



A NEW SIMPLE METHOD FOR THE pK_a EVALUATION OF BRØNSTED ACIDS

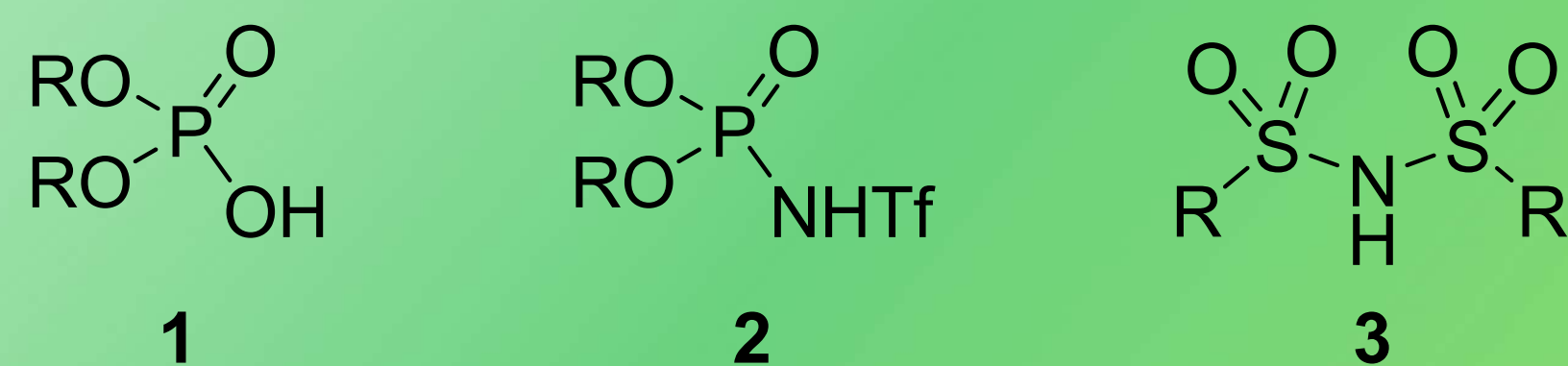
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Introduction

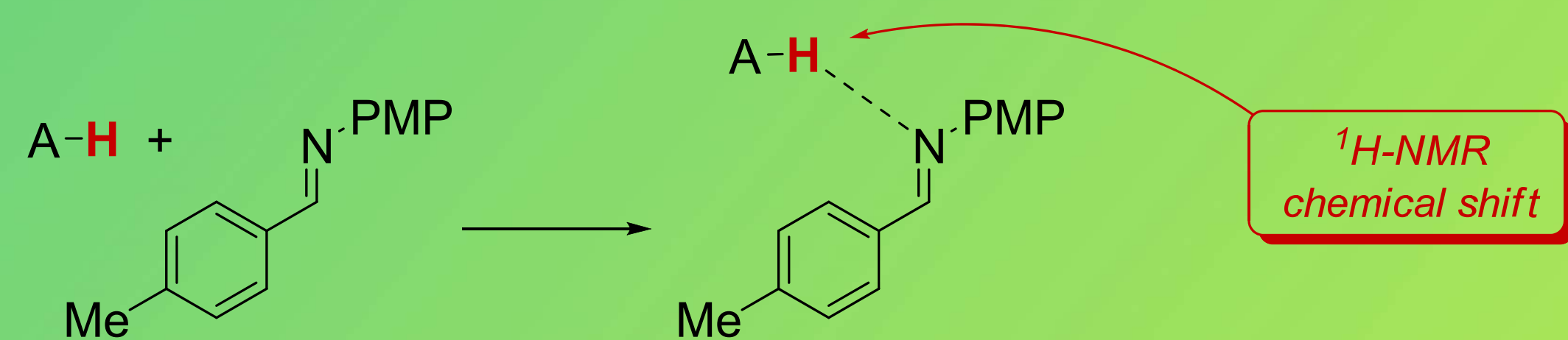
Over recent years, chiral Brønsted acid catalysis has emerged as a fast growing branch of asymmetric organocatalysis. Phosphoric acids (**1**), *N*-triflyl phosphoric amides (**2**) and bis(sulfonyl)imides (**3**) were introduced aiming to develop species of significantly higher acidity in order to access the activation of a wider range of substrates.



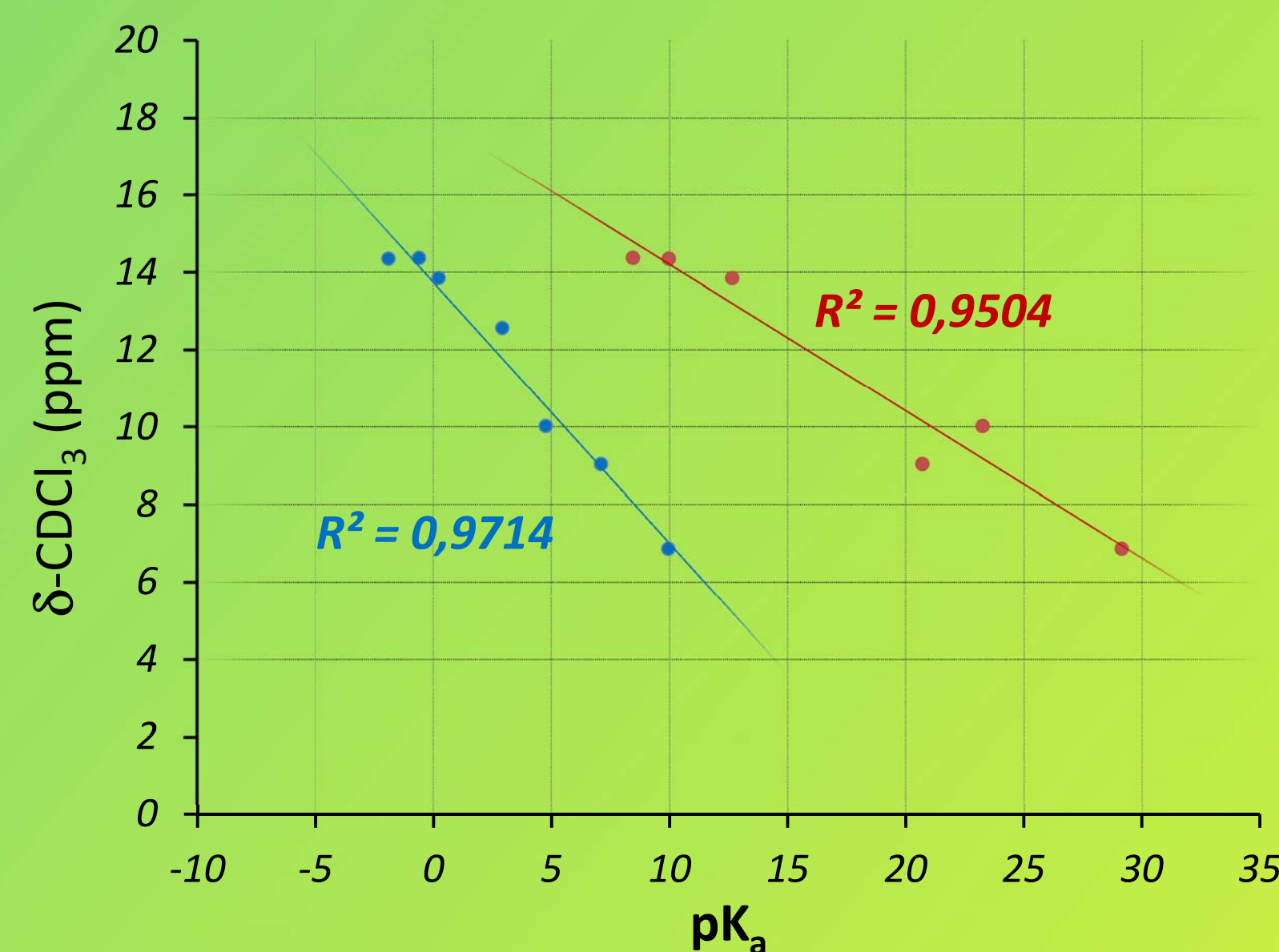
First efforts in the determination of a pK_a scale in DMSO of strong chiral Brønsted acids were reported by Berkessel et al. in 2010.^[1] Three years later Rueping and Leito proposed a UV-Vis spectroscopic method for evaluating pK_a scale in acetonitrile of the same classes of compounds, introducing also a correlation between acidity and catalytic activity.^[2] However, a more straightforward method for a quick determination of the relative acidity and reactivity of these compounds is still highly desirable; in this context, our aim is to develop a simple ¹H-NMR-based method.

Why a NMR method? Preliminary results

In the '70s Gutmann^[3] reported the establishment of a Lewis acidity scale through the measurement of the ³¹P-NMR shifts of the complexes between several Lewis acids and a Lewis base (tributylphosphine oxide). Similarly, it should be possible to achieve a Brønsted acidity/basicity scale using a Brønsted pair instead of a Lewis pair. Starting from these considerations, we have found that the ¹H-NMR shifts of complexes of several Brønsted acids **A-H** with an imine (**4**) in chloroform, present a linear correlation with respect to the Brønsted acids' pK_a values in water.



Acid	pK _a (H ₂ O)	pK _a (MeCN)	δ (ppm)
MsOH	-1,90	9,97	14,35
TsOH	-0,60	8,45	14,37
TFA	0,23	12,65	13,85
CF ₃ CH ₂ CO ₂ H	2,92	-	12,57
AcOH	4,76	23,25	10,02
<i>p</i> -NO ₂ -PhOH	7,10	20,70	9,04
PhOH	9,95	29,14	6,87



Results and discussion

Encouraged by this very preliminary results we investigated the behavior of the mentioned classes of compounds: phosphoric acids (**1a-c**), *N*-Triflyl phosphoric amide (**2a**) and bis(sulfonyl)imide (**3a**). The chemical shifts of the acidic proton of the complexes of imine **4** with thirteen different acidic species are reported below. The three used solvents (chloroform, acetonitrile and benzene) are representative of the most commonly used solvents in Brønsted acid catalysis.

Interesting considerations may be done on the observed values of chemical shifts:

- in chloroform phosphoric acids (15.3-15.9 ppm) seem to be more acidic than TFA (13.85), differently from the reported data in water; in benzene the same behavior as in chloroform is observed; in acetonitrile they have comparable acidity values;
- in acetonitrile a very good correlation between the literature pK_a values and experimental chemical shifts is observed, except for sulfonylimides **3a**;
- In chloroform *N*-Triflyl phosphoric amide **2a** and bis(sulfonyl)imide **3a** show an unexpected behavior: from the observed shifts (12.86 and 12.36 respectively) they should be considered weaker acids than TFA (13.85) and phosphoric acids (15.3-15.9 ppm); these results are clearly in contrast with the reported literature pK_a values in acetonitrile.

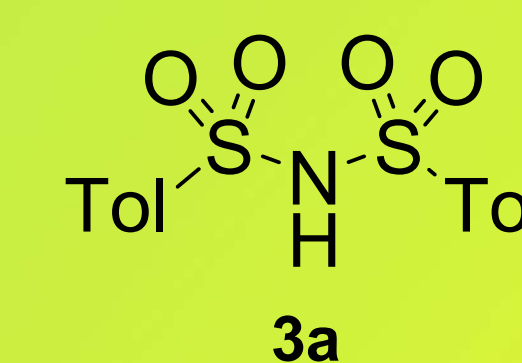
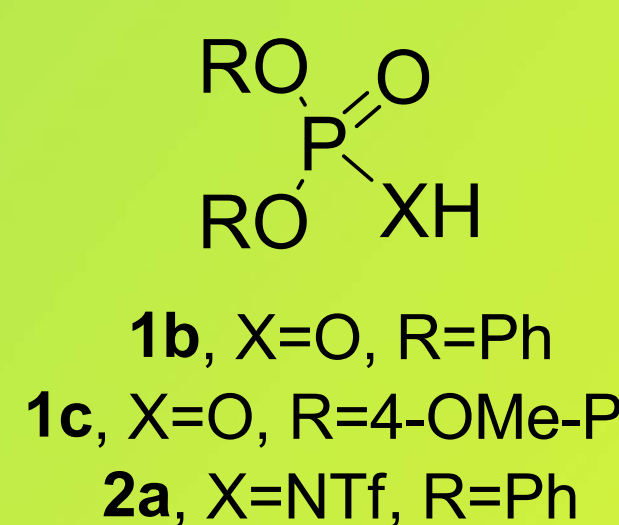
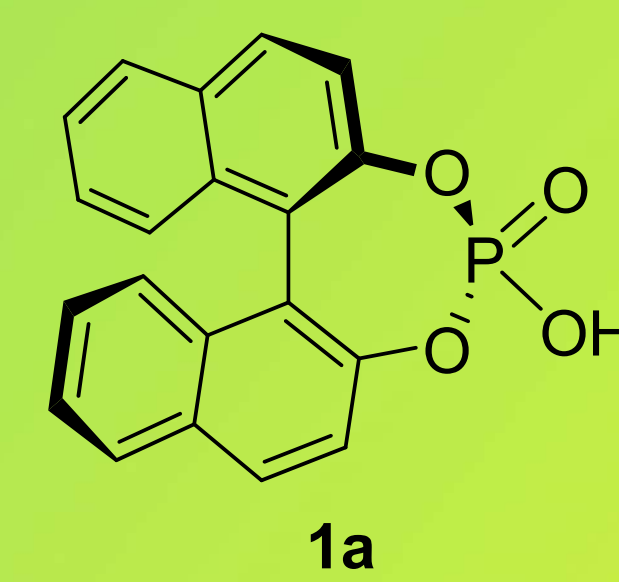
An explanation for the lower shift values for the two stronger acids (**2a** and **3a**) respect to phosphoric acids could be found in a recent work by Rueping and Gshwind,^[4] where a low temperature characterization of the complex between **1b** and an imine shows the presence of three species:

Acid	pK _a		δ (ppm)		
	(H ₂ O)	(MeCN)	CDCl ₃	AN-d ₃	PhH-d ₆
TfOH	-11,9	2,6	9,12	12,5	↓
MsOH	-1,9	9,97	14,35	↓	↓
TsOH	-0,6	8,45	14,37	↓	↓
TFA	0,23	12,65	13,85	13,43	↓
CF ₃ CH ₂ CO ₂ H	2,92	-	12,57	8,37	12,7
AcOH	4,76	23,25	10,02	9	11,9
<i>p</i> -NO ₂ -PhOH	7,1	20,7	9,04	8,19	8,76
PhOH	9,95	29,14	6,87	-	↓
1a	-	12.5-14*	15,37	↓	15,67
1b	1,9	12.5-14*	15,82	13,19	16,09
1c	-	12.5-14*	15,34	13,48	15,83
2a	-	6.3-6.9*	12,86	14,07	13,63
3a	-	12,0	12,36	10,38	↓

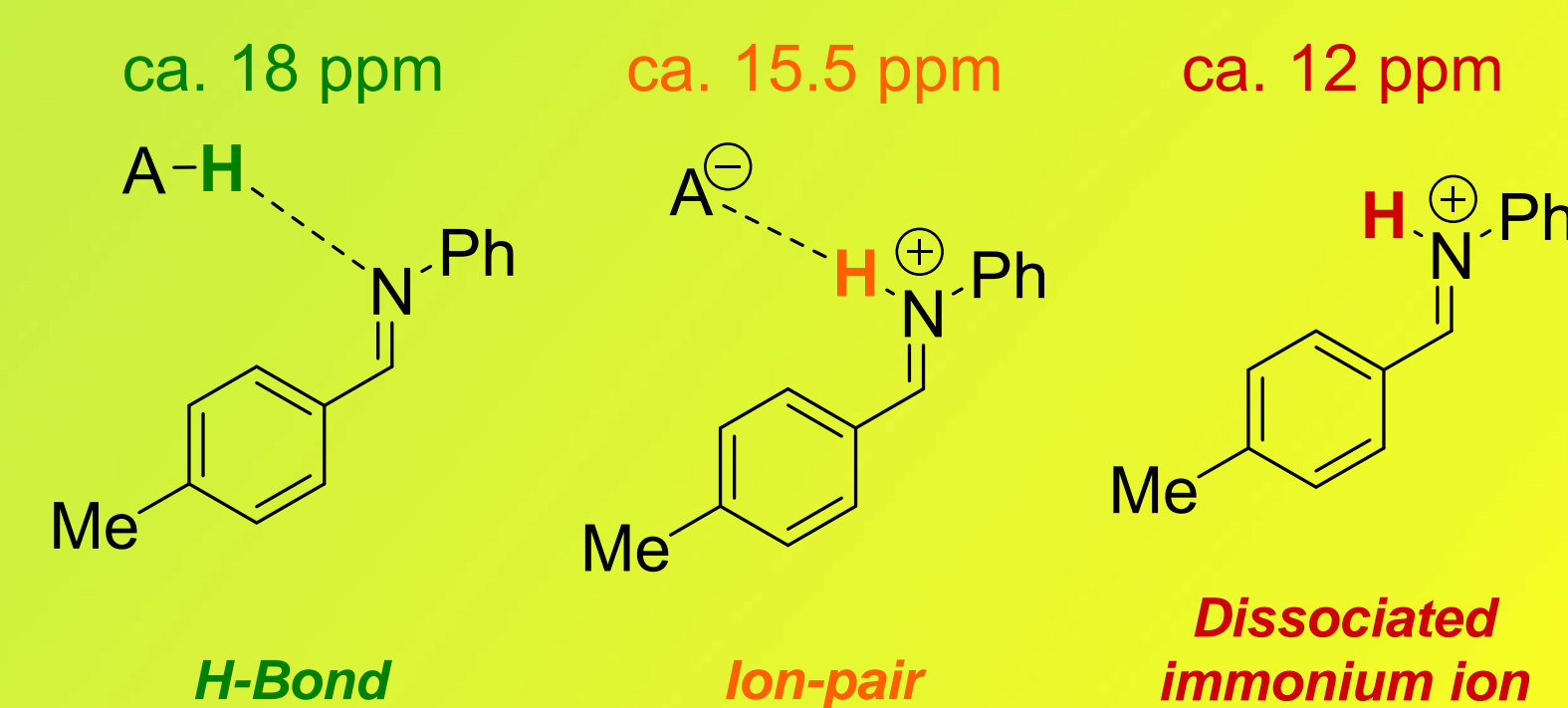
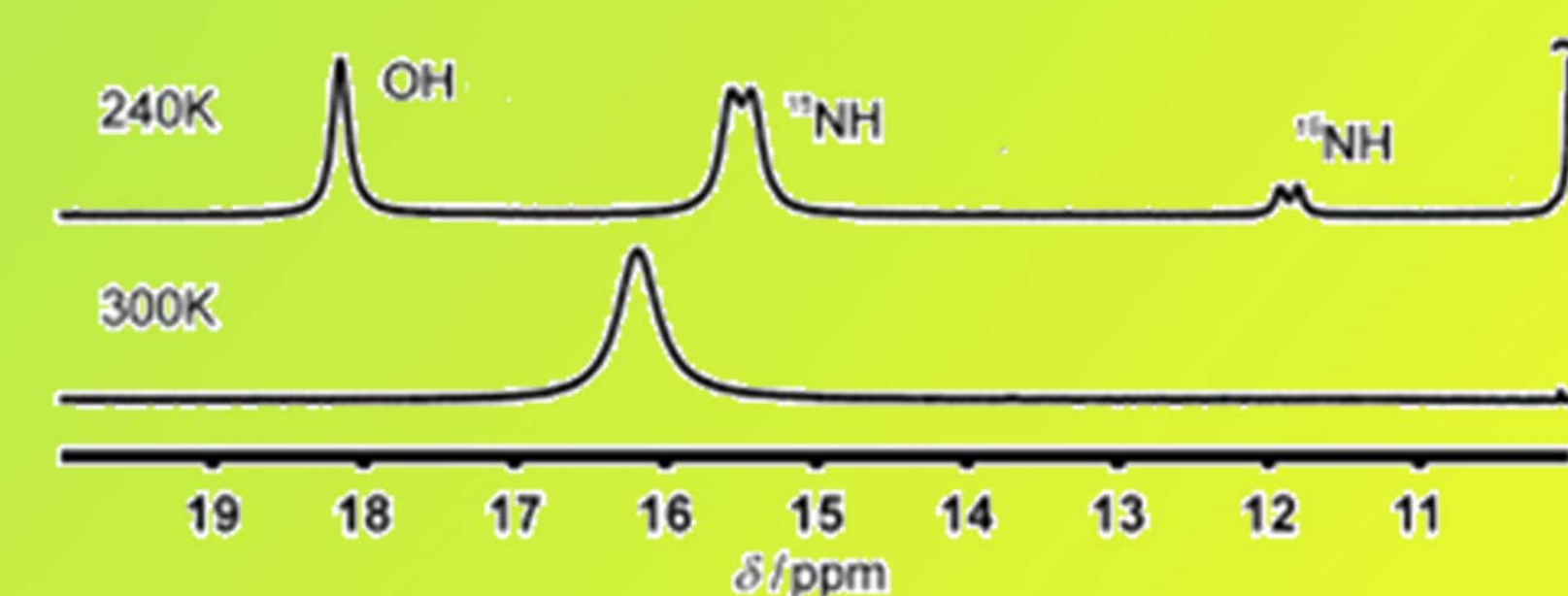
*) General values for phosphoric acids.

**) General values for *N*-Triflyl phosphoramides.^[2]

↓) The imonium salt is insoluble.

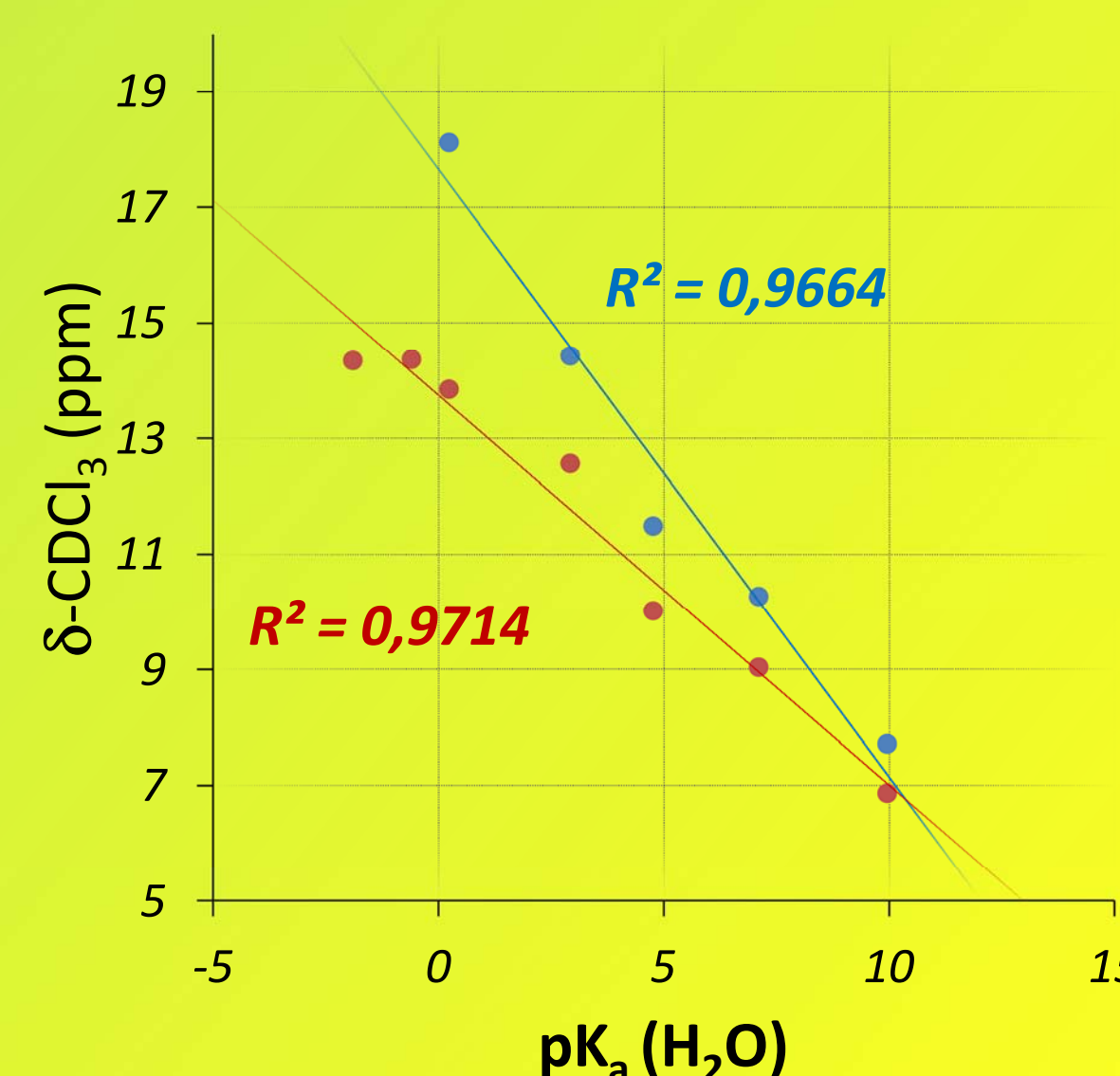


the two main peaks were due to the H-bond and to the ion-pair complexes (18 and 15.5 ppm respectively), whereas the third more little peak was due to the dissociated imonium cation (12 ppm). Since all these three species contribute to the averaged room temperature peak, we could hypothesize that a very strong acid characterized by a counterion prone to solvation will give a substantial amount of imonium ion responsible of the shifting of the NMR signal to high fields.



To extend the validity of the method and to verify the obtained results, pyridine was used instead of imine **4** as base. The data relative to the pyridinium complexes in chloroform are compared to the previous data for iminium salts in the graph and in the table reported below.

It is noteworthy that the anomalous behavior observed for the *N*-Triflyl phosphoric amide **2a** and the bis(sulfonyl)imide **3a** was confirmed also using pyridine as Brønsted base in NMR experiments.



Acid	pK _a		δ (ppm) CDCl ₃	
	(H ₂ O)	(MeCN)	Imine 4	Py
TfOH	-11.9	2.6	9.12	↓
MsOH	-1.9	9.97	14.35	↓
TsOH	-0.6	8.45	14.37	↓
TFA	0.23	12.65	13.85	18.12
CF ₃ CH ₂ CO ₂ H	2.92	-	12.57	14.43
AcOH	4.76	23.25	10.02	11.49
<i>p</i> -NO ₂ -PhOH	7.1	20.7	9.04	10.27
PhOH	9.95	29.14	6.87	7.72
1a	-	12.5-14*	15.37	↓
1b	1.9	12.5-14*	15.82	17.89
1c	-	12.5-14*	15.34	17.05
2a	-	6.3-6.9*	12.86	16.39
3a	-	12.0	12.36	15.32

Future developments

We are now extending the study to a greater number of acids. Furthermore we are still investigating the nature of the NMR signal through low temperature NMR experiments in order to verify the exposed hypothesis with respect to the behavior of the stronger Brønsted acids. In the attempt to find a correlation between the chemical shift and the catalytic activity of the acidic species, kinetic studies of several reactions are currently in progress.