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Alkylation of substituted phenols in DMF by MeI using TMGN (*bis*-1,1,8,8-(tetramethylguanidino)naphtalene) a proton sponge as base: a kinetics study by NMR spectroscopy.

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Abstract: Evaluation of a new proton sponge, *bis*-1,1,8,8-(tetramethylguanidino)naphtalene (TMGN), in substituted phenols *O*-alkylation by methyl iodide in DMF has been studied. Kinetic measurements were performed in *N,N*-dimethylformamide-*d7* and followed by ^{1}H NMR using stoichiometric amounts of reagents. Plot of the results shows that the reaction follows an almost perfect second order rate law. However the Hammett plots for substituted phenols are not linear but bell shaped. In order to separate the deprotonation and alkylation contribution to the kinetics, deprotonation of phenols by TMGN has been investigated by quantitative ^{13}C NMR. By combining these data a linear Hammett plot with a negative slope was obtained for the alkylation step and substituted phenol acidity constants in DMF, not accessible by NMR measurements, were determined which are in agreement with literature data.

Introduction

The functionalization of natural molecules plays an important role with the aim of obtaining new biologically active molecules. In the continuity of our laboratory's work, we decided to look for original methods for polyphenol selective *O*-alkylations. Classical approach generally requires numerous protection and deprotection steps.[1] Recent results from our lab, based on the use of microreactor technology, allowed us to selectively alkylate quercetin, a natural polyphenol, when the base is mixed with the alkylating reagent.[2] Phenol ether are usually synthesized under basic conditions following Williamson synthesis.[3] However Williamson synthesis using mineral bases is hazardous to apply in a microreactor of micrometric capillary size as the low solubility of such bases in organic solvents led to clogging. An alternative method based on more soluble but weaker organic bases is more adapted to micrometric flow reactor; 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) and tetrabutylammonium hydroxide are for example two appropriate organic bases.

Phenolates, obtained by deprotonation of the hydroxyl group by a strong base, are good nucleophiles. Considering that deprotonation step is complete, the phenolate alkylation is usually considered as the rate-determining step. For primary halides the *O*-alkylation step follows a SN_2 mechanism. Sodium phenolate alkylation with methyl iodide in dry sulfolane demonstrated faster kinetics

rates for electron donating group than for electron withdrawing groups.[4] The kinetics plot are correlated by Hammett with a negative slope (ρ = -1.1).[5] Phenol alkylation by ethyl iodide in acetonitrile has been kinetically studied by Kondo *et al.* on pre-formed phenolates and the data also are correlated by a Hammett plot with negative slope (ρ = -1.39).[6] Preparation of the corresponding phenolate anion was achieved by phenols deprotonation from tetramethylammonium hydroxide solution. Strong basicity of hydroxide base gives access to a completely deprotoned phenolate form while ammonium counterion assures a high solubility in organic solvents and a loose ion-pair. However tetrabutylammonium hydroxide is available only in protic solvents like water or methanol and the reaction of phenol with tetrabutylammonium hydroxide produce a molecule of water, which both hampers the reactivity.

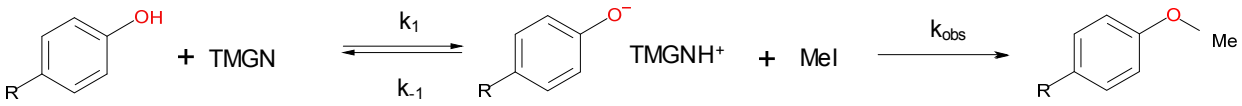
Recently, a new "proton sponge", *bis*-1,1,8,8-(tetramethylguanidino)naphtalene (TMGN), incorporating two hindered guanidine site on a naphthalene backbone, which is now commercially available has been described.[7] TMGN has several advantages over DBU we used previously: TMGN is more basic than DBU and more hindered. This last property is crucial in order to prevent any side alkylation of the base during the reaction while keeping a high deprotonation rate (figure 1).

TMGN
pKBH (MeCN) = 25.1

DBU
pKBH (MeCN) = 24.32

Figure 1. *bis*-1,1,8,8-(tetramethylguanidino)naphtalene (TMGN) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) structure and their relative basicity in acetonitrile.

Preliminary studies on *p*-nitrophenol *O*-methylation in the presence of TMGN and methyl iodide as the alkylating reagent produced very promising results, with a full respect of solubility conditions imposed by working on microsystem. Therefore, we decided to follow in the time alkylation of several substituted phenols, deprotonated *in-situ* by TMGN (scheme 1).



Scheme 1. Alkylation of substituted phenols by MeI using TMGN as base.

Substituted phenol *O*-methylation kinetics study

Kinetics for such chemical process is second-order, and first-order with respect to each reactant. Assuming a stoichiometric amount on each reagent, the kinetics equation is given by (1):

$$v = \frac{d[PhO^-]}{dt} = -k[PhO^-][MeI] \quad (1)$$

which is integrated into (2):

$$\frac{1}{[PhO^-]} - \frac{1}{[PhO^-]_0} = kt \quad (2)$$

It is by far easier to determine by NMR the phenolate or phenol to phenol methyl ether ratio. Assuming $[PhO^-] + [PhOMe] = [PhO^-]_0$ and defining conversion f as:

$$f = \frac{[PhOMe]}{[PhO^-] + [PhOMe]} \quad (3)$$

Equation (2) can be rewritten as (4)

$$\frac{1}{1-f} = k[PhO^-]_0 t + 1 \quad (4)$$

The rate of reaction can thus be determined by following the disappearance of phenolate and the appearance of phenol methyl ether. First attempts to follow the evolution of the reaction by ^{1}H NMR analysis after sampling, quenching under aqueous acidic media and extraction did not give precise and reproducible results. The main drawbacks were assigned to the difficulty to remove DMF from the crude sample, and the low reproducibility of the critical extraction step, partially due to the low volumes manipulated and the different hydrophobicities between the phenol and its methyl ether. In order to solve these drawbacks, we then turned our attention toward *in-situ* measurement of the extent of the reaction by ^{1}H NMR spectroscopy. The new practical and reproducible kinetics study was performed directly in a NMR tube using DMF-d^7 as the deuteriated solvent. First of all, a reference ^{1}H NMR spectrum was recorded for each phenol, and then a stoichiometric amount of TMGN is added. After addition of methyl iodide, the conversion of phenol to methyl ether conversion was followed (Figure 2). Determination of reaction rate is realized by comparison of aromatic peaks integration from both phenolate and reaction product.

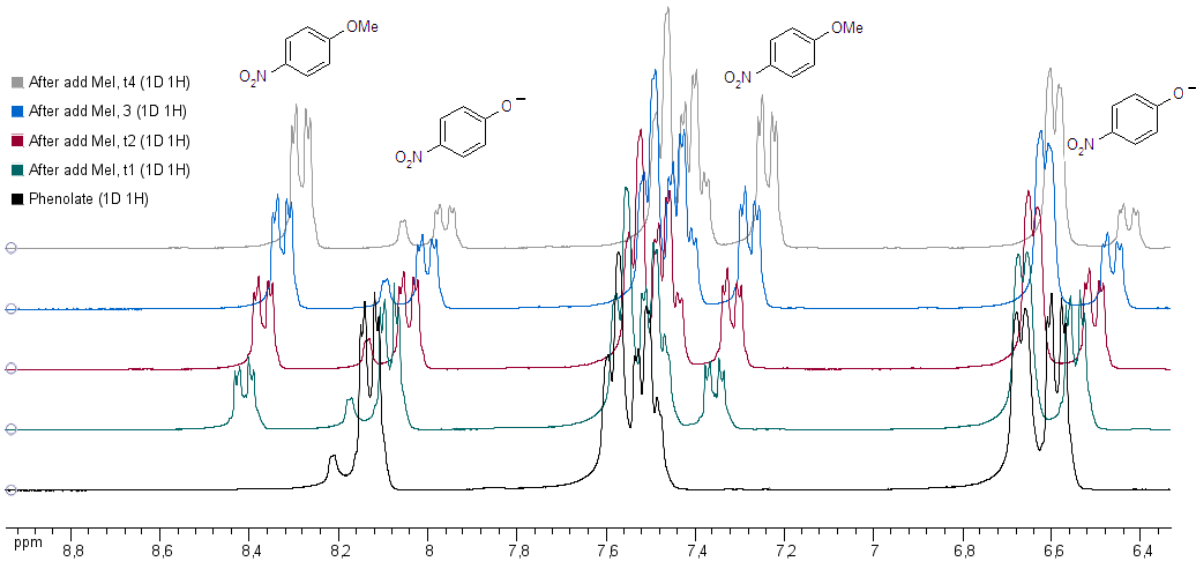


Figure 2. In-situ ^{1}H NMR showing the *p*-nitrophenol *O*-alkylation in the presence of TMGN in DMF-d^7.

The second rate order is well obeyed for the complete set of 8 substituted phenols (Figure 3). Table 1 gave slope and intercept which can be determined from this data. As expected, we can observe that the intercept is almost 1 for every substituted phenols, which demonstrates the quality of the date and the very good correlation coefficient for all phenols (table 1).

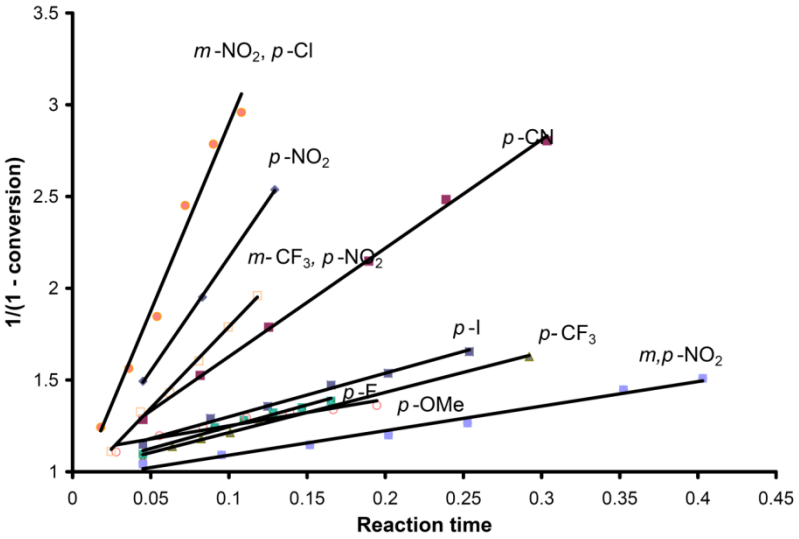


Figure 3. Second order kinetics plots ($1/(1-f) = f(t)$) for *O*-methylation of substituted phenols in the presence of TMGN and methyl iodide in DMF-d^7.

Table 1. Determination of reaction kinetics constant of substituted phenols, their corresponding substituent constant σ and linear correlation equation.

Substituent	σ[a]	Slope	Intercept	Standard deviation	$k_{observed}$ $mol^{-1}.l.s^{-1}$	$\log_{10} k_{observed}$
p-methoxy	-0.27	1.44	1.11	0.95	7.2	0.857
p-fluoro	0.06	2.38	1.01	1.01	11.9	1.076
p-iodo	0.18	1.37	1.06	1.06	6.85	0.836
p-trifluoro	0.56	2.19	0.99	0.99	10.95	1.039
p-cyano	0.64	5.91	1.04	1.04	29.55	1.471
p-nitro	0.78	12.30	0.93	0.93	61.5	1.789
m-nitro-*p*-chloro	0.90	20.40	0.86	0.86	102	2.009
m-trifluoromethyl,*p*-nitro	1.21	8.87	0.90	0.99	44.37	1.65
m,*p*-dinitro	1.49	1.34	0.96	0.96	6.7	0.826

a: σ values taken from literature.[8]

Nevertheless, contrary to preformed phenolate, the Hammett plot of kinetics constants from Table 1 is not linearly correlated but rather appears as a bell-shaped distribution (Figure 4).

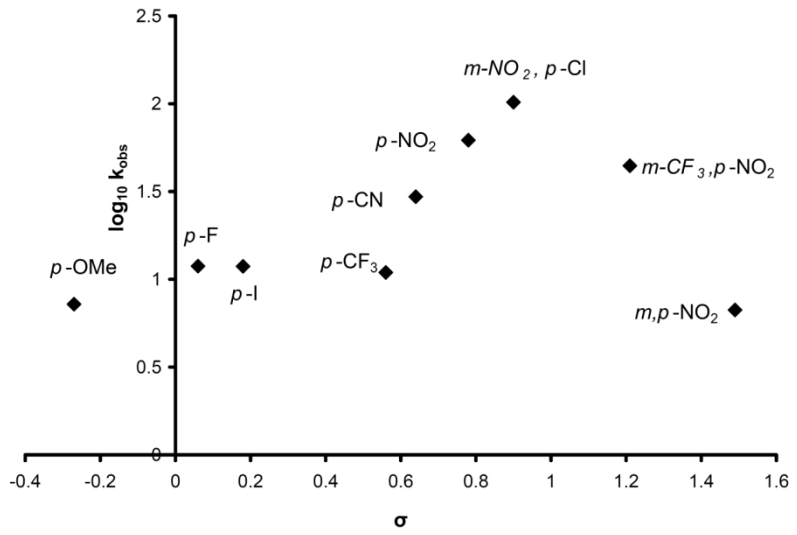


Figure 4. Hammett plot for the observed global alkylation rate of phenols by MeI in presence of TMGN.

Study of the deprotonation of phenols by TMGN in DMF

Our first mechanistic assumption was based on a complete deprotonation of phenols in DMF by TMGN and the observed kinetics rate was attributed to the rate determining alkylation step. If deprotonation kinetics or equilibrium can't be neglect in the case of low Hammett σ values, it would be important to evaluate the influence of the deprotonation step on the global kinetics constant (figure 5).

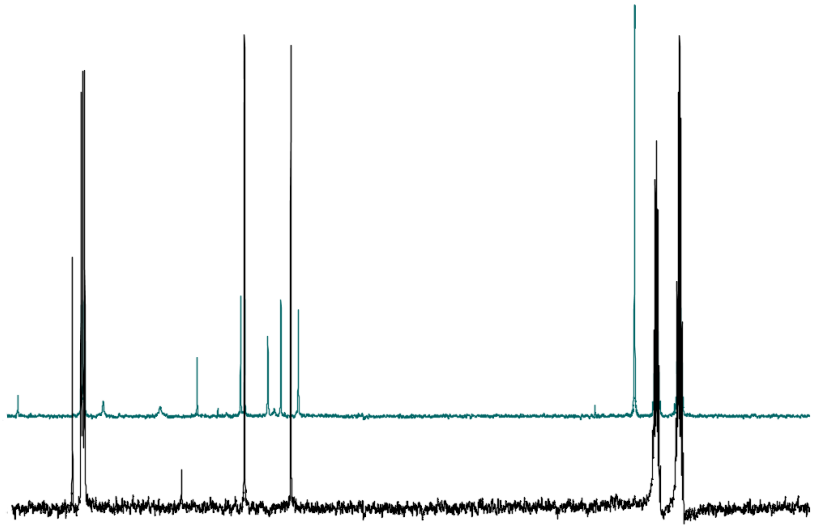


Figure 5. ^{13}C NMR (UDEFT no NOE) of *p*-nitrophenol before (down) and after (up) adding TMGN (1 equivalent).

In order to explain obtained results, we decided to realize some complementary experiments to evaluate the deprotonation equilibrium.[9] Phenol deprotonation by TMGN was followed by ^{13}C NMR using the so-called UDEFT no NOE pulse sequence.[10] Since ^{13}C NMR spectrometry is a powerful analytical tool, the small magnetic moment ant the long relaxation times of carbon nucleus lead to a low sensibility. Obtaining a good resolution spectrum needs a long acquisition time directly linked to the relaxation time of different carbons. Classical ^{13}C NMR experiments are not planned to follow fast kinetics study. The Uniform Driven Equilibrium Fourier Transform (UDEFT) experiment was proposed to alleviate the problems of nuclei with long T1 relaxation time like carbon, by simple modification of the Fourier

Transform (FT) pulse sequence. At the same time, an ^{1}H adiabatic decoupling allows us to prevent any NOE build-up and return exactly the ^{1}H magnetization along the Z axis at the end of the UDEFT module.

Reference spectrums were realized to determine ^{13}C chemical shift (δ_0) on *p*-nitrophenol, *p*-hydroxyanisol and *p*-trifluorocresol. Afterwards, TMGN was added stepwise (0.2 equivalent) and we observed difference of chemical shift between phenol form and phenolate intermediate ($\delta - \delta_0$). During the addition of the base, there is an equilibrium state between the phenol and the phenolate form, which lead to a movement of the aromatic carbons chemical shift observed on ^{13}C NMR spectrum. Significant displacements are observed in the case of *p*-nitrophenol, especially on the ipso carbon (Table 2 and Figure 5). The *ipso* ^{13}C NMR shift observed is linearly proportional to the phenolate concentration. Therefore, *p*-nitrophenol deprotonation by TMGN appears to be close to quantitative.[11] ^{13}C NMR spectrum of synthesized tetrabutylammonium *p*-nitrophenolate in deuteriated DMF-d^7 gives us a relative displacement ($\Delta\delta$) of 16.1 ppm after complete deprotonation. By comparison with such value deprotonation ratio after addition of TMGN as base is nearly 75%. However, differences calculated on *p*-trifluorocresol and *p*-hydroxyanisol are very low, even at one equivalent.

Table 2. Deprotonation induced ^{13}C NMR shifts (in ppm) after addition of TMGN on *p*-nitrophenol.

		Relative displacement at n equivalent of TMGN $\Delta\delta$ (ppm)				
Position	δ ppm	0.2	0.4	0.6	0.8	1.0
ipso	164.62	3.14	5.52	9.99	11.25	12.1
para	140.36	2.41	2.24	2.96	3.9	4.82
meta	126.38	0.14	0.09	0.58	0.74	0.84
ortho	116.08	0.42	0.62	1.6	1.95	2.19

In order to examine if our base is alkylated during the reaction time, a background reaction concerning the alkylation of TMGN in presence of methyl iodide has been followed by ^{13}C NMR. After eight hours, proton sponge alkylation appears complete. This particular result highlights a probable competitive reaction between deprotonation and TMGN alkylation. Furthermore, a second hypothetic alkylation of the base can be envisaged considering the *bis*-guanidine functionality of TMGN. Such undesired reactivity could have important effects on the kinetics outcome of the reaction considering the consumption of methyl iodide along the time. Nevertheless, an additional experiment in which TMGN is preliminary protonated by trifluoromethanesulfonic acid prior to be submitted to methyl iodide demonstrated that no methylated TMGN-H^+ can be detected even after 3 days. This result confirming that when TMGN is protonated, the methyl iodide is not consumed anymore. Our present work focuses on the quantification and evaluation of competitive methylation between substituted phenols with low Hammett σ values and TMGN. A precise description of this phenomenon is of particular importance for the later description of the scope and limitations of this methodology.

Correlation between experimental and deconvoluted kinetics data: Measurement of substituted phenol acidity constants in DMF

Correlation of σ values with rate of alkylation of substituted phenols in the presence of TMGN is a critical criterion. Since the experimental Hammett plot described by Lewis *et al.*[4] demonstrated to be linear with a negative ρ Hammett constant, and because its interpretation can be of extreme importance from a mechanistic point of view, our non linear Hammett plot has to be described carefully (Figure 4).

So, we can set three different sections apart. The first one corresponds to a very low deprotonation rate. It can be apply from *p*-OMe (σ = -0.27) to *p*-I substituent (σ = 0.18). Kinetics values for those compounds are almost equal. On intermediate sigma values, we observe an increase of the reaction rate, showing an evolution of deprotonation rate for corresponding phenols. A ^{13}C NMR deprotonation study on *p*-nitrophenol and *p*-trifluorocresol confirms this observation. The last part corresponds to high σ values on two *meta* and *para* disubstituted phenols, which appear to be completely deprotonated. In that case, reaction follows a second order kinetics law, with phenolate alkylation as the rate limitating step in perfect accord with the literature data. High σ values correlation corresponds to the expected kinetics of phenolate alkylation. By using linear correlation equation reported for all substituted phenols (equation 5), we can obtain deconvoluted values of k_{alk} considering a complete deprotonation of each compound (Figure 6, table 3).

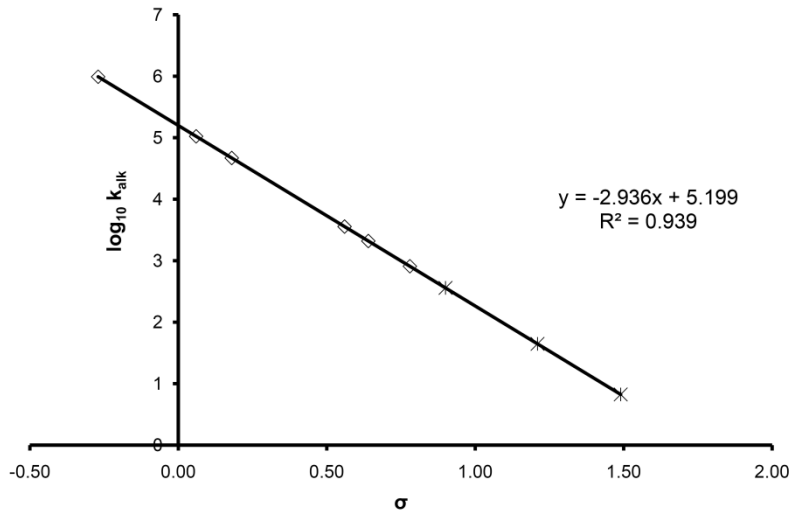


Figure 6. Hammett plot for estimated $k_{alkylation}$ (◇) based on fully deprotonated phenols (three points on the right (∗)).

Equilibrium constant K_{eq} of each phenol can be easily extract from both experimental and estimated k_{alk} data (equation 6).

$$\log k_{alkylation} = 2.886\ \sigma + 5.126 \quad (5)$$

$$\log K_{eq}\ (\text{estimated}) = \log k_{observed}\ (\text{experimental}) - \log k_{alk}\ (\text{estimated}) \quad (6)$$

According to our first mechanistic hypothesis, this reaction involves the deprotonation of phenol to form phenolate anion, which behaves as a substrate for further alkylation by MeI. Indeed the pK_{BH+} of TMGN in

acetonitrile is estimated to be 25.1.[7] pK_a in DMF-dimethylsulfoxide (DMSO), and DMSO-acetonitrile (ACN) and are related by equations (7) and (8):[12]

$$pK_a^{DMF} = 1.56 + 0.96\ pK_a^{DMSO} \quad (7) \qquad pK_a^{ACN} = 12.4 + 0.80\ pK_a^{DMSO} \quad (8)$$

By combining equations (7) and (8) equation (9) is obtained which correlates pK_a in DMF with pK_a in acetonitrile (ACN):

$$pK_a^{DMF} = -13.94 + 1.2\ pK_a^{ACN} \quad (9)$$

pK_{BH+} of TMGN in DMF is calculated to be around 16.3. Calculated equilibrium constants give us access to experimental phenol pK_a in DMF[12, 13] from TMGN estimated basicity with equation (10).

$$pK_{a\ PhOH\ exp} = pK_{BH+\ TMGN} - \log K_{eq} \quad (10)$$

Obtained values are compared to literature data (table 4, figure 7). It appears that TMGN isn't able to deprotonate totally every phenol of which the pK_a in DMF is comprised between 13.72 and 19.1.[13] Those results confirm our initial mechanistic hypothesis.

Table 3. Correlation between log $k_{observed}$, log k_{alk} and log K_{eq}

Phenol	σ	$\log_{10} k_{observed}$	$\log_{10} k_{alk}$	$\log_{10} K_{eq}$
p-methoxy	-0.27	0.86	5.99	-5.13
p-fluoro	0.06	1.07	5.02	-3.95
p-iodo	0.18	1.07	4.67	-3.60
p-trifluoromethyl	0.56	1.04	3.56	-2.52
p-cyano	0.64	1.47	3.32	-1.85
p-nitro	0.78	1.79	2.91	-1.12
m-nitro-*p*-chloro	0.90	2.01	2.56	-0.55
m-trifluoromethyl-*p*-nitro	1.21	1.65	1.65	
m,*p*-dinitro	1.49	0.83	0.83	

Table 4. Measurement of various *p*-substituted phenols acidity constants in DMF (literature and present study), their equilibrium constant and substituent constant.

Phenol	σ	$\log_{10} K_{eq}$	$pK_{a\ PhOH}^{exp}$	$pK_{a\ PhOH}$[a]	ΔpK_a
p-methoxy	-0.27	-5.13	18.43	19.11	0.76
p-fluoro	0.06	-3.95	17.25	17.59	0.41
p-iodo	0.18	-3.60	16.90	17.03	0.20
p-trifluoromethyl	0.56	-2.52	15.82	15.28	-0.49
p-cyano	0.64	-1.85	15.15	14.91	-0.19
p-nitro	0.78	-1.12	14.42	14.27	-0.11
m-nitro-*p*-chloro	0.90	-0.55	13.85	13.72	-0.12

a : pK_a have been calculated according to ref. 13 using σ Hammett values

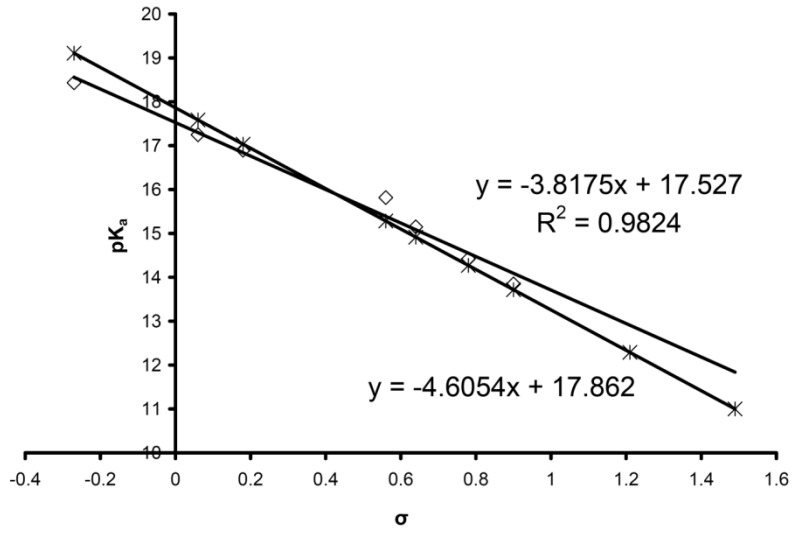


Figure 7. Relationship between σ substituent constant and corresponding phenol acidity constants from experimental (◇) and literature data (∗).

Conclusion

In conclusion, phenol alkylation in the presence of new proton sponge (TMGN) in DMF has been studied, the reaction follows a second order kinetics law, and however Hammett plot is bell-shaped. For high σ values, deprotonation has been demonstrated to be complete; nevertheless it appears that electron donating groups are only partially deprotonated by TMGN. The possible consumption of methyl iodide by the second guanidine nucleophilic site of TMGN after protonation has been ruled out. Observed kinetics constant measurement by 1H NMR combined to equilibrium constant measurement by quantitative 13C NMR, finally gave us access to the kinetics alkylation constants which follow a linear Hammett relationship and to phenol acidity constant. The calculated phenols acidity constants are in agreement with values from literature.

Experimental section

Materials and methods: Deuterated *N*,*N*-Dimethylformamide-*d7* from Euriso-Top is used in 0.75 mL vials. All organic compounds are using as received, without preliminary purification. All experiments are realized with an equimolar concentration of each product (0.2 $mol.l^{-1}$).

^{1}H NMR, ^{13}C NMR experiments were performed with a Bruker (Wissembourg, France) Avance 300 Ultrashield spectrometer at room temperature in DMF-d^7 with calibration on the solvent peak. Chemical shifts are given in δ. ^{13}C spectrums are done by using UDEFT no NOE pulse program.[10]

Tetramethylammonium salts: Tetramethylammonium salts containing the conjugate phenolates were prepared from tetramethylammonium hydroxide (in solution in methanol, 1 $mol.l^{-1}$)[6] and the relevant phenols directly in the NMR tube. Phenol (0.07 mmol) is mixing with 70 µL of tetramethylammonium hydroxide solution in 0.35 µL of deutaried DMF d_7. Measurements were done by ^{13}C NMR (UDEFT no NOE).

Alkylation kinetics study: Phenol (0.07 mmol) is solubilized in 0.35 mL of DMF d_7, then TMGN (0.7 mmol) is added. After obtaining ^{1}H and ^{13}C NMR reference spectrum, methyliodine is added (4.5 µL, 0.7 mmol). After stirring, several ^{1}H NMR spectrum are realized at different time. Conversion data f are determinate by integration of aromatics peaks. We observe the ratio between phenolate and phenolic ether. Calibration is realized on methoxy peak (3.8 – 4 ppm) corresponding to 3H integration. Phenolate concentration are deduct from conversion data (equation 11)

$$[PhO^-] = c\,(1- f) \qquad \text{(equation 11)}$$

Deprotonation kinetics: Phenol (0.07 mmol) is solubilized in 0.35 mL of DMF d_7, then ^{13}C NMR (UDEFT no NOE) reference spectrum are done. TMGN (0.2 eq, 0.014 mmol) is added in five times, and ^{13}C NMR chemical shift are observed.

TMGN alkylation: TMGN (0.07 mmol) is solubilized in 0.35 mL of DMF d_7, then ^{13}C NMR (UDEFT no NOE) reference spectrum is done, and then methyl iodine (4.5 µL, 0.07 mmol) is added. Variation of ^{13}C NMR chemical shift is observed during three day. For protoned TMGN H^+ study, one equivalent of trifluoromethylsulfonic acid is added at TMGN, and then a reference spectrum is done. Alkylation kinetics study is realized as described before.

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