New Formylating Agents − Preparative Procedures and Mechanistic Investigations[‡]

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The reactivity of new formylating agents related to formamide has been investigated both experimentally and theoretically. The reaction in 1,2-dichloroethane between tris(diformylamino)methane (**2**) and several arenes, catalyzed by $AlCl_3$ or BCl_3, was shown to proceed in good yields to afford the corresponding *para*-substituted aldehydes. The nature of the active electrophilic species was also investigated theoretically. Thus, the relative stability of the *O*- and *N*-protonated forms, as well as those of $AlCl_3$ adducts, of several formylating agents – diformamide, triformamide, *N*,*N*,*N*′,*N*′-tetraformylhydrazine, and tris(diformylamino)methane – were determined in the gas phase and in water or DCE by means of DFT calculations at the B3LYP/6-311++G(d,p) level, the solvents being modeled with the IPCM method. The amide oxygen atom in all cases appeared to be the most basic site, both in the Brønsted and Lewis sense, constituting a first step towards the understanding of the mechanism of this reaction.

Introduction

Despite the great importance of (hetero)aromatic aldehydes as intermediates in the chemical and pharmaceutical industries, and the continuing intense research in this field, there is still a need for new synthetic methods for the introduction of the aldehyde group into (hetero)aromatics. The introduction of a formyl group by C−C bond formation is generally achieved by means of various kinds of electrophilic aromatic substitutions, which can be subdivided further into two types of reactions: (a) reactions involving the acid-promoted generation of a formyl cation or a precursor thereof, such as formyl fluoride/boron trifluoride (Olah formylation),[1] CO/HCl (Gattermann−Koch reaction),[1,2] CO/HF,[1] HCN/HCl (Gattermann reaction),[3] and the Vilsmeier reagent,[1] formed from disubstituted formamides and phosphorus oxychloride or phosgene, and (b) reactions yielding primary products which are immediately oxidized to aldehydes, such as the synthesis of salicylaldehydes from phenols and paraformaldehyde in the presence of $SnCl_4$/trioctylamine[1,4] or the Duff reaction, yielding aromatic aldehydes from activated aromatic compounds and urotropine in the presence of acids.[1,5]

Nowadays, the Vilsmeier (or Vilsmeier−Haack) reaction is the most common method for formylation of aromatic rings. Nevertheless, it, like the other methods, has some significant disadvantages. The formylating agents in these reactions are often toxic (as in the cases of carbon monoxide, hydrogen cyanide, formyl fluoride, and phosgene), and they are also difficult to handle in large amounts. Furthermore, the scope of these reactions is limited. The Vilsmeier−Haack reaction is the method with the widest scope, but it is incapable of formylating simple alkylarenes (unless they are much more reactive than benzene). A further difficulty is the occurrence of phosphorus compounds in wastewater, which is a serious environmental problem, and the formation of highly toxic, carcinogenic dialkylcarbamoyl chloride in a side reaction. The dichloromethyl methyl ether/Lewis acid formylating system has an even wider scope than the Vilsmeier−Haack reagent, but it has not yet found practical use.[1,3,6]

Formamide Derivatives as Formylating Agents

Some time ago, we reported on a new synthetic method for the formylation of (hetero)aromatic compounds using triformamide (**1**)/$AlCl_3$ as the formylating system (Scheme 1).[7,8] This reaction is useful for the formylation of a wide range of substrates, including unsubstituted and alkyl-substituted aromatics, aromatic ethers, tertiary aromatic amines, fused aromatic rings, and thiophenes.

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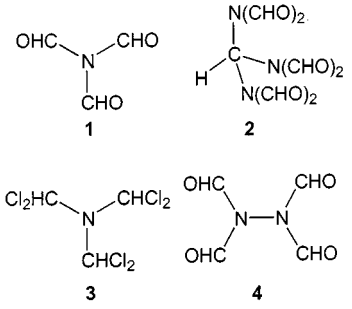


Scheme 1. New formylating agents based on formamide derivatives

In this paper we wish to introduce some other reagents based on formamide derivatives that can be used to formylate (hetero)aromatic compounds. We also present results of computational investigations aimed at elucidation of the reaction intermediates of these formylations.

The typical mechanism of electrophilic aromatic substitution reactions involves, as a preliminary step, the formation of the actual electrophilic species. In the case of amides, it is assumed that the Lewis basic site is the oxygen atom, by analogy with the behavior towards protonation.[9] However, there is no guarantee that the behavior towards the proton exactly matches that towards other Lewis acids. Thus, although one can easily formulate the generation of the electrophilic species as a Lewis acid/base process involving the amide oxygen atom as the basic site, the actual nature of the active species must be elucidated independently. For this purpose, we have carried out quantum chemical calculations aimed at quantitative determination of the extent of preference of formylating agents for protonation or Lewis acid complexation at either the oxygen or nitrogen atom in the amide group.

Results and Discussion

Formylations with Tris(diformylamino)methane

During the preparation of triformamide (**1**),[11,12] tris(diformylamino)methane[10] (**2**) is formed as a by-product.[8] In an improved method, **2** can be prepared from triformamide and sodium diformamide[13,14] in 80% yield.[8,15]

Tris(diformylamino)methane (**2**) is a stable, high-melting (142 °C), nonhygroscopic, and nonetching compound. The compound is nearly odorless and easy to handle. Although toxicological data are not available, its manipulation hazards may be estimated as similar to those of formamide.

Tris(diformylamino)methane (**2**) contains six formyl groups, plus an additional one masked as an orthoamide function, which seems to set a record for this type of compounds. In the presence of (strong) Lewis acids, it is capable of formylating activated arenes.[8,15] The efficiency of **2** as a formylating agent is higher than that of triformamide (**1**), since up to three out of the seven formyl groups in **2** can be used synthetically, whereas **1** can transfer only one of its three formyl groups.

In the presence of $AlCl_3$ or BCl_3, alkylarenes and aromatic ethers are formylated by tris(diformylamino)methane (**2**) in moderate to good yields (see Table 1). With $AlCl_3$ as the Lewis acid, yields are highest if a tris(diformylamino)-methane/$AlCl_3$ ratio of 1:6 to 1:8 is used (see Table 2). This corresponds to a ratio of 1:2 with regard to the number of formyl groups transferred, a value coincident with the ratio found in the Friedel−Crafts acylation of esters and anhydrides. 1,2-Dichloroethane proves to be the best solvent for the reaction, although other solvents, such as chlorobenzene and carbon disulfide, are also suitable. Solvents containing nitro groups, such as nitromethane and nitrobenzene, seem to suppress the formylating reaction, probably because of complexation of the Lewis acid.

Table 1. Formylation of activated aromatic compounds with **2**/Lewis acid in 1,2-dichloroethane

Substrate	Lewis acid[a]	Reaction conditions[b]	Procedure/workup[b]	Yield [%][c]	b.p. [°C/Torr]	Ref.
Toluene	$AlCl_3$	−15→0 (20)	I	55	84/12	204−205 °C/760 Torr[26]
Cumene	$AlCl_3$	−13→−1 (14)	II/A	38	41−42/0.2[d]	103−104 °C/10 Torr[26]
tert-Butylbenzene	$AlCl_3$	−15→−1 (16)	II/B	33	63/0.2	128−129 °C/760 Torr[27]
Hexylbenzene	$AlCl_3$	−13→−1→20 (15/2)	II/B	55	90−93/0.2	70 °C/2·10^{-5} Torr[28]
o-Xylene	$AlCl_3$	−19→−1 (15)	I	42[e]	96/0.2	223−225 °C/760 Torr[26]
p-Cymene	$AlCl_3$	−15→−3 (15)	II/B	45[f]	50−51/0.2	125 °C/20 Torr[29]
Biphenyl	$AlCl_3$	−13→−1 (16)	II/A	54	102/0.2	184 °C/11 Torr[30]
Diphenyl ether	$AlCl_3$	−13→1 (16)	II/B	20	98−101/0.2	158−159 °C/4 Torr[31]
Resorcinol dimethyl ether	$AlCl_3$	−13→2 (15)	II/B	45[g]	93/0.2 (m.p. 68 °C)	165 °C/10 Torr[26] (m.p. 70−71 °C[31])
p-Cymene	BCl_3	−13→−1 (15)	I	18[f]	50−51/0.2	125 °C/20 Torr[29]
Anisole	BCl_3[h]	−10→1 (14)	II/B	20	54/0.02	118−120 °C/13 Torr[5]

[a] Molar ratio substrate/**2**/Lewis acid (3:1:6). − [b] Initial and final reaction temperature [°C], and reaction time [h] in parentheses. See Exp. Sect. for synthetic and workup procedures. − [c] Product is always the *p*-substituted benzaldehyde. Yields are based on tris(diformylamino)methane under the assumption that 1 mol of the reagent supplies 3 mol of "formyl groups". − [d] n_D^{20}=1.5390 (1.5301[26]). − [e] Product: 3,4-dimethylbenzaldehyde. − [f] Product: 5-isopropyl-2-methylbenzaldehyde. − [g] Product: 2,4-dimethoxybenzaldehyde. − [h] Molar ratio substrate/**2**/Lewis acid (3:1:4).

Table 2. Influence of molar ratio of reagents on yield of formylation of *o*-xylene with tris(diformylamino)methane (**2**) in the presence of $AlCl_3$ (Procedure I)

Molar ratio[a] *o*-Xylene	$AlCl_3$	Yield%[b]
3	4[c]	42
3	5	46
3	6[c]	42
4	5[c]	47
4	6	59
4	8	65
6	6[c]	44
6	6	63
6	8	72
6	10	75
6	12	64[d]
14[e]	12	65
15.3[e]	4	45

[a] With respect to **2**. – [b] Product is 3,4-dimethylbenzaldehyde. Yield calculated for transfer of 3 formyl groups per molecule **2**. – [c] "Aged" $AlCl_3$ (partially hydrolyzed by repeated opening of the container). – [d] 1,2-Bis(3,4-dimethyphenyl)ethane (3 %) was obtained as a by-product. – [e] Reaction performed without additional solvent.

The reaction features a high *para* selectivity in the substrate, consistent with the high steric bulk of the attacking species. As can be appreciated from Table 1 and Table 2, in order to achieve satisfactory yields with formamide derivatives bearing one or more diformylamino groups, it is necessary to use at least 2 equiv. of Lewis acid. It is hence very likely that the primary adduct reacts with further Lewis acid to form the formylating species.

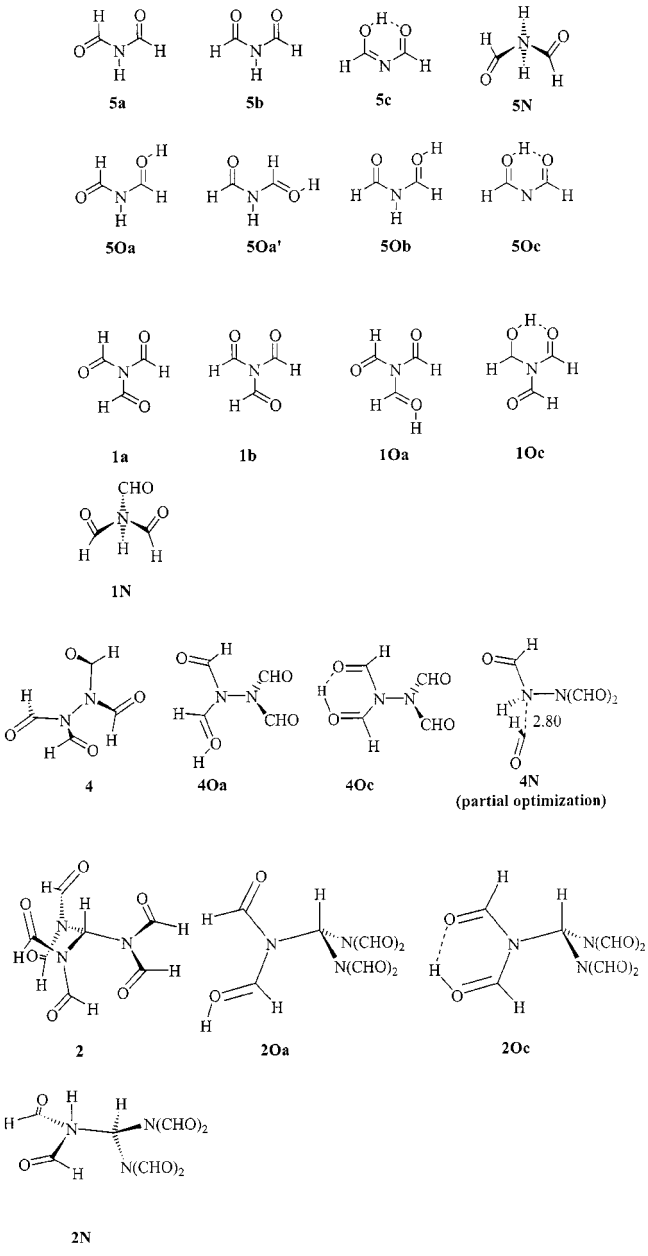
Lastly, we emphasize that the method we have presented can be performed using only stoichiometric amounts of the formamide derivative, and 2 equiv. of Lewis acid per formyl group transferred. E-factors (kg of waste per kg of product) of the new formylation procedures are in the range from 4 to 11; further investigations will show whether these values can be reduced by use of other types of catalysts. The comparable method with dichloromethyl methyl ether often employs a large excess of the formylating mixture (up to 18 equiv.),[16,17] and the regioselectivity is rather low.[18]

Formylation with Other Formamide Derivatives

The perchlorinated derivative of triformamide, tris(dichloromethyl)amine (**3**),[12] can be prepared from *N*,*N*-dimethylformamide and phosgene, followed by photochlorination of the resulting *N*,*N*-dimethylformamide chloride. In the presence of various Lewis and Brønsted acids, **3** also proves to be a good formylating agent, and it is suitable for the formylation of a wide range of aromatic compounds.[8] Thus, toluene reacts with **3**/$AlCl_3$ to give tolualdehyde, in a yield of 70% and a *p*/*o* ratio of 30:1. Similarly, anisaldehyde can be prepared from anisole and **3**/$ZnCl_2$ in 62% yield (*p*/*o* 24:1) (see Exp. Sect.). However, this complex subject will be dealt with in more detail in a forthcoming paper. Preliminary studies on the formylating ability of another formamide derivative, *N*,*N*,*N*′,*N*′-tetraformylhydrazine (**4**), are also encouraging.[19,20]

Quantum Chemical Calculations

The formamide derivatives discussed above (**1**–**5**) are activated through complexation with a Lewis acid. All these bases are structurally related to formamide, and contain at least two basic sites: a nitrogen atom and an oxygen atom. In order to provide information on the nature of the electrophilic species thus formed, we determined the relative stability of the species that can be formed by protonation or adduct formation with a Lewis acid. Thus, the site and energetics of protonation and $AlCl_3$ adduct formation by some formamide derivatives were investigated computa-



Scheme 2. Calculated structures of formamide derivatives **1**–**5** and their protonated forms

tionally by means of DFT calculations. All calculations were performed with Gaussian 98;[21] the stabilities were determined both for the isolated species and in solution, the solvent effect on the equilibria being modeled by the IPCM continuum method.[22] Atomic charges (see below) were calculated with the NBO method.[23] The bases studied were: diformamide [$HN(CHO)_2$] (**5**), triformamide [$N(CHO)_3$] (**1**), *N*,*N*,*N*′,*N*′-tetraformylhydrazine [$(CHO)_2N-N(CHO)_2$] (**4**), and tris(diformylamino)methane {$HC[N(CHO)_2]_3$} (**2**). The structures and conformations thus obtained are shown in Scheme 2 and 3. Geometrical features are only given in the Supporting Information as PDB files, except where such features are discussed in the text. Even though the analysis for formamide had previously been carried out in our laboratories,[9] we repeated the same calculations to ensure maximum homogeneity in data comparison.

Absolute and relative proton affinities were calculated (for the most stable conformer only) as follows. For $HCONH_2$, $HN(CHO)_2$, $N(CHO)_3$, $(CHO)_2N-N(CHO)_2$, and their protonated forms, gas-phase data were obtained at the B3LYP/6-311++G(d,p) level and geometry, including zero-point vibrational energy corrections (ZPE). All species were thus characterized as minima on the respective potential energy surfaces, except where noted. Energies in water were calculated at the IPCM-B3LYP/6-311++G(d,p) level at the gas-phase geometry, assuming a dielectric permittivity of $\varepsilon = 78.5$. For the larger species $HC[N(CHO)_2]_3$ and associated protonated forms, the smaller 6-31+G(d,p) basis set was used, other methods being the same. Absolute and relative proton affinities (PA) (Table 3) were obtained with reference to the most stable conformers of the neutral and the protonated forms, where applicable.

Table 3. Calculated proton affinities and protonation sites

Species	PA[a]	$\Delta E_{(g)}$[b][c]	$\Delta E_{(aq)}$ [b][c]
Formamide	196.0[d]		
$HCONH_3^+$		+17.4	+11.3
$HC(OH)NH_2^+$		(0.0)	(0.0)
Diformamide (**5**)	187.8		
$H_2N(CHO)_2^+$		+24.7	+21.7
$HN(CHO)(CHOH)^+$		(0.0)	(0.0)
Triformamide (**1**)	185.4		
$HN(CHO)_3^+$		+28.5	+28.4
$N(CHO)_2(CHOH)^+$		(0.0)	(0.0)
N,*N*,*N*′,*N*′-Tetraformylhydrazine (**4**)	180.7		
$(CHO)_2NH-N(CHO)_2^+$ [e]		–	–
$(CHO)_2N-N(CHO)(CHOH)^+$		–	–
Tris(diformylamino)methane (**2**)	192.5		
$HC[N(CHO)_2]_2[NH(CHO)_2]^+$		+22.5	+31.6
$HC[N(CHO)_2]_2[N(CHO)(CHOH)]^+$		(0.0)	(0.0)

[a] Proton affinity for *O*-protonation. – [b] Energies [kcal/mol] in the gas phase calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level, including zero-point vibrational energy corrections (ZPE); energies in water at the IPCM-B3LYP/6-311++G(d,p) level with the gas-phase geometry, assuming $\varepsilon = 78.5$, except for the protonated forms of **2**, calculated with the 6-31+G(d,p) basis set. – [c] Energy difference between the two tautomeric protonated forms, referenced to the most stable *O*-protonated form (**c** in the gas phase, **a** in water; see text). – [d] Experimental PA: 196.5 kcal/mol (ref.[32]). – [e] Not a minimum on the potential energy surface (expulsion of HCO^+; see text).

Diformamide (5)

Conformational analysis of the simplest member revealed that the conformer with the carbonyl groups farthest apart (**5a**) is more stable (by 6 kcal/mol) than that with those groups eclipsed (**5b**). In addition to these, the possibility of the enol form (**5c**) being present should be considered. Even though amides are known to be enolized only to a very small extent, species containing an $N(CHO)_2$ moiety might be stabilized by intramolecular hydrogen bonding (see Scheme 2). However, **5c** proved to be substantially less stable (17 kcal/mol) than **5a** or **5b**.

Various possible conformations of its *O*-protonated forms (**5Oa–c**) were considered, including the closed species (**5Oc**), formally related to **5c**. All lie within 6 kcal/mol of each other, the closed form **5Oc** being the most stable thanks to its internal stabilization. However, 5**Oa**′ (related to the most stable neutral conformer 5**a**, and presenting the typical arrangement of protonated amido groups,[9,24]) is only slightly less stable (1.8 kcal/mol), whereas **5Ob** (with eclipsed carbonyl groups as in **5b**) is the least stable. Geometry optimization of the other conceivable conformer deriving from **5b** led to the **5Oa**′ structure. AM1 semiempirical geometry optimization of all conceivable conformers of the *N*-protonated form (**5N**), on the other hand, resulted in the single structure depicted in Scheme 2.

Proton affinities (Table 3) were obtained with respect to the most stable conformers of the neutral (**5a**) and the protonated forms (**5Oc** and **5N**). The data indicate a stronger gas-phase basicity of oxygen relative to nitrogen by 25 kcal/mol, and thus by a larger margin than in formamide (17 kcal/mol; cf. 15 kcal/mol[9]).

Calculations in water indicated a similar relative stability of **5a** and **5b**, with **5a** still being the most stable conformer (with $\Delta E = 4$ kcal/mol). Again, the enol form **5c** is much less stable. With regard to the conformers of **5O**, we note that the closed form **5Oc**, somewhat more stable in the gas phase (see above), is not particularly favored in water, being 1.7 kcal/mol less stable than the reference conformer **5Oa**′. In any event, a marked preference for *O*-protonation is again indicated, as judged from the relative PAs of 22 kcal/mol.

At this point, we can provide an initial assessment of the conformational and keto/enol effect on the proton transfer: (a) the enol form is much less stable than the keto form both in the gas and aqueous phases, and (b) the various conformers of the *O*-protonated form differ by at most 6 kcal/mol in energy, the closed form being the most stable in the gas phase but not in water. Hence, (a) the neutral enol form is disregarded in all further calculations, and (b) for consistency, relative proton affinities in the gas or water phases are calculated as the energy difference between different conformers; given the small spread of their stabilities, however, the final outcome in terms of *O*-protonation vs. *N*-protonation is not affected. Such considerations are also applicable to the other bases.

Triformamide (1)

The two possible conformers for neutral **1** (**1a**, **1b**) differ in the orientation of a CO group, and are remarkably similar in energy both in the gas phase and in water (ΔE = 1−3 kcal/mol). The protonation site in **1** is, again, oxygen rather than nitrogen, with a slightly larger energy gap (28 kcal/mol) in both phases.

N,*N*,*N*′,*N*′-Tetraformylhydrazine (4)

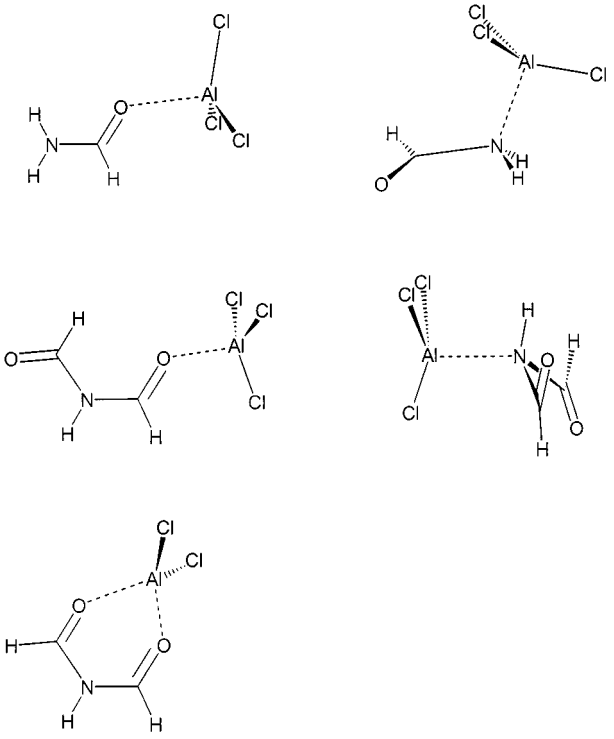
Because of the size of this system, conformational analysis on the neutral species was carried out at the AM1 level, in order to pinpoint the most stable conformer for further calculations (Scheme 2). Only the *O*-protonated species could be characterized as an energy minimum (two conformations, **4Oa** and **4Oc**). In contrast, geometry optimization of **4N** resulted in a major lengthening (> 2.8 Å) of an H(O)C−N bond involving the protonated nitrogen atom, essentially corresponding to the expulsion of a formyl cation. Thus, the partially optimized structure of **4N** may be viewed as a loose complex between neutral *N*,*N*,*N*′-trisformylhydrazine and the HCO^+ ion. The lengthening of the bond between N and the acid residue is a general phenomenon in protonated amides; expulsion of the ionic acyl group has been predicted for *N*-protonated nitrosamine ($H_3N\cdots NO^+$) and phosphorous acid triamide [$H_3N\cdots P(NH_2)_2^+$], as well as for *O*-alkyl-protonated formic acid and methyl formate ($HOR\cdots HCO^+$).[9] While this occurrence prevents us from quantitatively estimating the nitrogen basicity of **4**, it nevertheless further points out the higher stability of the *O*-protonated form. By comparison with **5** and **1**, we can infer that the same conclusions hold in water as well.

Tris(diformylamino)methane (2)

This base can be envisaged as three closely spaced but unrelated diformamide (**5**) systems. For this large and flexible species, no conformational analysis was carried out, but each individual formamido group was assumed to lie in the conformation previously found to be more stable for **5** (Scheme 2). Not surprisingly, the picture is similar to that of **5**, the oxygen again being the preferred protonation site (by 22 and 32 kcal/mol for the gas and aqueous phases, respectively).

Aluminum Chloride Affinities

Complexation with a Lewis acid such as $AlCl_3$ is a method widely adopted for carbonyl group activation, including that of amides, towards nucleophilic addition. The complexation is normally thought of as taking place at the oxygen atom; nevertheless, this needs to be confirmed independently. To this end, we ran the same series of calculations as seen for proton transfer in order to determine the relative stability of *N*- and *O*-adducts with $AlCl_3$. Furthermore, the ability of **2** to transfer several formyl groups (see above) suggests the intermediate formation of a complex in which $AlCl_3$ loses a chloride ion (as $AlCl_4^-$) and acts as a bidentate acceptor towards a diformamide unit (see Scheme 3). To test the viability of this, we also ran calculations on such a structure.



Scheme 3. Calculated structures of complexes between formamide, diformamide (**5**), and $AlCl_3$

On the basis of the results reported in the preceding section, which showed a remarkable similarity of behavior between the various derivatives investigated, we restricted the calculations to formamide itself as the Lewis base model, and to diformamide (**5**). The calculations were run at the same level as seen before, except that the estimation of the absolute $AlCl_3$ affinity was performed correcting for the basis set superposition error (BSSE) by the counterpoise method.[25] We chose DCE (ε = 10.4) for IPCM calculations, since this was the solvent in which the reactions of interest had been carried out. These results are presented in Table 4, and the pertinent structures in Scheme 3. Complexation occurs with a small (20−24°) but appreciable deviation from planarity of the $AlCl_3$ moiety; most other structural features resemble the corresponding protonated form.

Protonation Sites, Proton and $AlCl_3$ Affinities

The absolute calculated PAs for *O*-protonation of **1**, **2**, **4**, and **5** (180−190 kcal/mol) are all lower than that for formamide (ca. 196 kcal/mol), despite their larger molecular size. This indicates a strongly reduced basicity for these compounds relative to a simple amide group, although the general features are preserved; thus, all compounds considered are oxygen bases rather than nitrogen bases. The least basic is **4**, presumably thanks to the known base-weakening effect of the hydrazo group,[9] whereas the most basic one is **2**, which agrees with its larger molecular size (and polarizability). The strong base-weakening effect of the added for-

Table 4. Calculated affinities for $AlCl_3$

Species	Gas phase[a] $AlCl_3$ affinity[b]	$\Delta E_{(g)}$ [c]	DCE[a] $AlCl_3$ affinity[b]	$\Delta E_{(DCE)}$ [c]
Formamide	40.6		42.1	
$HCONH_2\cdots AlCl_3$		+14.8		+19.6
$H_2N-CHO\cdots AlCl_3$		(0.0)		(0.0)
Diformamide (**5**)	34.3		28.5	
$(OHC)_2NH\cdots AlCl_3$		+20.6		+18.8
$HN(CHO)CHO\cdots AlCl_3$		(0.0)		(0.0)

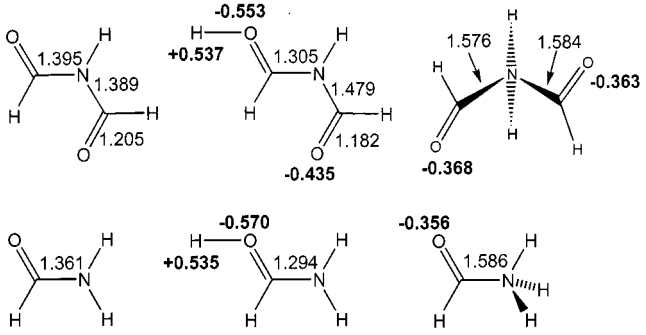
[a] Energies [kcal/mol] in the gas phase calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level; energies in 1,2-dichloroethane (DCE) at the IPCM-B3LYP/6-311++G(d,p) level with the gas-phase geometry, with $\varepsilon = 10.4$. All results are corrected for basis set superposition error. – [b] $AlCl_3$ affinity for adduct formation through oxygen. – [c] Energy difference between the two adducts, referenced to the *O*-adduct.

myl group is made evident by the smaller PA of **1** as compared to **5**. This decrease in basic strength is readily interpreted if the canonical resonance form of an *O*-protonated amide is considered, with the positive charge delocalized onto to the nitrogen atom bearing a partial positive charge. Such a resonance form is diminished in importance for the bases under consideration, since the nitrogen atom bears one or two strongly electron-withdrawing formyl groups, which obviously destabilize such resonance forms and, as a consequence, the overall stability of the ion (however, see below).

In the case of simple amides, the stability of the *N*-protonated form is enhanced in water. Thus, for $HCONH_2$, the energy gap between *O*- and *N*-protonated forms decreases from 17 kcal/mol in the gas phase (cf. 15 kcal/mol[9]) to 11 kcal/mol in water (Table 3). It is similar for MeCONHMe (in which the substitution pattern at nitrogen is the same as for **5**), with the energy gap decreasing from 14 kcal/mol in the gas phase to 7 kcal/mol in water.[24] Although the level of stabilization was found to be overestimated because of the limitations of the IPCM method,[24] it was consistently encountered, and ascribed to stronger hydration of the *N*-protonated form. Thus, for example, the data in Table 3 allow the hydration energy of $HC(OH)NH_2^+$ (−74 kcal/mol) to be estimated as less exothermic than that of $HCONH_3^+$ (−81 kcal/mol). A similar relationship holds for the hydration energies of $MeC(OH)NHMe^+$ (−63) and $MeCONH_2Me^+$ (−70).[24]

For compounds **5**, **1**, and **2**, in contrast, the relative stabilities of the two tautomeric ions either are unaffected by water or the *N*-protonated forms become even less stable. For example, the hydration energy of **5Oa′** (−75 kcal/mol) is only slightly less exothermic than that of **5N** (−78 kcal/mol). In principle, this might be due to enhanced solvation of **5Oa′**, or to diminished solvation of **5N** (or both). An analysis of the geometry and atomic charges of **5Oa′** and *O*-protonated formamide (Scheme 4) showed no great differences.

In both cases, the charges residing on the acidic hydrogen atom [$q(H) = +0.537$ and $+0.535$, respectively] were very similar, as were the charges on the acyl oxygen atom [$q(O) = -0.553$ and -0.570, respectively]; in fact, the variation in $q(O)$ for **5Oa′** [$\Delta q(O) = +0.003$] was smaller than



Scheme 4. Selected calculated bond lengths (normal typeface) and NBO atomic charges (boldface) for formamide, diformamide (**5**), and their protonated forms

that for $HC(OH)NH_2^+$ [$\Delta q(O) = +0.031$], or in other words the charge was developed at the protonated oxygen atom to a relatively smaller extent. The C–N bond (r_{CN}) was, again, shortened by a similar amount ($\Delta r_{CN} = -0.090$ and -0.067 Å, respectively). There is, however, one structural feature that sets **5Oa′** apart from $HC(OH)NH_2^+$: The bond between N and the unprotonated CO group ($r_{C'N}$) is markedly lengthened ($r_{C'N}$ = 1.389 to 1.479 Å, with $\Delta r_{C'N} = +0.090$ Å), with the carbonyl oxygen atom acquiring a large positive charge [$\Delta q(O') = +0.123$]. Thus, **5Oa′** can be viewed as an incipient complex between the neutral imido tautomer of formamide and a formyl cation, $HO-CH=NH\cdots[HCO]^+$ (although the C–N bond length is much too short to indicate a real bond break). It is, however, not obvious whether the charge distribution in this structure would in fact result in enhanced solvation.

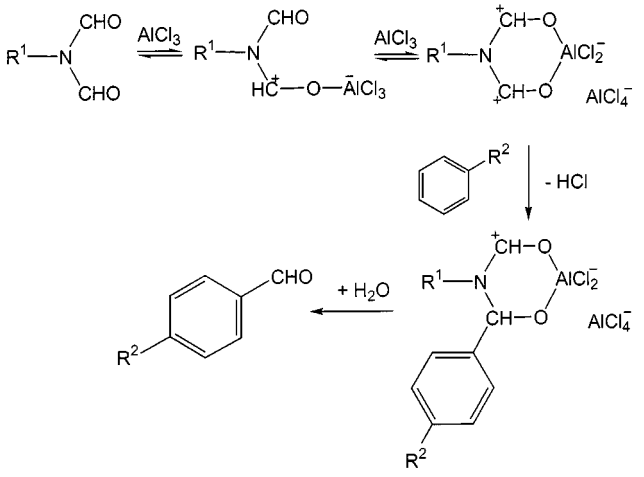
On the other hand, the structure and charge distribution of **5N** are also peculiar. In addition to the expected lengthening of both C–N bonds, a substantial positive charge is formed on the carbonyl oxygen atoms (from −0.550 and −0.558 to −0.363 and −0.368), indicative of substantial participation of both carbonyl groups in charge delocalization in **5N**, which probably accounts for its diminished solvation.

With regard to $AlCl_3$ complexation, for both formamide and **5**, *O*-complexation is favored by 15–21 kcal/mol in both phases. That is, the general behavior closely resembles that observed towards protonation. The solvent effect is

relatively small, consistent with the low dielectric permittivity of DCE. We would also like to point out that the bidentate complex in Scheme 3 is also a stable species on the potential energy surface, as confirmed by vibrational analysis.

Electrophilic Species and Formylation Mechanism

All the calculated data discussed above point to greater basicity of the oxygen, rather than the nitrogen, in the formamido group, both in the Brønsted and in the Lewis senses. It is therefore possible to point to an *O*-complexed structure such as those depicted in Scheme 3 for the reactive electrophilic species in the formylation reaction. We can thus propose a general mechanism such as that shown in Scheme 5, which also highlights the coordination of a further carbonyl group to $AlCl_3$, thus accounting for the ability of formamide derivatives to transfer more than one formyl group, as found experimentally (and predicted theoretically).



Scheme 5. Proposed mechanism for the electrophilic formylation of arenes with formamide derivatives and Lewis acids

Conclusion

Arene formylation can conveniently be carried out in satisfactory yields with formamide derivatives in the presence of Lewis acids. Quantum chemical calculations provide cogent indications of the nature of the electrophilic species involved in this reaction. Thus, in the attack by a proton or by $AlCl_3$ (protonation or Lewis acid adduct formation, respectively), the amide oxygen atom is the most basic site, both in the gas phase and in water or DCE as solvents. The formation of a chelate complex between the two adjacent carbonyl oxygen atoms in a diformamide group and $AlCl_3$ is also supported. All these results reinforce the proposition that the attacking electrophilic species is formed by attachment of the Lewis acid to the oxygen atom of the formamide derivatives, and endorse the proposed reaction mechanism (Scheme 5).

Experimental Section

Formylation of Toluene with 2 and Various Amounts of $AlCl_3$. − (Typical) Procedure I: Dry $AlCl_3$ (90 mmol) was added with stirring to a mixture of toluene (45 mmol) and dry 1,2-dichloroethane (25 mL), cooled in an ice/salt bath. After a few minutes, tris(diformylamino)methane (**2**) (15 mmol) was added. The reaction mixture was stirred in the cooling bath with exclusion of moisture for 20 h, during which the temperature rose to 0 °C. The viscous, reddish brown mixture was carefully hydrolyzed by addition of 100 mL of ice-cold water, and steam-distilled. The organic layer of the distillate was separated, and the aqueous phase extracted three times with 10 mL of 1,2-dichloroethane. The combined organic layers were dried with sodium sulfate and filtered, and the solvent was evaporated at ordinary pressure. *p*-Tolualdehyde (b.p. 84 °C/12 Torr) (204−205 °C/760 Torr[26]) was isolated by fractional vacuum distillation. Yield 25 mmol (55%).

Formylation of Aromatic Compounds with 2/Lewis Acid. − (General) Procedure II: A stirred mixture of the aromatic compound (40−60 mmol) and 1,2-dichloroethane (25−40 mL) was cooled in an ice/salt bath. The Lewis acid was added first, over 5 min, followed by tris(diformylamino)methane (**2**). During the reaction time stated, the temperature of the reaction mixture rose from ca. −15 °C to 0 °C (see Table 1). After hydrolysis by careful addition of 100 mL of water, the organic layer was separated and the aqueous phase was extracted three times with 10 mL of 1,2-dichloroethane. − **Workup A:** The organic layers were combined, and the solvent was evaporated at reduced pressure. The residue was treated with 100 mL of a saturated sodium hydrogen sulfite solution, 3 mL of methanol, and ca. 250 mg of tetrabutylammonium hydrogen sulfate. The bisulfite adduct separated upon stirring and was isolated by filtration. The adduct was cleaved by addition of either 100 mL of 8% $NaHCO_3$ solution or 20 mL of 10% HCl. The aldehyde was extracted from the mixture three times with 10 mL of ether. The combined organic layers were dried with sodium sulfate and filtered, and the solvent was evaporated. The aldehyde was obtained by fractional distillation of the residue through a 15-cm Vigreux column. − **Workup B:** The combined organic layers were dried with sodium sulfate and filtered, and the solvent was evaporated at reduced pressure. The aldehyde was obtained by fractional distillation of the residue through a 10-cm Vigreux column.

Formylation of Aromatic Compounds with 3/Lewis Acid. − (a) Tolualdehyde from 3 and $AlCl_3$: Compound **3** (7.3 g, 30 mmol) was added over 10 min, at 5 °C and with stirring, to a cooled mixture of dry toluene (25 g, 0.27 mmol) and $AlCl_3$ (11 g, 80 mmol). The cooling bath was removed and the mixture was stirred for 15 h at 20 °C. The reaction mixture was hydrolyzed with 50 mL of water and steam-distilled. The organic phase of the distillate was separated and the aqueous phase was extracted three times with CH_2Cl_2. The organic phases were combined and dried with sodium sulfate. The drying agent was removed by filtration. The solvents were removed from the filtrate by distillation at ordinary pressure. Tolualdehyde (2.31 g, 70%; 97% *p*-isomer, 3% *o*-isomer) was isolated by distillation (b.p. 80 °C/12 Torr). − **(b) Anisaldehyde from 3 and $ZnCl_2$:** $ZnCl_2$ (2.18 g, 31.6 mmol) was added to a solution of **3** (4.2 g, 15.8 mmol) in anisole (20 mL, 187 mmol), whereupon the mixture turned red. The mixture was heated with stirring for 3 h at 60−65 °C, hydrolyzed with 100 mL of water, and steam-distilled. Dichloromethane (30 mL) was added to the distillate in order to produce better phase separation. The organic phase was separated and the aqueous phase was extracted three times with 50 mL of dichloromethane. The combined organic phases were dried with sodium

sulfate. The solvents were evaporated, and the residue was distilled in vacuo through a 20-cm Vigreux column. Yield: 1.33 g (62%) anisaldehyde (96% *p*-isomer, 4% *o*-isomer), b.p. 80 °C/0.01 Torr.

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