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Alkylation of Substituted Benzoic Acids in a Continuous Flow Microfluidic Microreactor: Kinetics and Linear Free Energy Relationships

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Supporting Information

ABSTRACT: Alkylation of para-substituted benzoic acids by iodomethane using an organic superbase, 1,8-bis-(tetramethylguanidino)naphthalene (TMGN) in DMF was chosen as a model reaction to test the quality of the control of experimental parameters in a continuous flow microfluidic reactor as it is expected to follow a perfect second order kinetics with a large dynamics by varying the substituents. These conditions may be directly used for the synthesis of natural product esters. Because TMGN reacts slowly with iodomethane, the three different mixing strategies between substrate, base and alkylating reagent were compared. The rate constants were determined for the reaction with a set of alkylating agents and in different solvents. In order to test the quality of the obtained data, temperature effect and free energy relationships, which are expected to follow predictable laws, were investigated. The kinetics vary over 6 orders of magnitude and follows a perfect Arrhenius law, allowing the determination of the energies, enthalpies, and entropies of activation. Finally, we established a Hammett linear relationship for a series of 16 substituted benzoic acids, leading to a reaction constant ρ of −0.65 for this reaction. The quality of the obtained kinetics allowed us to discuss the outliers. All kinetics were obtained with less than 0.5 mmol of substrate.

INTRODUCTION

Chemistry in continuous flow microreactors has received considerable attention over the past decade.[1] In microreactors, potentially explosive and hazardous reactions can be safely conducted,[2a−c] short-lived intermediates can be trapped to increase chemical yield,[2d] a cascade of reactions can be carried out without the necessity of isolating intermediates, and alternatively it is possible to use high-pressure and/or -temperature conditions.[2e] Continuous flow microreactors have found broad applications in multistep organic synthesis[3a] and in the synthesis of complex natural products.[3b−d] One more advantage of microreactors is that they provide an opportunity for greener chemistry and faster process development.[3e−g] Scale-up of microreactors can be easily achieved by using multiple microreactors in parallel.[4] The efficiency of a given reaction in a microreactor compared to that in batch relies critically on the mixing process of the reagents.[5a−e] Most of the mixing evaluation reactions are based on highly nonlinear reactions such as Bourne's reactions,[5b−d] and the iodine-iodate Villermaux−Dushman reaction, which leads to complicated kinetics valid only in a limited range of concentrations.[5e] Furthermore, these conventional methods are based on spectrophotometric determination of the products rather than using the isolated product yield.[6] We were interested, therefore, to find and to study in a continuous flow microreactor, a second-order reaction with isolable products and variable rates by varying the substrate without changing the reaction kinetics. The reaction of substituted benzoate with iodomethane, which is a well-known S_N2 reaction, seems to fulfill these criteria. Chlorobenzyl Merrifield resins (chloromethylated polystyrene−1% divinylbenzene) were efficiently alkylated by cesium salts of amino acids without quaternization of their protected amine group and using *N*,*N*′-dimethylformamide (DMF) as solvent.[7a,b] The scope of this reaction has been extended to the alkylation of crowded carboxylic acids using hexamethylphosphoramide (HMPA) as solvent[7c] and has been used in several syntheses[7d,e] including the synthesis of short-lived ^{11}C propyl and butyl esters.[7f] Kondo et al. demonstrated that the reaction of tetramethylammonium benzoate salts with alkyl halides in acetonitrile follows a second-order kinetics.[8] Instead of using cesium or tetraalkylammonium salts, Ono et al. used 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as the base to efficiently deprotonate benzoic acid in toluene at room temperature.[9a] However, in these conditions the obtained $DBUH^+I^-$ salt is insoluble, and the resulting white slurry precludes its use in a microsystem. In another study, Mal et al. employed the same procedure for the *O*-methylation of various carboxylic acids in acetone and in acetonitrile as solvent.[9b] However, one of the most serious side reactions in these syntheses is the alkylation of DBU by iodomethane. Barton et al. reported that the hindered guanidine bases they synthesized were much more stable toward alkylation.[10a,b] Barton's bases enable the alkylation of crowded carboxylic acid such as adamantane-1-carboxylic acid even with a secondary alkyl halide such as isopropyliodide.[10c] This reaction has been used during the total synthesis of salinomycin.[10d] In order to apply the results of this work to the synthesis of more complex molecules such as phenol acids we used DMF as solvent, which was a good solvent in carboxylate cesium or sodium salt alkylation.[11] Furthermore, the high polarity of DMF avoids the

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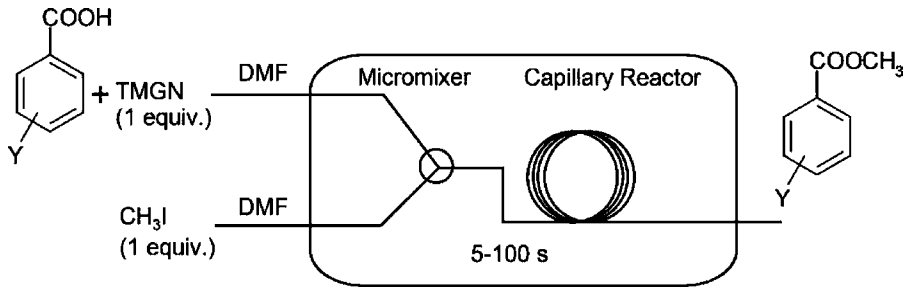

Figure 1. Experimental setup. It comprises a commercially available micromixer (NanoMixer) and a fused silica-based capillary tubular reactor.

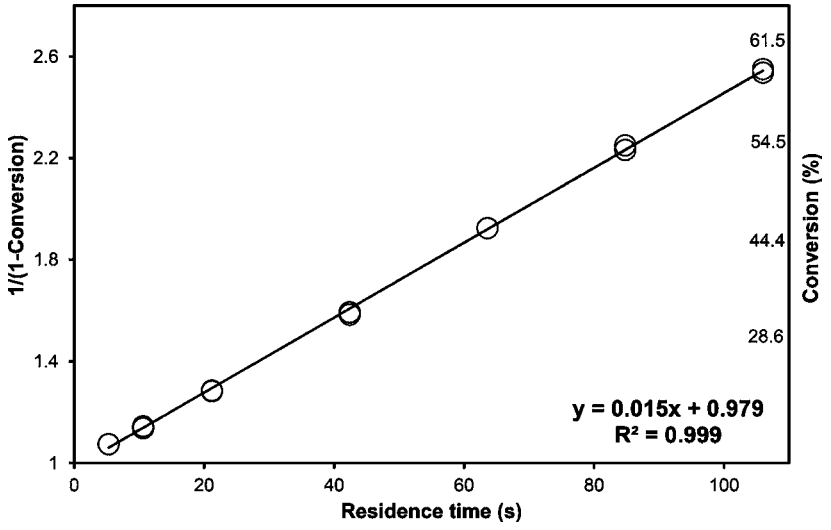

Figure 2. Second-order kinetics plot of benzoic acid alkylation by iodomethane in the presence of TMGN and in DMF at 20 °C.

formation of aggregates or strong ion pairs which complicate the kinetics of the reaction.[12] We chose 1,8-bis-(tetramethylguanidino)naphthalene (*N*″,*N*‴″-1,8-naphthalene-diyl-bis[*N*,*N*,*N*′,*N*′-tetramethyl]-guanidine, TMGN) as a base as it is even less reactive than Barton's bases toward alkylation.[13a] Its backbone is the well-known 'proton sponge' 1,8-bis(dimethylamino)naphtalene (DMAN) which does not react with methyl iodide but which, unfortunately, is not basic enough.[13b,c] The ionization constant (pK_{BH^+}) of TMGN in acetonitrile (25.1) is higher than that of DBU (24.33).[14a−c] By using the linear correlations between acidities in DMF and in acetonitrile, pK_{BH+} of TMGN in DMF is estimated to range from 16.4 to 17.5.[14d] pK_a's of benzoic acids in DMF are in the range of 10.6 for 4-nitrobenzoic acid to 13.0 for 3,4-dimethylbenzoic acid.[14e] Therefore, TMGN is able to fully remove acidic hydrogen of all benzoic acids. Furthermore, in those conditions either for DBU or TMGN the salt of the protonated base cation with iodide remains soluble in DMF, which is a requirement for experimental studies in micro-reactors.

While several groups have developed their own continuous flow microreactors dedicated to organic synthesis,[15] the setup we used in this study has the advantage of being based on commercially available devices and thus can be reproduced easily. We present here results obtained with this setup on the kinetics of alkylation of substituted benzoic acid deprotonated by TMGN, which is focused on the comparison of three mixing strategies of the three reagents, TMGN, benzoic acid, and iodomethane, which may be mixed in any combination, the influence on the rate of the alkylating agents and of the solvent, the temperature dependence of reaction rate, and finally the linear free energy relationships for this reaction. The linear correlation obtained shows that continuous flow microreactors may be used in physical chemistry experiments with the consumption of very small amounts of reagents.

RESULTS AND DISCUSSION

Fused glass capillary tubes with inherent microscale internal dimensions provide modular and inexpensive building blocks for the on-demand assembly of microfluidic reactors.[16] All the microfluidic experiments were carried out in a setup (Figure 1) composed of two streams of reagent solutions in DMF simultaneously delivered by a high-pressure syringe pump to a micromixer followed by a fused silica-based capillary tubular reactor which are all readily available commercial devices. The two syringes containing the reagents are connected via 0.30 m capillaries (i.d. 50 μm) to the micromixer. Because of the high pressure drop along these inlet tubes, the liquid flows only in one direction, and no backmixing occurs. The micromixer is followed by a 3.0 m fused silica-based capillary (i.d. 75 μm) which is the tubular reactor.[17] The capillary tubular reactor is kept at the desired temperature in a water bath. For the micromixer, we utilized a commercially available multilaminating distributive micromixer chip.[17a] This mixer has been used previously for time-resolved studies of protein conformation by NMR.[17b] A similar PDMS device has also been used for the controlled polymerization of *N*-carboxy anhydrides.[17c] It is one of the more efficient mixing devices in this flow range.[17d] In our case, slightly worse results were obtained with a simple MicroTee filled with porous material.

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The flow rates were varied from 5 μL·min^{-1} to 150 μL.min^{-1} to give residence times of 5 to 105 s (SI Table S1). This flow rate range corresponds to a Bodenstein number *Bo* varying from 90 to 1810. For these large *Bo* numbers, no dispersion occurs, and plug flow is assumed in the capillary tubular reactor.[18] The concentrations of the remaining benzoic acid and methyl benzoate were determined by GC/MS with electron ionization (EI) after silylating the quenched reaction mixture. To ensure the quality and integrity of the data generated, we added three internal standards, one in each syringe and another one in the collected sample. The absolute average and the relative average deviation were 3% and less than 0.5%, respectively (SI Tables S2 and S3). The conversion, *f*, used in kinetics analysis, was calculated from the integrated areas of benzoic acid methyl ester and silyl ester peak (f = (peak area of methyl ester)/(peak area of methyl ester + peak area of silyl ester)) since it is more reliable than the absolute area of remaining benzoic acid or of produced methyl ester alone. The kinetics constants k were determined graphically by plotting the function $1/(1-f)$, against residence time (t) which resulted in a straight line with a slope equal to $k\times[YC_7H_5O_2^-]_0$, where $[YC_7H_5O_2^-]_0$ is the initial concentration of the substituted benzoic acid. In all the experiments, unless otherwise mentioned, the solution of benzoic acid and base (TMGN) in DMF was in one syringe, whereas the solution of the alkylating reagent, MeI, also in DMF, was kept alone in the second syringe.

Figure 2 shows the results obtained for an initial concentration of benzoic acid of 26.7 mM and molar ratios of TMGN and iodomethane to benzoic acid of 1.0 and 1.1, respectively. These concentrations have been applied for all the experiments described in this paper. The straight line relationship (n = 7; R^2 = 0.999) which we observed up to a conversion of 60% shows that the second-order kinetics not only is observed at the initial stage of the reaction but also remains verified up to a nearly preparative yield.

There are two other combinations for introducing the three reagents (benzoic acid, the base TMGN, and iodomethane) into the micromixer. Since it might lead to different selectivity in case of complex molecules, their kinetics were also recorded. The two combinations in which reagents cannot react irreversibly (i.e., benzoic acid and TMGN in one syringe and iodomethane in another syringe or benzoic acid and iodomethane in one syringe and TMGN in another syringe) gave quite similar rate constants 0.57 and 0.55 mol^{-1}·L·s^{-1}, respectively (Table 1, entries a, b) close to the value obtained in batch which is 0.64 mol^{-1}·L·s^{-1}. These three experiments were repeated several times using different capillaries and micromixer units and at different periods. From these data the dispersion of results may be estimated to be around 4%. However, the last combination (benzoic acid in one syringe, TMGN and iodomethane in another syringe) does not follow a clean second-order kinetics for residence times beyond 60 s and gives a lower reaction constant nearly half of the previous value (Table 1, entry c). Investigation by mass spectrometry and NMR techniques show that the side reaction is the hydrolysis of MeI as well as TMGN protonation by residual water. Improved results were obtained using DMF dried overnight over molecular sieves and using a small amount of molecular sieve in each syringe (Table 1, entry d).

Table 1. Effect of reagent combination on the reaction rate constant of the alkylation of TMGN deprotonated benzoic acid by iodomethane in DMF at 20 °C[a]

entry	syringe A	syringe B	k (mol^{-1}·L·s^{-1})
a	benzoic acid, TMGN	iodomethane	0.57 ± 0.02[b,c]
b	benzoic acid, iodomethane	TMGN	0.55 ± 0.07[b,d]
c	benzoic acid	iodomethane, TMGN	0.24[b]
d	benzoic acid	iodomethane, TMGN	0.32[e]

[a]Conditions: benzoic acid 26.7 mM and molar ratios of TMGN and iodomethane to benzoic acid of 1.0 and 1.1, respectively. [b]HPLC grade DMF used as received. [c]Average and standard deviation from three independent studies. [d]Average and standard deviation from three independent studies. [e]DMF dried overnight on molecular sieves, with a small amount of molecular sieves added in each syringe.

Effect of the Alkylating Reagent and Solvent. We next investigated a set of alkylating reagents. For all alkylating agents the reaction remained cleanly second order. The observed reaction rate constants are displayed in Table 2. The k value order observed for iodomethane, iodoethane and 2-iodopropane, respectively 0.57, 0.063, 0.039 mol^{-1}·L·s^{-1} (Table 2, entries a, b, and c), follows the expected trend for methyl, primary, and secondary alkyl halides in S_N2 reactions.

Table 2. Effect of alkylating reagent and solvent on the reaction rate constant of benzoic acid alkylation in the presence of TMGN[a]

entry	solvent	alkylating reagent	temperature (°C)	k (mol^{-1}·L·s^{-1})[b]
a	DMF	iodomethane	20	0.57 ± 0.02[b]
b	DMF	iodoethane	20	0.063 ± 0.006
c	DMF	2-iodopropane	50	0.039 ± 0.001
d	DMF	benzyl bromide	20	0.28 ± 0.05
e	DMF	*tert*-butyl bromoacetate	20	0.74 ± 0.03
f	acetonitrile	iodomethane	20	0.074 ± 0.01
g	toluene	iodomethane	20	–

[a]Conditions: benzoic acid 26.7 mM and molar ratios of TMGN and iodomethane to benzoic acid of 1.0 and 1.1, respectively, in HPLC grade solvents used as received. [b]Average and standard deviation from two or three independent measurements.

No reaction was observed for 2-iodo-2-methylpropane suggesting that elimination to 2-methylpropene is the main reaction. Benzyl bromide and *tert*-butyl bromoacetate were very reactive with k values of 0.28 and 0.74 mol^{-1}·L·s^{-1}, respectively (Table 2, entries d and e). Roberts et al. reported that the reactivity of *tert*-butyl bromoacetate was 2.2 times higher than that of benzyl bromide in the alkylation of the cysteine thiol of glutathione in water/DMSO (between 10 and 20%).[19] Here the observed ratio in DMF is 2.7. The effect of the solvent on the reaction rate constants was also investigated and as expected the reaction in acetonitrile is much slower than in DMF with k values of 0.074 and 0.57 mol^{-1}·L·s^{-1} respectively (Table 2 entries a, f). The rate observed in acetonitrile is one-third the value (0.26 mol^{-1}·L·s^{-1}) which can be obtained using the Hammett equation given by Kondo et al.[8d] using the preformed ion with tetramethylamonium as counterion. No trace of the expected ester was observed by GC/MS when the reaction was conducted in toluene at 20 °C (Table 2, entry g). This result is at first glance surprising since Ono et al.[9a] described the alkylation of benzoic acid by iodoethane using DBU as base in toluene at room temperature. These conditions (DBU, toluene) cannot be tested in our microdevice because by reproducing the experiment in batch we observed that white

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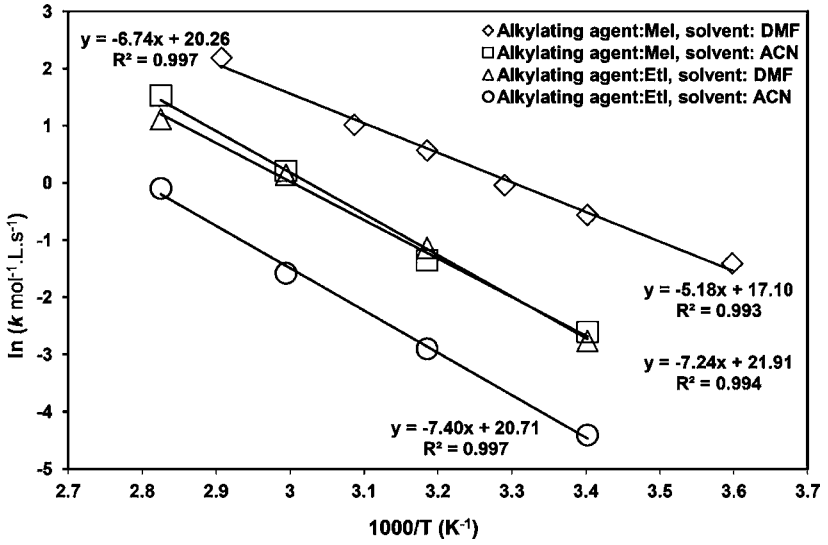

Figure 3. Arrhenius plot for the alkylation of benzoic acid deprotonated by TMGN in acetonitrile or DMF by iodomethane or iodoethane.

Table 3. Effect of alkylating agents and solvents on activation parameters of benzoic acid alkylation in the presence of TMGN[a]

entry	solvent	alkylating agent	$\Delta H^{\circ\ddagger}$ (kJ·mol^{-1})	$\Delta S^{\circ\ddagger b}$ (J·mol^{-1}·K^{-1})	$\Delta G^{\circ\ddagger b}$ (kJ·mol^{-1})	E_a (kJ·mol^{-1})
a	DMF	iodomethane	40.3	−112.2	73.3	43.1
b	DMF	iodoethane	53.1	−86.4	78.6	56.1
c	acetonitrile	iodomethane	57.2	−72.7	78.2	60.2
d	acetonitrile	iodoethane	58.5	−82.7	82.6	61.5

[a]Conditions: benzoic acid 26.7 mM and molar ratios of TMGN and iodomethane to benzoic acid of 1.0 and 1.1, respectively, in HPLC grade solvents used as received. [b]Standard conditions: T = 20 °C, reagent concentrations = 1 mol·L^{-1}.

slurry appears rapidly in the toluene solution. Furthermore, the estimated half-life of the reaction from batch study at dilution level of this work is higher than 10 h which precludes observing it in a microfluidic device. In summary, the continuous flow microfluidic reactor allowed us to screen rapidly and quantitatively the reactivity of different substrates using less than 0.5 mmol and to investigate various solvents.

Temperature Effect. The effect of the temperature for the alkylation of benzoic acid itself by iodomethane in DMF was then investigated in the range of 4−70 °C (SI, Table S4). Kinetics for each temperature, even the highest (SI Figures S3−S7), show no deviation for short residence time, which proves that the thermal equilibrium is quickly achieved in the tubular reactor. Otherwise, the kinetics would be slower at short residence time for temperature above ambient temperature and faster at temperature below ambient temperature.

The rate constants were used to construct an Arrhenius plot (Figure 3) which is linear (R^2 = 0.993) in the studied temperature range (4−70 °C) and gives a value of 43.1 kJ·mol^{-1} for the activation energy. From these data the enthalpy and the entropy of activation are estimated to be $\Delta H^{\ddagger}$ = 40.3 kJ·mol^{-1} and $\Delta S^{\ddagger}$ = −112.2 J·K^{-1}·mol^{-1} leading to a standard free energy of activation $\Delta G^{\ddagger}$ = 73.3 kJ·mol^{-1} at 293 K in standard conditions (c_0 = 1 mol·L^{-1}) (Table 3, entry a). Kondo et al. found $\Delta H^{\ddagger}$ = 61.9 kJ·mol^{-1} and $\Delta S^{\ddagger}$ = −66.0 J·K^{-1}·mol^{-1} for the alkylation of tetramethyl ammonium benzoate salt by iodoethane in acetonitrile.[8c]

In order to be able to compare our data with Kondo's results we conducted three experiments by changing the solvent-alkylating agent pairs: (i) DMF, iodoethane; (ii) acetonitrile, iodomethane, and (iii) acetonitrile, iodoethane (Table 3, entries b, c, d, respectively). For the alkylation of benzoic acid by iodoethane in acetonitrile our results $\Delta H^{\ddagger\ddagger}$ = 58.5 kJ·mol^{-1} and $\Delta S^{\ddagger}$ = −82.7 J·K^{-1}·mol^{-1} (Table 3, entry d) are in agreement with Kondo's data quoted above. The slightly lower enthalpy of activation (3.5 kJ·mol^{-1}) may be due to a looser ion pair as the charge is more hidden in protonated TMGN. As expected, the enthalpy of activation is always smaller for the same reaction in DMF than in acetonitrile (Table 3 entries a and c for alkylation by MeI, and b and d for alkylation by EtI). The behavior of iodomethane in DMF is singular with a much lower enthalpy of activation $\Delta H^{\ddagger}$ = 40.3 kJ·mol^{-1} and a more negative entropy of activation $\Delta S^{\ddagger}$= −112.2 J·K^{-1}·mol^{-1} (Table 3, entry a). These results show that continuous flow microfluidic devices enable us to determine activation parameters based on a very broad range of rate constants covering 6 orders of magnitude using a very small amount of substrates as only less than 0.5 mmol of benzoic acid were used here per temperature.

Substituent Effect. We then used our setup to determine the reaction rate of substituted benzoic acids over a wide range of Hammett σ constant values (−0.66 to 0.78). A summary of the results is presented in Table 4. Most of the benzoic acids used were para-subsituted, but some more functionalized benzoic acids were also studied including meta,para- and ortho,meta-disubstituted benzoic acids.[14e,20] Hammett σ values for para-substituted benzoic acid were obtained from the classical Jaffe's or Hansch's tables.[20a,b] Hammett σ values for ortho-substituents were obtained by multiplying those of *para* values with 0.65.[20c] For 2,3- and 2,4-dimethoxy benzoic acids, σ constants were obtained by summing the corresponding ortho,meta and ortho,para values.[20d] Values of pK_a in DMF for dimethoxy substituents were obtained from pK_a values in DMSO by Exner et al.[20e] using the equation proposed by

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Table 4. Reaction rate constants for the alkylation of substituted benzoic acids by iodomethane in the presence of TMGN and in DMF at 20 °C

entry	substituent	σ	pK_a in DMF	k ($mol^{-1}·L·s^{-1}$)[k]
a	4-NO_2	0.778[a]	10.6[f]	0.175 ± 0.004
b	4-CN	0.628[a]	11.02[g]	0.249 ± 0.002
c	4-I	0.276[a]	11.65[h]	0.72 ± 0.04
d	3,5-$(OCH_3)_2$	0.24[b]	11.84[j]	0.53 ± 0.05
e	4-Br	0.232[a]	11.6[f]	0.65 ± 0.10[l]
f	4-Cl	0.227[a]	11.5[f]	0.46 ± 0.07[l]
g	4-F	0.062[a]	11.84[i]	0.56 ± 0.01
h	4-H	0.00	12.3[f]	0.57 ± 0.02[l]
i	2,3-$(OCH_3)_2$	−0.054[c,d]	12.01[j]	1.95 ± 0.35
j	3,4-$(OCH_3)_2$	−0.15[b]	12.50[j]	0.75 ± 0.03
k	4-CH_3	−0.170[a]	12.6[f]	0.47 ± 0.05
l	3,4-$(CH_3)_2$	−0.24[b]	13.0[f]	0.45 ± 0.04
m	4-OCH_3	−0.268[a]	12.78[i]	0.90 ± 0.06
n	4-OH	−0.357[a]	13.25[i]	0.32 ± 0.04
o	2,4-$(OCH_3)_2$	−0.442[c,d]	12.58[j]	1.18 ± 0.10
p	4-NH_2	−0.660[a]	13.96[f]	0.31 ± 0.02
q	(4-NH_3^+)	0.600[e]		0.31 ± 0.02

[a]From references 20a and b. [b]From reference 20h. [c]Calculated using σ_{ortho} = 0.65 × σ_{para} based on reference 20c. [d]Sum of the corresponding ortho-, meta- and para constants based on reference 20d. [e]From reference 20b. [f]From reference 14e. [g]From reference 20i. [h]From reference 20g. [i]From reference 20j. [j]Calculated using pK_a values in DMSO from reference 20e and pK_a(DMSO) to pK_a(DMF) correlation from reference 14e. [k]Average and standard deviation from 2 or better independent measurements. [l]From 3 independent measurements.

Maran et al.[14e] The reported ρ values for the Hammett plot of pK_a of benzoic acid in DMF vs σ constants are −2.36 (n = 8) and −2.49 (n = 13) from Kolthoff et al. and Bartnicka et al. respectively.[20f,g] In this work we obtained a ρ value of −2.29 for 16 substituents from a compilation of literature data.

The Hammett plot of $\log(k_Y/k_0)$ versus σ constant, displayed in Figure 4, shows that there is a good correlation between the logarithm of relative rate constants of the substituted benzoic acids alkylation and the values of σ for most para-substituted benzoic acids. The obtained ρ Hammet constant reaction value for the data marked with the ○ symbol is −0.65 (n = 8, R^2 = 0.995). A ρ value of −0.92 for alkylation of substituted tetramethylammonium benzoate with iodomethane in acetonitrile has already been reported by Kondo et al. (n = 4, R^2 = 0.9895).[8d] In DMF as in acetonitrile, the Hammett alkylation constant ρ is much smaller ($\rho^{DMF}_{Alkylation}$ = −0.65, $\rho^{ACN}_{Alkylation}$ = −0.92) than the Hammett ionization constant ρ ($\rho^{DMF}_{Ionization}$ = −2.29; $\rho^{ACN}_{Ionization}$ = −2.49) showing that compensation of solvation effects is taking place during the alkylation. Indeed, during ionization the system is going from neutral to charged benzoate, whereas during alkylation the system is going from localized charge on benzoate anion to delocalized charges in the transition step which leads to a smaller difference in the transition states. The Hammett alkylation constant ρ is smaller in DMF than in acetonitrile as expected due to the higher reactivity in DMF than in acetonitrile (Table 2).

The quality of the kinetics data pushed us to find a correlation including more substituted benzoic acids. Our first trial was based on using Hammett substituent constant σ^- values[20b] but we found that the nonlinearity was much more pronounced (SI Table S5 and Figure S1). Several correlations based on quantum-calculated descriptors were also investigated and proved to be unsuccessful. Hollingsworth et al.[21a] demonstrated that calculated Löwdin charges are effective parameters for the description of benzoic acids pK_a values in water. Thus, we tried to use them (SI Table S6) to correlate reaction rate constants using the six substituents included in our set, but they did not yield better linear correlations. Molecular electrostatic potential minimum V_{min} is another descriptor used to quantify substituent effects in benzene[21b] and benzoic acids.[21c] Again, we observed that some benzoic acids fail to give a well-fitting regression line (SI, Table S7 and Figure S2).

If we look back to the data, Figure 4 shows that outliers can be divided into three groups: bulky halogens (4-I and 4-Br), alkyl substituents (4-Me and 3,4-Me_2), and benzoic acids bearing two reactive sites (4-NH_2 and 4-OH). Deviation of *p*-

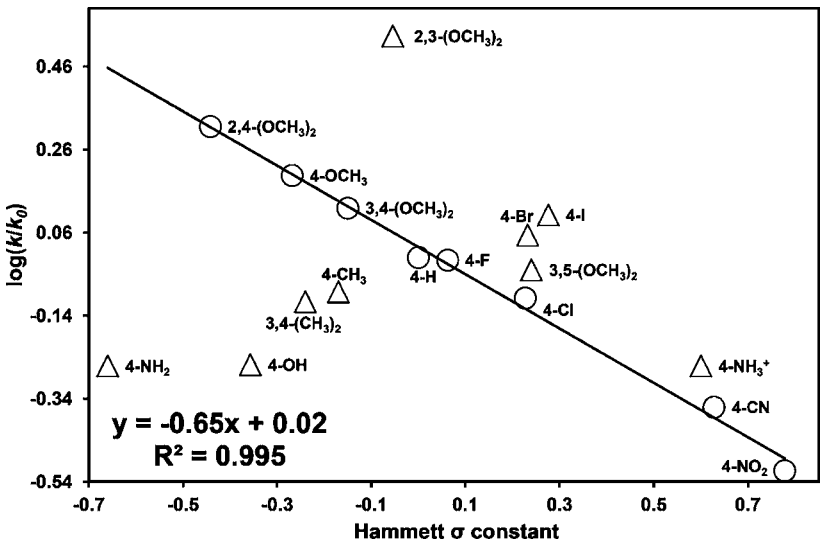

Figure 4. Log_{10} of the rate constant for the alkylation of benzoic acids by iodomethane versus Hammett substituent constant, σ, in the presence of TMGN and in DMF at 20 °C. Data represented with ○ symbols are taken into account in the Hammett linear free energy correlation, and Δ symbols refer to the outliers.

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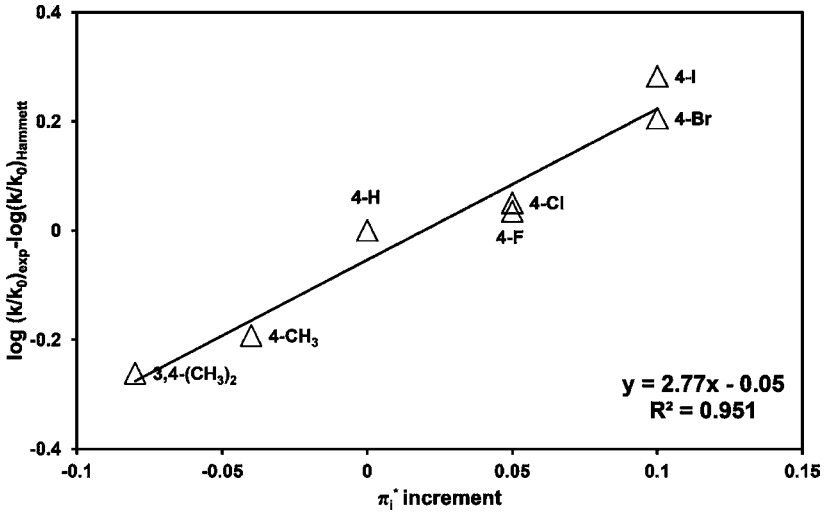

Figure 5. Difference between observed $\log(k/k_0)$ and predicted $\log(k/k_0)$ for Hammett correlation outliers versus the Kamlet–Taft π^* parameter substituent incremental values for aromatic compounds.

amino- and hydroxybenzoic acids from normal Hammett behavior has already been reported in the literature. *p*-Aminobenzoic acid may exist as a zwitterion in the solution leading to protonation of the amino site.[22a] When we use $\sigma_{NH_3}^{+}$ instead of σ_{NH_2}, the point displaces much closer to the fitted straight line (Figure 4). McMahon and Kebarle have shown that in the gas phase the lowest-energy anion derived from *p*-hydroxybenzoic acid appears to be *p*-carboxyphenoxide ion rather than *p*-hydroxybenzoate, because phenoxide ion receives resonance stabilization while no equivalent stabilization by the OH group is available to the *p*-hydroxybenzoate anion.[22b] No methoxy benzoic acid or its methyl ester was detected by GC/MS, but the existence of this *p*-carboxyphenoxide ion in conjugated form is in agreement with the reactivity which is lower than expected from Hammett's correlation of *p*-hydroxybenzoic acid.

A brief survey of the data shows that bulky halogens (4-I, 4-Br) are more reactive and alkyl substituents (4-Me, 3,4-Me_2) are less reactive than expected. Several authors, such as Herbst and Jacox,[23a] Kochai and Hammond,[23b] Kloosterziel and Backer,[23c] Miron and Hercules,[23d] have already described the abnormal behavior for *p*-methyl-substituted benzene in different reactions that they attribute to the strong sensitivity of the hyperconjugation effect to the solvent. Nagarajan et al. studied the rate of deprotonation of the 2-methyl group in 1,2,3-trimethylpyrazinium ion by benzoates in D_2O.[23e] They observed a deviation from Bronsted's equation for *o*-halobenzoate which is increasing with the group size, i.e. I > Br > Cl > F. This led us to suspect that these variations may be due to the solvation effects. Bartnicka et al.[20g] showed that the Hammett acidity reaction constant for benzoic acid ionization is well correlated by Kamlet and Taft solvatochromic parameters for the solvent,[24a] with a good confidence for 10 very different solvents:

$$\rho_{\text{Ionization}}^{\text{Solvent}} = -(0.898 \pm 0.198)\alpha^{\text{Solvent}} + (0.916 \pm 0.427)\beta^{\text{Solvent}} + (1.790 \pm 0.241)$$

where α^{Solvent} and β^{Solvent} are the Kamlet–Taft parameters which describe respectively the ability of a solvent to donate a proton in a solvent-to-solute hydrogen bond and a measure of the solvent ability to accept a proton (donate an electron pair) in a solute-to-solvent hydrogen bond.

This equation does not depend on π^* solvent dipolarity/polarizability parameter which measures the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect. The halogen-substituted benzene series have a higher π^* than unsubsituted benzene ($\pi^* = 0.59$), arranged in ascending order of size from fluorine to iodine ($\pi^*_F = 0.62$, $\pi^*_{Cl} = 0.71$, $\pi^*_{Br} = 0.79$, $\pi^*_I = 0.81$), but the π^* values of alkyl substituents are lower than that of unsubsituted benzene ($\pi^*_{Me} = 0.55$), whereas their α and β parameters are nearly constant.[24a] A less complete list of values is available for para-substituted benzoic acid but follows the same trends: $\pi^*_H = 0.74$, $\pi^*_{Cl} = 0.74$, $\pi^*_{Br} = 0.79$, and $\pi^*_{Me} = 0.70$.[24a] This variation clearly is in line with our observation that bulky halogens (4-I, 4-Br) are more reactive, and that alkyl substituents (4-Me, 3,4-Me) are less reactive than expected. Figure 5 shows the good correlation obtained for the difference between the observed $\log(k/k_0)$ and the value $\log(k/k_0)$ predicted by the Hammett equation using the $\rho = 0.65$ value we found based on the π^* incremental values calculated according to Hickey et al. tabulated values.[24b] It must be pointed out that between $\sigma = -0.3$ to $\sigma = 0.3$, where the outliers are located, the π^* additive values are correlated to σ, whereas $V_i/100$, α and β increment are independent (see SI, Figures 8–11). Unfortunately, the Kamlet–Taft parameter substituent incremental values for aromatic compounds are not precise enough; for example, they do not include substituent position, which precludes a quantitative treatment. Such a stabilization of the ground state versus the transition state has been proposed for interpreting the curved Hammett relationship during the reaction of various nucleophiles with substituted aryl benzoates.[25] Clearly the influence of π^* solvent dipolarity/polarizability parameter on the reactivity of benzoic acids reactivity in DMF deserves further studies.

CONCLUSION

A microfluidic setup based on commercially available devices was developed to study the kinetics of reactions in continuous flow mode, and the results were compared to the results obtained in batch mode. We chose as the model reaction, benzoic acid alkylation by iodomethane in DMF using an organic superbase TMGN for deprotonation because this

reaction is synthetically useful and is a good candidate for physical chemistry correlations. As expected, this reaction follows a very clean second-order kinetics which is preserved up to complete conversion in the continuous flow microreactor. The use of an organic superbase allowed us to try the three possible reagent combinations: (i) benzoic acid + MeI, TMGN; (ii) benzoic acid + TMGN, MeI; but also (iii) TMGN + MeI, benzoic acid, as the proton sponge base is only slowly alkylated in our conditions. The first two combinations exhibited nearly the same kinetics as the batch values, whereas the last one was shown to be very sensitive to residual water. The rate constants for the reaction between different alkylating agents and benzoic acid and in different solvents were also determined. This setup enabled us to study the effect of temperature on this reaction during which the variations of rate constant cover 6 orders of magnitude. The plot of the conversion versus flow rate was found to be linear at all temperatures, which proves that the thermal equilibrium is rapidly established. From this data, energy, enthalpy, and entropy of activation of benzoic acid alkylation by MeI in DMF are estimated to be 43.1 $kJ{\cdot}mol^{-1}$, 40.2 $kJ{\cdot}mol^{-1}$, and -112.2 $J{\cdot}K^{-1}{\cdot}mol^{-1}$, respectively. The activation parameters obtained in acetonitrile are in agreement with previously published values. Finally, the alkylation kinetics of a series of para-substituted benzoic acids was studied. Their reactivities are well correlated with Hammett reaction constant of -0.65. The quality of the data allowed us to ascertain the origin of the deviations which were explained using the Kamlet and Taft solvatochromic parameters. It must be pointed out that reaction rates were measured consuming less than 0.5 mmol of substrate per condition. The very good correlations obtained for Arrhenius plot and Hammett free energy relationships demonstrate that capillary continuous flow microreactors, well-known for their synthetic application, also provide sound physical chemistry data. These data are now used to develop the selective alkylation of multifunctional natural products in our laboratory.

EXPERIMENTAL SECTION

Materials. All chemicals were in the highest purity available and were used as received without further purification. For some experiments (specified in the text), DMF was dried over 3 Å pore freshly activated molecular sieves.

Methods. The high pressure syringe pump (pumping force up to 1926 N) was fitted with two 8 mL stainless steel syringes which are driven simultaneously. The two syringes, containing the reagents, are connected via 0.30 m capillaries with internal diameter smaller (*i.d.* 50 μm) than the one of the capillary reactor to the micromixer. As micromixer, we utilized a commercially available multilaminating distributive micromixer chip. Capillary reactor internal diameter and length were 75 μm and 300 cm respectively. In order to provide heating (up to 70 °C) or cooling (down to 4 °C) the capillary tubular reactor was immersed in a water bath equipped with a thermostat or an ice/water bath.

For different flow rates, 240 μL sample of reaction medium was collected at the outlet of the tubular reactor and quenched in a mixture of 400 μL of dichloromethane and 50 μL of formic acid. For each flow rate, two samples were taken directly and analyzed independently. A volume of 30 μL of the taken sample was diluted by 400 μL of iodoanisole in dichloromethane solution. This sample, was later derivatized by 50 μL of BSTFA and 20 μL of pyridine and was kept overnight for GC/MS analysis. To control the system performance, two internal standards, 1,3,5-trimethoxybenzene (TMB) and 1,4-dimethoxybenzene (DMB), were dissolved in reagents inlet streams. 4-iodoanisole is another internal standard that was added to the samples to control the analysis, just before being analyzed.

Batch kinetics studies were conducted in a 10 mL vial containing the required volume solution of acid and base in DMF. To begin the reaction, a stoichiometric volume of alkylating reagent was injected as rapidly as possible. During the experiments samples of 240 μL volume, were withdrawn at different times and were quenched. Quenching medium, dilution and derivatization, as well as the analysis method, were exactly those that were applied in continuous method.

All samples were analyzed on an ion trap mass spectrometer using electron ionization (EI, 70 eV) fitted with a gas chromatograph equipped with a split/splitless injector and an autosampler. Separations were accomplished using a 60 m × 0.25 mm column coated with a 5% diphenyl/95% dimethyl polysiloxane film of 0.50 μm thickness. Liquid injections of 1 μL were introduced into the injector heated at 250 °C with a 50:1 split ratio and a mobile phase (helium) flow rate of 1 mL/min. All analyses were carried out using a linear temperature program from 50 °C to 250 °C at 10 °C/min followed by a plate at 250 °C for 10 min. The mass spectrometer was scanned from 40 to 400 (m/z).

ASSOCIATED CONTENT

Supporting Information

Flow rates used in kinetics studies and their corresponding residence times, results of a typical GC/MS quantification experiment and statistical analysis, tables of calculated Löwdin charges and relative V_{min} values for different substituted benzoic acids, benzoic acid alkylation by iodomethane rate constant logarithm versus σ^- and V_{min}, second-order kinetics plot of benzoic acid alkylation by iodomethane at different temperatures, and plot of Kamlet–Taft V_i, α, β, and π^* parameter substituent incremental values versus Hammett σ constant. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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