization and trimerization of indole in aqueous sulfuric acid at different temperatures ranging from 288 to 318 K, we propose, in the same range of temperature, an evaluation of the protonation equilibrium of indole by using the same theoretical methods.

EXPERIMENTAL

Materials

Solvents and reagents were purchased from Aldrich and used after the usual purification. Aqueous sulfuric acid solutions were prepared by diluting the concentrated acid, and their composition was determined by automatic potentiometric titrations against standard solutions of NaOH. Indole dimer hydrochloride (which was used instead of indole dimer sulfate) was prepared following the literature:^(13–16) A chilled solution of indole in 1,2-dichloroethane was saturated with dry hydrogen chloride, a white precipitate was obtained, filtered, washed with 1,2-dichloroethane and dried under vacuum. NMR, UV–Vis and IR spectra of the precipitate coincide with literature;^(13–16) NMR, UV–Vis and IR spectra of the compound match those already published thus confirming the goodness of the synthesis.^(13,14,22)

Reaction kinetics

The kinetic runs were performed in a well-stirred thermostated reactor at 298 K and at atmospheric pressure, containing weighed samples of sulfuric acid (volume, $0.1 L^{-1}$) at $0.5 \text{ mol } L^{-1}$. The desired concentration of substrate ($1-6 \text{ mmol } L^{-1}$) was obtained by dilution of an ethanol solution of the substrate. All the operations were carried out under nitrogen in order to avoid indole oxidation. Small amounts of the solution were drawn at different times, and the samples were analysed by HPLC, using a Perkin Elmer 250 pump equipped with a Phenomenex (C-8 5 µm) column and a diode array Perkin Elmer LC 235 UV detector. From a practical point of view, the interval of concentrations used for studying the reaction is compelled by the necessity of balancing the solubility of reagent and products with the equilibrium conversion. As a matter of fact, conversion of indole at concentrations lower than 1 mmol L^{-1} is too low for kinetics purpose because of the sensibility limits of the analytical method.

Nonlinear regression analysis

The regression of the data was carried out on simultaneous algebraic differential equations numerically evaluated at each experimental point (X_{i}, Y_i) . Mass balance is the regression function (*f*) that accounts for the constraints of the model.^[25–27] The minimization of the square residual

$$S = \sum_{i=0}^{i=n} \left[Y_i - f(X_i, k_D, k_T) \right]^2$$
(1)

Errors and correlation matrix of the kinetic constants have been evaluated using a first-order approximation of the expectation surface at the convergence point and the variance (σ) approximated to the normalized residual mean square [$\sigma^2 \cong s^2 = S/(n-2)$].^[25] Figure 1 shows a typical plot of measured versus calculated concentrations of the species involved in the oligomerization reaction. It is noteworthy that the experimental point is well behaved around the identity line suggesting a good reliability of the model.

Quantum chemical calculation and theoretical determination of indole pK_a value

Recently,^[23] a thorough *ab initio* study on the indole molecule was carried out combining the information derived from different quantum chemical calculations to derive accurate predictions of its aqueous pK_a value. Besides the vibrational analysis performed within the framework of generalized second-order vibrational perturbation theory,^[28] gasphase basicity and proton affinity values were computed by different approaches relying on both several model chemistries and high-level single-point energy corrections computed at coupled cluster level of theory with single, double and perturbative triple excitations (CCSD(T));^[29] the results obtained were then employed to benchmark the corresponding predictions yielded by different density functional theory methods. Aqueous pK_a values of indole were predicted at T = 298.15 K with remarkable accuracy (i.e. well within 0.3 pK_a unit of the recent experimental data^[10]) when the solvation free energy is computed by the SM8^[30] implicit solvation model.

In the present work, the geometries of indole and its protonated form were optimized in the gas phase employing the Becke, three-parameter, Lee–Yang–Parr (B3LYP)^[31] functional in combination with the correlation consistent basis set^[32] of triple- ζ quality augmented by diffuse functions (aug-cc-pVTZ). To provide the high-level corrections on the electron



Figure 1. Experimental versus calculated concentration of indole oligomerization. Run conditions: indole concentration initial time 0.005 mol L^{-1} , T 288 K and H₂SO₄ 0.5 mol L^{-1}

correlation energy that are necessary for reliably computing the gasphase basicity for indole, single-point energy calculations were carried out at CCSD(T) level of theory and using the aug-cc-pVTZ basis set on these optimized geometries. Solvation effects in the temperature that range 288-318K were investigated by means of the SM8T^[33] implicit model; to our knowledge, this framework is the only one developed and specifically parameterized to study the temperature dependence of solvation energy of both neutral and charged compounds, as, for example, recently used by Gupta et al. in their investigation on a set of different amines.^[34] Gaussian 09^[35] and GAMESS softwares^[36] were used for geometry optimizations and calculations of the gas-phase basicity, while the SM8T computations were carried out by using the GAMESSPLUS package.^[37] Vibrational analysis performed at B3LYP/aug-cc-pVTZ level of theory on the previous optimized geometries led to the calculation of zero-point energy, entropy, and thermal corrections to enthalpy and Gibbs free energy for both indole and its protonated form.

RESULTS AND DISCUSSION

Protonation equilibrium of indole

In Scheme 1, the protonation of indole (1) in aqueous acid solution is reported. Indole is a weak base that is slightly protonated at the carbon in three positions. Equation (2) is the relationships of the equilibrium constant of indole protonation. Equation (2) derives from the definition of $pK_{\rm IH}$ of the conjugated acid of indole, the latter being a fairly weak base.

$$K_{I} = \frac{c_{2}}{c_{1}c_{H} + \gamma_{2}\gamma_{H} +}$$
(2)

In Table 1, several values of $pK_{\rm IH}$ and of equilibrium constant $K_{\rm I}$ are reported. Despite of the large number of studies on the argument, there is no general agreement on the value of the equilibrium constant of indole protonation. As a matter of fact, at 298 K, the most accepted values of pK is -3.6, but recent studies suggest values much higher close to -2.5 in agreement to the earlier studies of Berti, which suggested a value of -2.8 calculated by H₀ acidity function. Similar values have been proposed by Andonowsky and Stojkovich by using X excess acidity function. More recently in our preliminary paper, relating the kinetics of indole oligomerization, we used the Mc activity coefficient function to evaluate the value of the $pK_{\rm IH}$ obtaining a value close to that measured by Andonowsky and Stojkovich.^[10,38-40]

Evaluation of the temperature dependence of $\ensuremath{\mathsf{pK}_{\mathsf{IH}}}$ by quantum chemical calculations

The difficulties encountered in a reliable evaluation of the indole protonation constants especially at temperature higher than 298 K induced us to employ quantum mechanical calculation for evaluating its value at various temperatures. Following the methodology of our previous study,^[23] which led to an excellent agreement between experimental and predicted data, to compute the aqueous pK_a value, we employed a thermodynamic cycle that determines the overall solution phase reaction free

 $\int_{6}^{4} \int_{2}^{3} H^{*} = 1$

Scheme 1. Indole protonation equilibrium

Table 1. Protonation equilibrium of indole in 0.5 mol L^{-1} aqueous H₂SO₄: K_{I} calculated by using different activity coefficient functions from pK_{IH}

Activity coefficient function	рК _{ІН} а	10 ³ <i>K</i> ^a	Т (К)	Reference
H _o	-2.8	1.59	298	[37]
H	-3.6	0.32	298	[11]
Х	-2.2	6.33	298	[36]
Mc	-2.4	4.0	298	[10]
${}^{a}K_{I} = K_{IH}^{-1}.$				

energy, $\Delta G^*_{(aq)}$, by combining the corresponding gas-phase basicity of indole, $\Delta G^{\circ}_{(g)}(Ind)$, to the free energies of solvation. The geometries of indole and its protonated form were first optimized at B3LYP level of theory using the aug-cc-pVTZ basis set; then, as previously reported in the Experimental section, for computing the $\Delta G^{\circ}_{(g)}(Ind)$ with the smallest error, high-level corrections on the electron correlation energy were computed by performing single-point calculations at CCSD(T) level of theory on the B3LYP/aug-cc-pVTZ optimized geometries. Similar approaches were proven to be very effective (refer to Ervin and De Turo^[41] and Pickard *et al.*^[42] for examples and references therein) in predicting gas-phase free energies for a variety of compounds. By means of the CCSD(T)/aug-cc-pVTZ//B3LYP/augcc-pVTZ free energy data, the corresponding gas-phase basicity for indole, $\Delta G^{\circ}_{(q)}(Ind)$, was calculated, according to Eqn (3):

$$\Delta G^{\circ}_{(g)}(\mathsf{Ind}) = G^{\circ}_{(g)}(\mathsf{Ind}) + G^{\circ}_{(g)}(\mathsf{H}^{+}) - G^{\circ}_{(g)}(\mathsf{Ind}\mathsf{H}^{+})$$
(3)

where $G^{\circ}_{(g)}(\text{Ind})$ and $G^{\circ}_{(g)}(\text{IndH}^{+})$ refer to gas-phase Gibbs free energy of indole and its protonated form, respectively. For the proton in the gas phase, the free energy was computed by employing the standard equations of thermodynamics and of Sackur–Tetrode equation.^[43]

After having obtained the $\Delta G^{\circ}_{(g)}$ (indole gas-phase basicity) at a given temperature, following the thermodynamic cycle used in the previous work,^[22] the corresponding overall free energy change in solution, $\Delta G^*_{(aq)}$, was computed by adding to the former the change in free energy of solvation. The solvation free energies for both the indole and its protonated form were calculated by carrying out single-point calculations with the SM8T implicit model. For the latter calculations, we employed the M06-2X functional^[44] and the 6-31G(d) basis set, given the good results provided by this combination of functional and basis set as reported in literature for computing the solvation free energy (refer to Chamberlin et al.[45] for example). The results of $\Delta G_{solv}(Ind)$ (indole solvation free energy) and of $\Delta G_{solv}(IndH^+)$ (indole-protonated form free energy of solvation) are reported in Table 2. As expected, there are a decreasing trend of the Gibbs free solvation energy as temperature rises; the much large values observed (above 10 times) for the protonated indole are ascribed to the stabilization effect of the carbonium ion solvation, which is more effective on the charged molecules than the uncharged ones.

The term of the free energy change related to the conversion between the different standard states used for the gas phase and the aqueous solution was taken into account, and the solvation free energies of indole and of its protonated form were computed. Finally, at each considered temperature, by employing the **Table 2.** Solvation free energies of $\Delta G_{solv}(Ind)$ and its protonated form, $\Delta G_{solv}(IndH^+)$, obtained by SM8T implicit model at different temperatures by employing the M06-2X/ 6-31G(d) level of theory

Т (К)	$\Delta G_{solv}(Ind)$ (kJ mol ⁻¹)	$\Delta G_{solv}(IndH^+)$ (kJ mol ⁻¹)
288	-23.7	-252.8
298	-22.6	-250.8
308	-21.6	-249.6
318	-21.1	-249.0
288 298 308 318	-23.7 -22.6 -21.6 -21.1	-252.8 -250.8 -249.6 -249.0

corresponding free energy change in solution, the aqueous pK_a was derived by using Eqn (4):

$$pK_a = \frac{\Delta G^*(aq)}{RT \ln(10)} \tag{4}$$

where R is the universal gas constant and T is the temperature (K). In Table 3, the results of these calculations at the different temperatures considered in the present work are reported.

Figure 2 shows the Van't Hoff plot of protonation equilibrium constants, the reaction is slightly exothermic, and the entropy is negative because of the reduction of mole number (pK_{IH} is calculated considering that the conjugated acid of indole as the acid, which dissociates to indole and H⁺). As a matter of fact, indole is a weak base, and only a small fraction is in the protonated form under the condition investigated.

tions pe	rformer at differen	t temperat	ures	
Т (К)	ΔG^* (kJ mol ⁻¹)	р <i>К</i> _{IН} ^а	10 ³ <i>K</i> l ^a	Reference
288 298 308 318	13.5 14.5 15.4 16.3	-2.45 -2.54 -2.61 -2.68	3.55 2.88 2.46 2.09	[this work] ^[22] [this work] [this work]
${}^{a}K_{I} = K_{IH}^{-1}$				

Table 3. Protonation equilibrium of indole in 0.5 mol L^{-1}

aqueous H₂SO₄ obtained by quantum mechanical calcula-



Figure 2. Protonation equilibria: Van't Hoff plot of protonation equilibrium constant in the range 288–318 K: $\Delta H = -13$ kJ mol⁻¹ and $\Delta S = -93$ J mol⁻¹ K

Evaluation of activity coefficients of indole, indole dimer and trimer in solution

Equation (5) is the thermodynamic definition of pK_{IH} of indole rewritten in the Mc activity function notation.^[46] The n_{bb} Mc term represents the activity coefficients of reagents and products where Mc is the activity coefficient function of the primary nitroanilines in H₂SO₄, while n_{bb} (n_{bb} = 1.152) is the specific coefficient of indole in sulfuric acid with respect to Mc function.^[46]

$$pK_{IH} = Log\left(\frac{c_2}{c_1c_H + \gamma_1\gamma_H +}\right) = Log\frac{c_2}{c_1c_H +} + n_{bb}Mc$$
(5)

The uncertainty on the protonation equilibria of indoles reflects the experimental evidence that oligomerization reactions may take place during equilibrium measurements, causing a poor reliability of the titration.^[10] Recently, we have investigated^[23] the indole protonation equilibrium by quantum chemical calculations obtaining computed values very close with the most recent experimental data. The calculated pK_{IH} value at 298 K is -2.54 being in close agreement with our previous evaluation of $pK_{\rm H}$ by using Mc acidity function.^[10] In addition, a temperature dependence of the equilibrium constants has been evaluated. Equations (2) and (3) allow the calculation of the concentration of (2), which is the electrophile to be taken into account in kinetic calculation. Furthermore, for the Mc function, it has been quantified a temperature dependence by an empirical relationship with respect to the Mc(298) (Eqn (6), which is the activity function measured at 298 K.^[46]

$$Mc(T) = \left(\frac{200}{T} + 0.03292\right)Mc(298)$$
(6)

The term ($\gamma_2/(\gamma_1 \gamma_{H^+})$), which represents the deviation from ideality of the solution, can be reduced to $(1/\gamma_1)$, if we consider that charged ions have comparable activity coefficients. This is acceptable in a range of sulfuric acid concentration where activity coefficients of the charged species are the function of the ionic strength (typically lower than 0.5 mol L⁻¹).^[47] From a molecular point of view, this means that each ion has similar interaction both with solvent molecules and with the other ions.^[46] For instance, in this range of concentrations, it is possible to reliably estimate the activity coefficient of ionic species in solution by correlation models for aqueous electrolytes, which are the function of the ionic.^[47]

As pointed out by several authors, ^[48,49] the activity coefficient of the uncharged species in diluted aqueous solution of sulfuric acid shows a typical salting-out effect, thus following the Sechenov relationship (Eqn (7)), where *b* is the Sechenov parameter characteristic of the indole and C_A is the concentration of sulfuric acid.^[49]

$$Log \gamma_1 = b C_A \tag{7}$$

Typically, Sechenov parameter is calculated by solubility data, but because of difficulty on the evaluation of the solubility of (1) in sulfuric acid because of the parallel oligomerization reaction, the evaluation of the Sechenov parameter for indole can be obtained by using the methods proposed by Yates and co-workers, who derived the values of the parameter (b = 1.5) by comparing H₀ and H₁ acidity functions.^[49] The comparison of the activity coefficients calculated by literature of Sechenov parameters at 298 K with those obtained from Mc activity function is reported in Table 4.^[49] The quite good agreement of the two methods (e.g. compare entries 1, 2 and 5) suggests that, at the concentration of

Table 4 diluted e	• Activity	coefficient of u	uncharged	molecules in
Entry	T (K)	Activity model	γ_1^a	Reference
1	298	Sechenov	0.75	[46]
2	288	Mc	0.676	This work
3	298	Mc	0.682	This work
4	308	Mc	0.687	This work
5	318	Mc	0.693	This work
^a γ ₂ / (γ ₁ γ	$v_{\rm H}$ +) $\approx 1 / \gamma_1$			

sulfuric acid and indole employed in the present study, a reliable evaluation of the activity coefficient of (1) can be obtained starting from the values of the Mc activity function. Furthermore, the Mc activity function has been calculated by titration of nitro-anilines measured at different temperatures,^[46] in this way, the temperature variation of the activity coefficients can be estimated by using Eqn (4). This method allows to obtain reliable behaviour of the activity coefficients for uncharged molecules of various nature if applied in a concentration range of sulfuric $(0-1 \text{ mol L}^{-1})^{[47]}$ acid where different charged species have practically the same activity coefficient. Large deviation can be encountered at higher acid concentration where the activity coefficients of charged species differ noticeably because of the lacking in the pure electrostatic nature of their interactions (between them and with the solvent).^[47]

As a matter of fact, also the activity coefficients of the equilibria of dimerization and trimerization can be calculated by using this method because the ionic strength of the media is the same and activity coefficient of the ionic species does not depend on the nature of the ions.

Dimerization and trimerization equilibria of indole

It has been pointed out that the oligomerization of (1) is reversible in aqueous acid at 298 K.^[10] This is quite singular features of this molecule because the starting indole is a weak base, while the oligomers (3) and (4) are fully protonated aliphatic amines, which are stabilized by solvation in acid aqueous solution.

Schemes 2 and 3 show dimerization and trimerization of (1). The resulting carbonium ion (2) is an electrophile that is able to attack the nonprotonated indole giving (3): the corresponding 3 substituted indole dimer (3-(indolin-2yl) indole (3); Scheme 2 and Eqn (8)). The latter is in protonated form, and it reacts further with



Scheme 2. Indole dimerization equilibrium



Scheme 3. Indole trimerization equilibrium

indole to the trimer (3,3'-(-2-aminophenethylidene) di-indole (**4**); Scheme 3 and Eqn (9). Besides, in H_2SO_4 0.5 mol L $^{-1}$, this compound is a fully protonated *ortho*-substituted alkyl-aniline, which does not react further with indole under the condition investigated.

$$K_D = \frac{C_3}{C_1 C_2} \frac{\gamma_3}{\gamma_2 \gamma_2} \tag{8}$$

$$K_T = \frac{C_4}{C_3 C_1} \frac{\gamma_4}{\gamma_3 \gamma_1} \tag{9}$$

Equations (8) and (9) show the thermodynamic constant of (**3**) and (**4**) formation, respectively. As pointed out in the previous section, the values of the activity coefficients of (**1**) in both equilibria of dimerization and trimerization (Eqns (8) and (9)) are considered equal to that of indole protonation equilibrium (Eqn (5)) and calculated by Eqn (10).

$$\frac{\gamma_2}{\gamma_1\gamma_H} = \frac{\gamma_3}{\gamma_1\gamma_2} = \frac{\gamma_4}{\gamma_1\gamma_2} = \frac{1}{\gamma_1} = 10^{n_{bb}M_c}$$
(10)

Such an evaluation of the activity coefficients holds because the value of the activity coefficient of the individual ionic species is approximately the function of the mere ionic strength and not of the type of ion.^[47] Starting from this hypothesis, the non ionic species (**1**) is the same in all equilibria; for this reason, the value of the activity coefficient term in each equilibrium relationship (Eqns (5), (8) and (9)) is constant, and it could be calculated from the Mc activity function value of sulfuric acid at the concentration of 0.5 mol L⁻¹, (Eqn (10)) and taking into account the specific n_{bb} values of indole (Table 4).

It is clear that the formation of the dimer depends on the protonation of (1) (Scheme 1, Eqn (5)); then, the value of K_D is the function of pK_{IH} , (1) and H⁺ concentrations, as well as to the activity coefficient term that could be considered equal to that of the equilibrium of indole protonation. In this way, we can rewrite Eqn (8) as Eqn (11), which is composed of all known terms, being c_1 and c_3 , the measured concentration of (1) and (3) at equilibrium and c_{H^+} is the H⁺ concentration, which derives from dissociations of sulfuric acid reported in literature,^[50,51] while the activity coefficient term is calculated from Mc and n_{bb} values.^[12,46] In the same way, the calculus of K_T is carried out by rewriting Eqn (9) as Eqn (12), where c_1 , c_3 and c_4 are the measured concentration of (1), (3) and (4), respectively, and the activity coefficients ratio, for the reasons explained in the previous section, is the same of Eqn (11).

$$K_{\rm D} = \frac{K_{\rm I}c_3}{c_1^2 c_{\rm H} + \gamma_1 \gamma_2} \frac{\gamma_3}{\gamma_1 \gamma_{\rm H} + \gamma_2} = \frac{K_{\rm I}c_3}{c_1^2 c_{\rm H} + \gamma_1} = 10^{2n_{bb}M_c}$$
(11)

$$K_T = \frac{c_4}{c_3 c_1} \frac{\gamma_4}{\gamma_3 \gamma_1} = \frac{c_4}{c_3 c_1} = 10^{n_{bb} M_c}$$
(12)

In Tables 5–8, the calculated values of the equilibrium constants of dimerization and trimerization at different temperatures, starting from indole, from dimer and from the trimer, are reported.

The results of Table 5–7 show that the K_D and K_T , measured starting from (1), (3) or (4), have a good reliability also by varying the temperature. This suggests that the variation of the starting substrate does not influence the final concentrations of (1), (3) and (4) because they reach the equilibrium without noticeable

Table 5.	Equilibria d	of (1) oligom	erization in 0.5 mol	L^{-1} aqueous H_2SO_4 i	n the range 2	288–318 K	
Т (К)	((10 ³ n	(1) nol L ⁻¹)	(3) (10 ³ mol L ⁻¹)	(4) (10 ³ mol L ^{-1})	γ^{-1}	$10^{5} K_{\rm D} ({\rm L mol}^{-1})$	$10^2 K_{\rm T} ({\rm L mol}^{-1})$
	to	t _{end}	t _{end}	t _{end}			
288	5.0	1.1	0.57	0.89	1.479	5.42	23.7
298	6.3	1.62	0.77	1.03	1.466	3.99	11.8
308	5.0	1.8	0.53	0.62	1.454	2.74	9.01
318	5.0	2.3	0.58	0.45	1.443	2.19	5.06
t _o , initial t	time; t _{end} , fi	nal time; the	e final time concent	ration is obtained fro	om the average	je of five independent r	neasurements.

Table 6.	Equilibria of (3) in 0.	5 mol L^{-1} ad	queous H ₂ S	O_4 in the range 288–	-308 K		
Т (К)	(1) (10^3 mol L^{-1})	(10 ³ m	3) ol L ⁻¹)	(4) (10 ³ mol L ^{-1})	γ^{-1}	$10^5 K_{\rm D}$ (L mol ⁻¹)	$10^2 K_{\rm T} ({\rm L mol}^{-1})$
	t _{end}	to	t _{end}				
288	0.82	1.02	0.32	1.48	1.479	5.39	22.9
298	0.98	1.01	0.26	1.47	1.466	3.88	11.6
308	1.2	1.04	0.2	1.45	1.454	2.66	9.12
t _o , initial ti	me; t _{end} , final time.						

Table 7.	quilibria of (4) in 0.	5 mol L $^{-1}$ aqueous H	₂ SO ₄ in the	range 288-	-308 K					
Т (К)	(1) (10 ³ mol L ⁻¹)	(3) (10 ³ mol L ⁻¹)) 10 ³ m	I) ol L ⁻¹)	γ^{-1}	$10^{5} K_{\rm D} ({\rm L mol^{-1}})$	$10^2 K_{\rm T} ({\rm L mol}^{-1})$			
	t _{end}	t _{end}	to	t _{end}						
288	0.81	0.20	0.99	0.41	1.479	5.31	22.9			
298	1.12 0.32 0.94 0.33 1.466 3.67 11.1									
308	1.14 0.29 1.0 0.21 1.454 2.65 8.91									
t _o , initial tir	me; t _{end} , final time.									

Table 8. Indole oligomerization averaged equilibrium con-
stant at different temperatures

T (K)	$10^5 K_{\rm D} ({\rm Lmol}^{-1})$	10 ⁵ SD	$10^2 K_{\rm T} ({\rm Lmol}^{-1})$	10 ² SD
288	5.37	±0.18	23.2	±2.1
298	3.85	±0.18	11.5	±1.2
308	2.68	±0.19	9.01	±1.7
318	2.19	±0.36	5.06	±1.1
The int	ervals of confidenc	e of $K_{\rm D}$ ar	nd K _T at 318 K are c	btained

taking into account only the measurements for indole.

parasitic reactions. To say the truth, a perceptible colouration of the solution is observed at the higher temperature after quite long time (after 20 h), but the concentration of the dyed substances is below the experimental error and for the sake of simplicity neglected. Table 8 reports the averaged values of the equilibrium constants of dimerization and trimerization employed in the nonlinear regression of the kinetics.

Figure 3 shows the Van't Hoff plot of dimerization and trimerization equilibrium constants in the range 288-318 K. It is interesting to observe that ΔH of reaction of dimer and trimer formation $(-24 \text{ and } -37 \text{ kJ mol}^{-1}, \text{ respectively})$ is compatible with literature data.^[52] On the contrary, the large difference of ΔS (28 and $-65 \,\text{J}\,\text{mol}^{-1}$ K, respectively) between dimer and trimer is not easily explainable especially because dimerization shows a positive ΔS , although there is a reduction of mole numbers, which is, from thermodynamic point of view, not a common behaviour. As a matter of fact, this positive value in the variation of entropy observed for the dimerization equilibrium can be ascribed to the large variation of entropy observed in the protonation equilibrium of indole, which is responsible for the large decrease of the global entropy of the reaction. In other words, the change of nature of the ion may explain this behaviour because (2) is a carbonium ion, while (3) is an ammonium salt. It is likely that the stabilization of the carbonium ion (2) requires a number of water of solvation larger than those needing for (3). On the contrary, the negative variation of entropy of (4) from (3) is in agreement with the overall mole reduction because of the addition of (3) to (1). In this case, it is likely that the



Figure 3. Dimerization and trimerization equilibria: Van't Hoff plot of dimerization and trimerization equilibrium constants in the range 288–318 K. Dimerization: $\Delta H = -24 \text{ kJ mol}^{-1}$ and $\Delta S = 28 \text{ J mol}^{-1} \text{ K}$; trimerization: $\Delta H = -37 \text{ kJ mol}^{-1}$ and $\Delta S = -65 \text{ J mol}^{-1} \text{ K}$

solvation grade of (**3**) and (**4**), which are both protonated amines, slightly influences the overall entropy variation.

Kinetics of indole oligomerization

Figure 4 shows the time versus concentration profile at 288 K of indole oligomerization. The formation of (**4**) is much slower than that of (**3**); however, the latter cannot be considered at stationary state. As a matter of fact, the reactivity of the dimer shows measurable reaction rate in reaching equilibrium as can be observed in Fig. 5 where the reactivity of the dimer at 308 K is reported. The reactivity of (**4**) at 288 K is reported in Fig. 6. It is evident that (**4**) reacts to give (**1**) and (**3**) at measurable reaction rate. This suggests that a kinetic scheme that take into account of all the stage of the reaction needs to give a reliable fitting of the experimental data.

These considerations, however, were already present in the preliminary study, and the kinetic model proposed in that preliminary paper is now tested at different temperatures.^[10] The kinetic model is a straight formulation of the equilibria in terms of reaction rate by considering that the reverse kinetic constants are obtained from the direct one divided by the respective equilibrium constant measured at infinite time of reaction, that is, $k_{DR} = k_D/K_D$ and $k_{TR} = k_T/K_T$. Equations (11)–(13) are the



Figure 4. Time versus concentration profiles of indole oligomerization. Run conditions: T 288 K and H₂SO₄ 0.5 mol L⁻¹. Δ = (1), \circ = (3), \Box = (4)



Figure 5. Time versus concentration profiles of (**3**) reactivity in H_2SO_4 0.5 mol L⁻¹. Run conditions: T 308 K and H_2SO_4 0.5 mol L⁻¹. Δ = (**1**), \circ = (**3**), \Box = (**4**)



Figure 6. Time versus concentration profiles of (4) in H_2SO_4 0.5 mol L⁻¹. Run conditions: T 288 K and H_2SO_4 0.5 mol L⁻¹. $\Delta = (1)$, $\circ = (3)$, $\Box = (4)$

mathematical formulation of the kinetic model, and the results of the fitting of these simultaneous equations with experimental data are reported in Table 9.

$$-\frac{dc_1}{dt} = k_D c_1 c_2 - k_{DR} c_3 + k_T c_1 c_3 - k_{TR} c_4$$
(13)

$$\frac{dc_4}{dt} = k_T c_3 c_1 - k_{TR} c_4 \tag{14}$$

$$c_1^0 + 2c_3^0 + 3c_4^0 = c_1 + c_2 + 2c_3 + 3c_4$$
(15)

The measured values of the kinetic constants k_D and k_T at different initial concentrations of indole, as well as those obtained starting from (**3**) and (**4**), are quite in good agreement (at 298 K, k_D k_T are in the range 380–510 and 0.094–0.098 L mol⁻¹ s⁻¹, respectively). Similar results are observed at 288, 308 and 318 K, thus suggesting that the kinetic constants are barely the function of the temperature and not to the starting substrate, almost in the limit of the experimental error. As a matter of fact, the kinetic constant calculated by fitting the simultaneous Eqns (11)–(13) with time versus concentration profile of the reactivity of (**1**), (**3**) and (**4**) gave similar values suggesting a good reliability of the model (Table 9). In

Table 9.	Kinetic constan	its calculated by	y nonlinear fitting of the	e experimental data					
10 ³ init concentr (mol L	tial ation ⁻¹)	Т (K)	k_D (L mol ⁻¹ s ⁻¹)	$10^3 k_{DR} (s^{-1})$	k_T (L mol ⁻¹ s ⁻¹)	$10^4 k_{7R} (s^{-1})$	е k _D a	10 ³ ɛk ⁷ ª	10 ⁸ o ²
(1)	3.0	298	410	1.06	0.1	0.84	3.1	1.1	2.4
(1)	5.0	298	450	1.17	0.096	0.81	2.4	1.2	2.8
(1)	6.3	298	380	0.99	0.089	0.75	2.9	1.3	2.6
(1)	5.0	288	360	0.67	0.07	0.30	2.1	1.3	1.8
(1)	5.0	298	450	1.17	0.096	0.81	2.4	1.2	3.2
(1)	5.0	308	876	3.27	0.15	1.65	3.4	1.4	8.5
(1)	5.0	318	1200	5.48	0.21	4.15	4.1	1.8	3.6
(3)	0.97	288	400	0.74	0.068	0.29	1.9	1.1	2.1
(3)	1.01	298	500	1.30	0.094	0.81	2.5	1.3	2.7
(3)	1.02	308	006	3.36	0.14	1.54	3.0	1.6	3.4
(4)	0.94	288	280	0.52	0.070	0.30	2.1	1.3	1.9
(4)	0.89	298	510	1.32	0.098	0.83	2.8	1.4	2.8
(4)	0.92	308	780	2.91	0.16	1.76	3.2	1.5	3.1
^a The error	of the regression	on variables (k_D	, and k_T) is calculated by	numerical evaluation c	of the first derivatives of t	he σ^2 function. The val	ues of the corre	sponding correla	tion matrix
are compr	lised between L	0.15 and 0.54.							

Activation parameters

In Figs 7 and 8, the Eyring plot of k_D , k_T , k_{DR} and k_{TR} is reported. The corresponding activation parameters are evaluated by fitting the linearized Eyring–Evans–Polanyi equation (Eqn (16)).

$$RLn\frac{k}{T} = -\Delta H^{\ddagger}\frac{1}{T} + RLn\frac{k_B}{h}\Delta S^{\ddagger}$$
(16)

Journal of Physical Organic Chemistry

As expected, the enthalpy of activation of the direct reactions is lower than that of the reverse ones because of the enthalpy of reaction of dimerization and trimerization that is summed to that of the activated state. An interesting feature is, however, the values of the entropy of activation that are negative both for direct and reverse reactions. This suggests that the formation of (**3**) and (**4**), which both cause a reduction of the overall number of moles, is anyway accompanied by a negative variation of the entropy of the respective activated complexes because of their solvation. It is likely that the activated complexes are in highly solvated state; in this way, it is reasonable to account a negative ΔS^{\ddagger} also in the reverse reaction because of the large number of



Figure 7. Evring plot of dimerization and trimerization direct kinetic constant: $\Delta H_{kD}^{\dagger} = 33 \text{ kJ mol}^{-1}$, $\Delta S_{kD}^{\dagger} = -83 \text{ J mol}^{-1} \text{ K}^{-1}$, $\Delta H_{kT}^{\dagger} = 29 \text{ kJ mol}^{-1}$ and $\Delta S_{kT}^{\dagger} = -169 \text{ J mol}^{-1} \text{ K}^{-1}$. $\Box = \text{RLn } k_{D}$, $\circ = \text{RLn } k_{T}$



Figure 8. Eyring plot of dimerization and trimerization reverse kinetic constant: $\Delta H_{kDR}^{+} = 57 \text{ kJ mol}^{-1}$, $\Delta S_{kDR}^{+} = -108 \text{ J mol}^{-1} \text{ K}^{-1}$, $\Delta H_{kTR}^{+} = 65 \text{ kJ} \text{ mol}^{-1}$ and $\Delta S_{kTR}^{+} = -109 \text{ J mol}^{-1} \text{ K}^{-1}$. $\Box = \text{RLn } k_{DR}$, $\circ = \text{RLn } k_{TR}$

G. QUARTARONE ET AL.

water necessary for stabilizing the activated state by solvation. Then, the entropy of the activated complex is lower than that of both reagent and products because of the much ordered structured of the highly solvated transition state. This is confirmed by the constancy of ΔS^{\dagger}_{kDR} and ΔS^{\dagger}_{kTR} relative to the reverse reactions of dimerization and trimerization, respectively (Fig. 8). In fact, it is to be emphasized that both products ((**3**) and (**4**)) and transition states should have similar molecular structure, but they should differ for the respective solvation environment.

CONCLUSIONS

The main thermodynamic and kinetic parameters of indole oligomerization in 0.5 mol L^{-1} H₂SO₄ have been measured here. Calculation of both equilibria and kinetics of oligomerization are based on the values of the protonation equilibria of indole evaluated at different temperatures by using a computational approach, by which a reliable value of pK_{IH} has been calculated taking into account the experimental one at 298 K. In this way, activation parameters relative to the Eyring-Evans-Polanyi equation of indole protonation have been calculated. Besides, it appears that solvation of reagent, products, intermediates and transition plays a role of paramount importance in the overall behaviours of the system. It is noteworthy that the entropy of formation of (3) is positive despite of the reaction formerly proceeds with reduction of mole number, thus suggesting a strong influence of solvation between reagent and product. On the contrary, from (3) to (4), entropy variation is negative following the expected behaviour. Furthermore, the important role of solvation is clear also from the kinetics point of view. As a matter of fact, the negative entropy variations of the transition states evidenced by the Eyring-Polanyi equation relative to the kinetic constant of dimerization and trimerization (k_D and k_T , direct kinetic constant and k_{DR} and k_{TR} , the reverse ones), suggest the formation of a highly solvated activated complexes whose complex solvation environment in a highly ordered state, explain this behaviour. Indole backbone is present in a large variety of biologically active molecules; for this reason, a detailed study of the thermodynamic and kinetic properties of their reactions may be of aid for the comprehension of several complex biological path.

Acknowledgement

Financial support by Ca' Foscari University of Venice is gratefully acknowledged (ADIR fund 2012).

REFERENCES

- G. Penieres-Carrill, J. G. Garcia-Estrada, J. L. Gutierrez-Ramirez, C. Ivarez-Toledano, *Green Chem.* 2003, *5*, 337.
- [2] A. M. Restivo, A. A. Arslan, G. L. Goldberg, Obstet. Gynecol. 2005, 105, 455–465.
- [3] R. J. Sundberg, Indoles, Academic Press, San Diego CA, 1996.
- [4] N. Robertson, S. Parsons, E. J. MacLean, R. A. Coxall, A. R. Mount, J. Mater. Chem. 2000, 10, 2043–2047.
- [5] N. Otero, M. Mandado, R. A. Mosquera, J. Phys. Chem. A 2007, 111, 5557–5562.
- [6] G. Quartarone, T. Bellomi, A. Zingales, Corros. Sci. 2003, 45, 715–733.
- [7] G. Quartarone, L. Bonaldo, C. Tortato, Appl. Surf. Sci. 2006, 252, 8251–8257.
- [8] M. Düdükcü, F. Koleli, Prog. Org. Coat. 2006, 55, 324-329.

- [9] A. Popova, M. Christov, A. Zwetanova, Corros. Sci. 2007, 49, 2131–2143.
- [10] G. Quartarone, L. Ronchin, C. Tortato, A. Vavasori, Int. J. Chem. Kin. 2009, 41, 108–112.
- [11] R. L. Hinman, J. Lang, J. Am. Chem. Soc. 1964, 86, 3796–3806.
- [12] N. C. Marziano, G. Cimino, R. Passerini, J. Chem. Soc, Perkin Trans. II 1973, 1915–1921.
- [13] H. Ishii, K. Murakami, E. Sakurada, K. Hosoya, Y. Murakami, J. Chem. Soc. Perkin Trans. I 1988, 2377–2385.
- [14] Y. Wu, W. G. Lobeck, Jr., R. P. Ryan, J. Med. Chem. 1972, 15, 529–534.
- [15] B. Oddo, Gazz. Chim. Ital. 1913, 43, 385-391.
- [16] O. Schmitz-Dumont, Ber. Deut. Chem. Ges. **1930**, 63, 323–329.
- [17] W. E. Noland, C. F. Hammer, J. Org. Chem. 1960, 25, 1525–1535.
- [18] B. Pal, V. S. Giri, P. Jaisankar, Catal. Commun. 2005, 6, 711–715.
- [19] F. Terrier, M. J. Pouet, J. C. Halle, S. Hunt, J. R. Jones, J. Chem. Soc, Perkin Trans. II 1993, 1665–1672.
- [20] H. A. Albar, A. S. Shavali, M. A. Abdaliah, Can. J. Chem. 1993, 71, 2144–2149.
- [21] S. Lakhdar, M. Westermayer, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, J. Org. Chem. 2006, 71, 9088–9095.
- [22] V. Bocchi, G. Palla, Tetrahedron 1986, 42, 5019-5024.
- [23] A. Pietropolli Charmet, G. Quartarone, L. Ronchin, C. Tortato, A. Vavasori, J. Phys. Chem. A 2013, 117, 6846–6858.
- [24] M. A. V. Ribeiro da Silva, J. I. T. A. Cabral, J. R. B. Gomes, J. Phys. Chem. A 2008, 112, 12263–12269.
- [25] D. M. Bates, D. G. Watts, Non linear regression analysis & its applications, John Wiley & Sons, Hoboken, NJ, USA, 1988.
- [26] B. C. Garrett, M. J. Redmon, R. Steckler, D. G. Truhlar, K. K. Baldridge, D. Bartol, M. W. Schmidt, M. S. Gordon, *J. Phys. Chem.* **1988**, *92*, 1476–1488.
- [27] J. H. Mathews, Numerical methods for computer science, engineering and mathematics, Prentice-Hall international, London, 1987.
- [28] a) J. M. Martin, T. L. Lee, P. R. Taylor, J.-P. François, J. Chem. Phys. 1995, 103, 2589–2602; b) A. Pietropolli Charmet, N. Tasinato, P. Stoppa, S. Giorgianni, A. Gambi, *Mol. Phys.* 2011, 109, 2163–2172; c) V. Barone, J. Chem. Phys. 2005, 122, 014108; d)A. Pietropolli Charmet, P. Stoppa, N. Tasinato, S. Giorgianni, V. Barone, M. Biczysko, J. Bloino, C. Cappelli, I. Carnimeo, C. Puzzarini, J. Chem. Phys. 2013, 139, 164302.
- [29] K. Raghavachari, G. W. Trucks, J. A. Pople, M. Head-Gordon, Chem. Phys. Lett. **1989**, 157, 479–483.
- [30] A. V. Marenich, R. M. Olson, C. P. Kelly, C. J. Cramer, D. G. Truhlar, J. Chem. Theory Comput. 2007, 3, 2011–2033.
- [31] A. D. Becke, J. Chem. Phys. 1993, 98, 5648-5652.
- [32] a) T. H. Dunning, Jr., J. Chem. Phys. 1989, 90, 1007–1023; b) D. E.
 Woon, T. H. Dunning, Jr. J. Chem. Phys. 1993, 98, 1358–1371.
- [33] A. C. Chamberlin, C. J. Cramer, D. G. Truhlar, J. Phys. Chem. B 2008, 112, 3024–3039.
- [34] M. Gupta, E. F. da Silva, H. F. Svendsen, J. Phys. Chem. B 2012, 116, 1865–1875.
- [35] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, *et al. Gaussian 09, Revision C.01*, D. J. Gaussian, Inc., Wallingford CT, **2009**.
- [36] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, *et al. J. Comput. Chem.* **1993**, *14*, 1347–1363.
- [37] a) M. S. Gordon, M. W. Schmidt, Advances in electronic structure theory: GAMESS a decade later, in: *Theory and Applications of Computational Chemistry: the first forty years* (Eds: C. E. Dykstra, G. Frenking, K. S. Kim, G. E. Scuseria), Elsevier, Amsterdam, **2005**, 1167–1189; b) M. Higashi, A. V. Marenich, R. M. Olson, A. C. Chamberlin, J. Pu, C. P. Kelly, J. D. Thompson, J. D. Xidos, J. Li, T. Zhu, *et al.* G. GAMESSPLUS version 2010-2, University of Minnesota, Minneapolis, **2010**.
- [38] C. A. Ramsden, J. A. Joule, V. V. Zhdankin in: *Handbook of Heterocy-clic Chemistry* (Ed: A. R. Katritzky), 3rd edn, Elsevier Science, Oxford, 2010, 394–397.
- [39] B. S. Andonowski, G. M. Stojkovich, Acta Chim. Slov. 2000, 47, 349–358.
- [40] G. Berti, A. Da Settimo, D. Segnini, Gazz. Chim. Ital 1961, 91, 571–579.
- [41] K. M. Ervin, V. F. De Turo, J. Phys. Chem. A 2002, 106, 9947–9956.
- [42] F. C. Pickard, D. R. Griffith, S. J. Ferrara, M. D. Liptak, K. N. Kirschner, G. C. Shields, *Int. J. Quantum Chem.* **2006**, *106*, 3122–3128.
- [43] D. M. Mc Quarrie, Statistical Mechanics, Harper and Row, New York, 1970, 86.
- [44] Y. Zhao, D. G. Truhlar, Theor. Chem. Acc. 2008, 120, 215–241.

- [45] A. C. Chamberlin, C. J. Cramer, D. G. Truhlar, J. Phys. Chem. B 2008, 112, 8651–8655.
- [46] N.C. Marziano, A. Tommasin, C. Tortato, P. Isandelli, J. Chem. Soc, Perkin Trans. II 1998, 2535–2540.
- [47] X. Ge, X. Wang, J. Chem. Eng. Data 2009, 54, 179–186.
- [48] E. M. Arnett, J. J. Burke, J. V. Carter, C. F. Douty, J. Am. Chem. Soc. 1972, 94, 7837–7852.
- [49] K. Yates, H. Wai, G. Welch, R. A. Mc Clelland, J. Am. Chem. Soc. 1973, 95, 418–426.
- [50] E. B. Robertson, H. B. Dunford, J. Am. Chem. Soc. 1964, 86, 5080.
- [51] H. Chen, D. E. Irish, J. Phys. Chem. 1971, 75, 2672.

[52] F. J. Hoyuelos, B. García, S. Ibeas, M. S. Muñoz, A. M. Navarro, I. Peñacoba, J. M. Leal, *Eur. J. Org. Chem.* **2005**, 2005, 1161.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website.