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Delineation of the Critical Parameters of Salt Catalysts in the N-Formylation of Amines with CO₂

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Abstract: N-formylation of amines combining CO₂ as a C1 source with a hydrosilane reducing agent is a convenient route for the synthesis of N-formylated compounds. A large number of salts including ionic liquids (ILs) have been shown to efficiently catalyze the reaction and, yet, the key features of the catalyst remain unclear and the best salt catalysts for the reaction remain unknown. Here we demonstrate the detrimental effect of ion pairing on the catalytic activity and illustrate ways in which the strength of the interaction between the ions can be reduced to enhance interactions and, hence, reactivity with the substrates. In contrast to the current hypothesis, we also show that salt catalysts are more active as bases rather than nucleophiles and identify the pKa where the nucleophilic role of the catalyst switches to the more active basic role. The identification of these critical parameters allows the optimum salt catalyst and conditions for an N-formylation reaction to be predicted.

Introduction

Carbon dioxide is a cheap, non-toxic and abundant waste product of the petrochemical industries making it an attractive C1 building block for chemical synthesis.¹ However, its inherent high stability limits its uncatalyzed reactions to high energy substrates. For all other applications efficient catalysts are needed to allow it to be effectively utilized as a reagent. Ionic liquids (ILs) and other simple salts are promising catalysts for a number of CO₂ related applications including the synthesis of cyclic carbonates,²⁻⁴ quinazolinediones,^{5,6} oxazolidinones,^{7,8} Nmethylamines,⁹ N-formylamines^{10,11} and other compounds.¹²⁻¹⁴ Synthetic modification of the cation and/or anion allows a nearinfinite number of salts to be prepared, 15,16 while simultaneously allowing their performance to be tuned for a desired application. However, the design of more efficient salt catalysts is frequently hampered by limited mechanistic understanding and incomplete structure activity relationships, in part due to a lack of benchmark reaction conditions.

Scheme 1: N-Formylation of Amines with \mbox{CO}_2 and hydrosilane reducing agents.



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ILs and other simple salts were shown to be efficient catalysts for the N-formylation of amines employing CO₂ as a C1 source in combination with hydrosilane reducing agents (Scheme 1).¹⁰ It was proposed that the nucleophilicity of the anion activates the hydrosilane reducing agent enabling the reduction of CO29,11,17 or, more recently, ILs were shown to act as a base during carbamate assisted activation (vide infra).¹⁸ In both cases, the activity of the salt predominantly depends on the nature of the anion with a well-defined trend in the halide series being $I^- < Br^-$ < Cl⁻ << F⁻.¹¹ Tetrabutylammonium fluoride ([TBA]F)^{9,11} and Cs₂CO₃¹⁹ were identified as particularly efficient catalysts for the N-formylation reaction with comparable activity to the best metal catalysts based on Fe,20 Rh,21 W22 and Cu.23,24 In addition, cooperative catalytic behavior was observed between Zn complexes and ILs.²⁵ Although, the activity of a salt is predominantly dependent on the anion, the cation also plays a significant role. Various functionalities can be introduced onto the cation to help activate the amine, CO₂ or the hydrosilane. However, apart from the effect of the cation on the solubility of the salt, in the case of alkali metal carbonates,19 the role of the cation has not been systematically investigated. Consequently, we decided to study a series of chloride salts (Figure 1) and investigate the underlying mechanistic reasons behind the observed differences in reactivity and then systematically modify the anion in order to obtain a complete picture of the behavior of salt catalysts.



Figure 1: Structures of the cations employed in this study (all as chloride salts).

Results and discussion

Under standardized reaction conditions (10 mol% catalyst, 1 bar CO₂, 25 °C, 6 h, solvent-free) with N-methylaniline as the substrate, 1-butyl-3-methylimidazolium chloride ([BMIm]Cl), the prototype IL catalyst reported for this reaction,¹⁰ afforded the Nmethylformanilide product in 3% yield (Table 1, entry 2). Slightly higher yields of 7, 11 and 15%, were obtained with 1-butyl-1methylpyrrolidinium chloride ([BMP]CI), 1-butyl-2,3dimethylimidazolium chloride ([BdMIm]CI) and tetrabutylammonium chloride ([TBA]Cl), respectively (Table 1 entries 3-5). The highest conversion was obtained with tetraphenylphosphonium chloride ([Ph₄P]Cl), which yielded the product in 16% (Table 1, entry 6). In contrast, no product was observed when the hydroxyl-functionalized imidazolium IL 1-hydroxyethyl-3-methylimidazolium chloride ([HOEMIm]Cl) was employed as the catalyst (Table 1, entry 1).

Table 1: N-formylation of N-methylaniline with a series of chloride salt catalysts.

H N		Catalyst (10 mol%)	
	$PhSiH_3 + C$ (1)	0 ₂ bar) 25 °C 6 h	
Entry	Catalyst	Solvent	Yield (%)
1	[HOEMIm]CI	-	0
2	[BMIm]Cl	-	3
3	[BMP]CI	-	7
4	[BdMIm]Cl	-	11
5	[TBA]CI	-	15
6	[Ph₄P]Cl	-	16
7	-	MeCN	0
8	[HOEMIm]CI	MeCN	7
9	[BMIm]Cl	MeCN	14
10	[BMP]CI	MeCN	16
11	[BdMIm]Cl	MeCN	20
12	[TBA]CI	MeCN	22
13	[Ph₄P]Cl	MeCN	20
14	-	DMF	13
15	[HOEMIm]CI	DMF	60
16	[BMIm]Cl	DMF	61
17	[BMP]CI	DMF	71
18	[BdMIm]Cl	DMF	71
19	[TBA]CI	DMF	70
20	[Ph₄P]Cl	DMF	72

Reaction conditions: catalyst (10 mol%), N-methylaniline (1 mmol), phenylsilane (2 mmol), solvent (1 ml), CO_2 (1 bar), 25°C, 6 h, average GC yield from three runs with decane as internal standard.

Although the differences are small, a trend in the reactivity is apparent, i.e. [HOEMIm]Cl < [BMIm]Cl < [BMP]Cl < [BdMIm]Cl < [TBA]Cl ~ [Ph₄P]Cl. With the addition of a polar aprotic solvent, such as acetonitrile, DMF or DMSO, a moderate to large increase in the reaction yields is observed and the differences between the activities of the salts diminish (Table 1, entries 8-13 and 15-20). In MeCN the order of the reactivity remains largely unchanged with [HOEMIm]Cl and [BMIm]Cl being the least active catalysts and [TBA]Cl together with [Ph₄P]Cl the most active. In the case of DMF, the trend is almost completely lost and only two groups of salts can be identified, such that [HOEMIm]Cl ~ [BMIm]Cl < [BMP]Cl ~ [BdMIm]Cl ~ [TBA]Cl ~ [Ph₄P]Cl (Table 1, entries 15-20). In DMSO, the highest polarity

solvent tested, almost no differences can be seen among the chloride salts tested with N-methylformanilide yields being around 55% (Table S1).

Interestingly, higher yields are obtained for salts with benign (alkyl-functionalized) cations rather than [HOEMIm]Cl and [BMIm]Cl, which can interact with both the substrate and CO₂ by H-bonding or form N-heterocyclic carbenes (NHCs) following in situ C(2)-H deprotonation.^{26,27} Hydrogen bonds play a key role in a number of salt catalyzed CO2 reactions such as the cycloaddition of CO₂ to epoxides,^{28,29} which like the Nformylation reaction, is also predominantly driven by the anion.³⁰ In addition, NHCs were shown to be excellent catalysts for the N-formylation of amines with CO₂ and hydrosilanes.³¹ However, neither H-bonding interactions nor NHCs seem to facilitate the reaction. We postulated that the cation only affects the reaction indirectly by ion pairing, thereby decreasing the reactivity of the anion.¹¹ H-bond donor groups can interact with halide ions, thereby increasing the ion pairing energy, resulting in the poor yields obtained with [HOEMIm]Cl and [BMIm]Cl. Consequently, we determined the relative strengths of the ion pair binding for the series of chloride salts by electrospray ionization mass spectrometry (ESI-MS).^{32,33} During the ESI-MS measurements, the salts aggregate into clusters, the magnitude of which depends on the cation-anion binding energies and sample concentration. Under the conditions employed, clusters of varying sizes from simple singly charged $\{[C]_2[A]\}^{1+}$ to quadruply charged {[C]₉₂[A]₈₈}⁴⁺ aggregates were observed, depending on the salt under study (Figure 2). The extensive clustering observed indicates that ion pairing, under the reaction conditions employed, is significant with a strong potential to affect the reaction rate.



Figure 2: ESI-MS of [BMIm]Cl recorded in DMF, 1 μ M. a) Low mass 50-1000 m/z. 139.1 and 313.2 m/z peaks correspond to [BMIm]⁺ and {[BMIm]₂Cl]⁺, respectively. b) High mass 450-4000 m/z showing {[BMIm]₃₋₉₂Cl₂₋₈₈} ⁽¹⁻⁴⁾⁺ peaks.

The extent of clustering is largely dependent on the ionic bond strength and, therefore, clusters were generated from pairs of different cations (i.e. from two salt catalysts with chloride as the anion), which were then fragmented to assess the relative bond strength of each ion pair.^{33,34} ESI-MS/MS fragmentation studies were performed on cluster ions of formula {[C1][A][C2]}⁺ with the most weakly bound cation dissociating from the cluster, and the remaining neutral ion pair not being observed. By generating mixed ion-clusters of all possible combinations of the

salts, followed by fragmentation studies, a relative cation-anion binding scale was generated. The relative binding strength of the ion pairs is [HOEMIm]Cl > [BMIm]Cl > [BMP]Cl > [BdMIm]Cl > [TBA]Cl > [Ph₄P]Cl, which is in complete agreement with the prediction, where more tightly bound ion pairs result in lower catalytic activity of the salt. Furthermore, the binding strength of the [Ph₄P]⁺ cation is, comparatively, so small that a mixed cluster of this cation was only generated with the other weakest interacting [TBA]⁺ cation. In all other cases, where a second salt was present, no {[Ph₄P]_xCl_y}^{x-y} clusters or [Ph₄P]⁺ mixed clusters were detected.

To quantify the trend and differences observed for the salts, binding energies (BEs) and binding free energies (BGs) of isolated ion pairs were estimated using DFT calculations (SI). The calculated BEs and BGs (Table 2) confirm the order of binding strength estimated by ESI-MS/MS. In addition, polar aprotic solvents such as DMF and DMSO can efficiently separate the ion pairs by charge screening, resulting in the loss of the reaction trend observed under solvent-free reactions. Combined, the ESI-MS/MS studies and DFT calculations support the proposed hypothesis that salts with lower BE exhibit higher catalytic activities. The influence of ion pairing on catalytic activity, however, can be reduced by the reaction solvent.

Table 2: DFT calculated binding energies and binding free energies of the salts studied (kcal·mol⁻¹).

Entry	IL	Binding energy	Binding free energy	_1
1	[HOEMIm]CI	103.2	104.7	2
2	[BMIm]CI	96.2	99.3	3
3	[BMP]CI	95.2	98.1	4
4	[BdMIm]Cl	94.0	97.5	5
5	[TBA]CI	89.2	91.0	6
6	[Ph₄P]Cl	81.8	83.2	7

Different anions can result in large changes in the catalytic activity as demonstrated with the halide series, where $I^- < Br^- < CI^- << F^-$.¹¹ In contrast, tetrafluoroborate (BF₄-) and hexafluorophosphate (PF₆-) salts are catalytically inactive.¹⁰ Based on these observations and the fact that [TBA]F can activate hydrosilanes in the reduction of carbonyls,^{35–39} the activity of salt catalysts was attributed to the nucleophilicity of the anion and its ability to activate the hydrosilane reducing agent prior to CO₂ insertion.^{10,11} A number of salts including [TBA]F,¹¹ Cs₂CO₃,¹⁹ glycine betaine,⁴⁰ zwitterionic P-ylide-CO₂ adducts⁴¹ and various carboxylates⁴² were proposed to act this way. However, more recent experimental evidence with tetra-nbutylammonium acetate ([TBA][OAc]) suggests that the reaction is base catalyzed.¹⁸

Hence, we decided to test a series of TBA⁺ salts with anions of varying basicity in order to examine the effect of the base strength on the N-formylation reaction (Table 3). To facilitate comparison, reaction conditions were employed that give intermediate N-methylaniline conversions with the most active [TBA]F and [TBA][OAc] catalysts (5 mol% catalyst, DMSO, 1 bar CO_2 , 25 °C, 1 h). The polar aprotic solvent DMSO was chosen

as it limits the effect of ion pairing (Table S1) and due to the availability of extensive pKa tables in this solvent.

Surprisingly, in the N-formylation of N-methylaniline, all catalysts with pKa ≥ 7.5 afforded N-methylformanilide in around 50% yield (the maximum expected based on the experimental conditions), whereas all salts with $pka \le 4.0$ were almost inactive (Table 3). A linear increase in activity is observed for catalysts of intermediate basicity with pKa values between 4.0 and 7.5 (Figure 3a). The only exception are para-substituted benzoate and phenolate anions (Table 3, entries 5, 9 and 11), where the yields are slightly lower than predicted from the linear trend, presumably due to steric factors. Hence, it would appear that the reaction is indeed base catalyzed by salts with pKa > 4.0, with a maximum activity reached at pKa values ≥ 7.5. The minor variations observed for anions with pKa values \geq 7.5 can be attributed to the difference in BEs and ion pairing (vide supra) and to varying degree of catalyst inhibition by the reversible binding of the anion to the hydrosilane.¹⁸

Table 3: N-formylation of N-methylaniline with a series of tetra-nbutylammonium salts with anions of varying basicity.

	1	Catalyst (5 mol%)	°
\bigcirc	≻ + PhSiH ₃ + CO ₂ — (1 bar)	25 °C 1 h	
Entry	Catalyst	pKa*	Yield (%)
1	[TBA]Br	0.9	0
2	[TBA]CI	1.9	1
3	[TBA][CF ₃ CO ₂]	3.5	1
4	[TBA][sacharinate]	4.0	1
5	[TBA][2,4-dinitrophenolate]	5.1	3
6	[TBA][thiobenzoate]	5.2	25
7	[TBA][2-carboxybenzoate]	6.2	32
8	[TBA][dichloroacetate]	6.4	36
9	[TBA][2-hydroxybenzoate]	6.6	26
10	[TBA][SAc]	6.7	38
11	[TBA][2,4-dihydroxybenzoate]	7.1	26
12	[TBA][NO ₂]	7.5	53
13	[TBA][4-nitrobenzoate]	9.1	49
14	[TBA][benzoate]	11.1	50
15	[TBA][benzotriazolate]	11.9	52
16	[TBA][OAc]	12.6	46
17	[TBA][phthalimide]	13.4	53
18	[TBA]F.3H₂O	15.0	51

Reaction conditions: catalyst (5 mol%), N-methylaniline (1 mmol), phenylsilane (2 mmol), DMSO (1 ml), CO₂ (1 bar), 25°C, 1 h, average GC yield from three runs with decane as internal standard. *pKa of conjugate acid (BH⁺). $^{43-46}$



Figure 3: Dependency of reaction yield on the pKa of the catalyst in DMSO in the N-formylation of a) N-methylaniline, b) 3,5-dimethylaniline and c) benzylamine.



Figure 4: The two highest energy transition states along the N-formylation pathway $% \left(\frac{1}{2} \right) = \left(\frac{1}{2} \right) \left(\frac{1}{2}$

Based on DFT calculations with NHCs,47 it was proposed that a base catalyst stabilizes the formation of a carbamate salt, which in turn activates the hydrosilane for CO₂ insertion (i.e. acting as a nucleophile) (Figure 4, TS1). Recently, a similar observation was made with [TBA][OAc], where a synergistic effect on the rate of CO₂ reduction between the [TBA][OAc] catalyst and Nmethylaniline was observed.¹⁸ From the activity-pKa trend recorded here, it would appear that for N-methylaniline, a catalyst with pKa values > 4.0 is required for the carbamate salt stabilization, with maximum stabilization reached for all TBA+ salts with pKa values ≥ 7.5 in DMSO irrespective of the structure of the anion. In addition, the stability of the carbamate salts are further enhanced by polar solvents,48 which can also partly explain the differences among the solvent free reactions and reactions carried out in MeCN, DMF and DMSO. However, since carbamate salt formation is predominantly dependent on the amine used the observed trend with N-methylaniline does not directly apply to other amines. In addition, the reaction mechanism was shown to be, at least in part, substrate dependent reflecting the tendency of some amines to spontaneously form carbamate salts.¹⁸ We therefore decided to evaluate two additional amines, 3,5-dimethylaniline (Table S2), which interacts strongly with CO₂, and benzylamine (Table S3), which spontaneously forms a stable carbamate salt with CO2 even in the absence of a base catalyst. With 3,5-dimethylaniline a similar trend to N-methylaniline is observed (Figure 3b). The only difference being the apparent onset of the base catalyzed reaction mechanism, as an upward trend is observed in the pKa range from 0.9 to 8 instead of the range from 4.0 to 7.5, where the activity plateaus. With benzylamine no clear upward trend is observed (Figure 3c). However, a small step change in conversion takes place between catalyst pKa values of 1.9 and 3.5, indicating that a base catalyst plays a role even for Nformylation of amines that spontaneously form stable carbamate salts.

These trends are consistent with the ability of the amine to form a carbamate salt, which depends on the basicity of the amine and inversely on the extent of its substitution.49 As a result, 3,5-dimethylaniline requires weaker bases for carbamate salt stabilization, whereas the N-substituted N-methylaniline requires stronger bases to achieve a comparable reactivity. In addition, the absence of a clear pKa-activity trend for benzylamine confirms the formation of a carbamate salt as the rate determining step for amines that do not spontaneously form stable carbamate salts. Reaction of the amine with a formoxysilane intermediate was proposed as a second base stabilized transition state along the reaction pathway (Figure 4, TS2),⁴⁷ which can explain the small increase in benzylamine conversion if the rate-determining step is shifted to the latter transition state. Overall, these trends confirm the reaction as base catalyzed and indicate the optimal base strength for each substrate.

While the base catalyzed reaction mechanism can explain the linear increase in the reaction rate observed for Nmethylaniline and 3,5-dimethylaniline, as well as the absence of such an increase for benzvlamine, it does not explain the catalytic activity of [TBA]Cl in the N-formylation of Nmethylaniline. Although, under the modified reaction conditions (5 mol% catatalyst, 1 h), N-methylaniline conversion with [TBA]CI remains around 1%, [TBA]CI is an active catalyst, which resulted in the reaction yield increase from 13 to 70% under the original reaction conditions (10 mol% catalyst, 6 h) in DMF (Table 1, entries 14 and 19). Since chloride is a conjugate base of a strong acid it is unlikely to act as a base. However, it can act as a nucleophile following the original reaction pathway proposed and directly activate the hydrosilane for CO₂ insertion.^{10,11} In addition, the base catalyzed pathway is, in principle, also dependent on nucleophilic activation of the hydrosilane, but the role is fulfilled by the carbamate formed rather than directly by the catalyst.⁴⁷ As a result, the role of the catalyst may be different, but the overall path remains mostly unchanged, thus allowing a large number of bases and nucleophiles to act as catalysts for the reaction. Nevertheless, the base catalyzed mechanism remains energetically favored for catalysts that can stabilize the carbamate salt.

Overall, including an earlier report on IL catalysts,¹⁰ three groups of salts can be identified (Figure 5). First are salts with non-nucleophilic/non-basic anions such as BF₄⁻ and PF₆⁻ which are inactive. The second group is mildly active and is composed of salts with nucleophilic anions such as Br, Cl⁻ and CF₃CO₂⁻. These promote the nucleophilic pathway towards N-formylamines for amines of low basicity. The third group comprises very active catalysts and is composed of salts with

basic anions such as F⁻ or OAc⁻. The transition from the nucleophilic pathway to the basic pathway is substrate dependent and for N-methylaniline appears around a catalyst pKa of 4, and no further benefit is observed by increasing the pKa above 7.5. In comparison, all tested catalysts appear to promote the basic pathway for 3,5-dimethylaniline, marked by a gradual increase in catalytic activity with increasing basicity of the anion, and only a small step increase is observed for benzylamine, where carbamate salt formation is not the ratedetermining step.

Inactive anions

F、F F、F

Nucleophilic anions

$$I \stackrel{\Theta}{\longrightarrow} Br \stackrel{O}{\longrightarrow} CI \stackrel{O}{\longrightarrow} F_{3}C \stackrel{O}{\longrightarrow} O$$

Basic anions



Figure 5: Examples of salt anions divided into three groups based on the promoted reaction pathway with N-methylaniline as the substrate.

Conclusions

By combining the ion pairing data with the anion data, structure activity relationships can be derived between the salt catalyst and its catalytic activity in the N-formylation reaction. First, the ion binding energy and associated ion pairing should be minimized either by the design of the salt, i.e. delocalized or buried charge on the cation to minimize ionic interactions with the anion⁵¹ and use groups that minimize non-covalent interactions.52 Alternatively, the use of polar aprotic solvents such as DMF which solvate and separate the ions can be used. Since hydrogen bonds significantly increase the ion binding energy, hydrogen bond donor groups on the cation should be avoided. Second, both nucleophilic and basic anions can be used as catalysts, but considerably higher activity is observed with basic anions with pKa > 4 and maximum above 7.5 for Nmethylaniline. Similar maxima appear above pKa values of 8 for 3,5-dimethylaniline and 3.5 for benzylamine. Further increasing the pKa of the anion above these pKa values provides little catalytic benefit, but allows for a wide window of modifications in order to reach the desired physical properties of the salt catalyst. The influence of the pKa also supports the role of salt catalysts as bases in the reaction, the role of carbamate salts in the ratedetermining step of the reaction, and indicates that almost any base with the desired pKa and physical properties (i.e. ensuring solubility of the catalyst in the reaction medium) can be used as a catalyst for this reaction.

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FULL PAPER

Unbound and basic: Almost all salts promote the N-formylation of amines with CO_2 . However, not all do it well. Herein, we present the physical parameters of salt catalysts critical for high activity. Namely their basicity, which is linearly proportionate to the catalytic activity of the salt and the extent of ion pairing, which also impacts significantly on the activity.



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Delineation of the Critical Parameters of Salt Catalysts in the N-Formylation of Amines with CO₂

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