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Hydrogen Bonds

α-Halogenoacetanilides as Hydrogen-Bonding Organocatalysts that Activate Carbonyl Bonds: Fluorine versus Chlorine and Bromine

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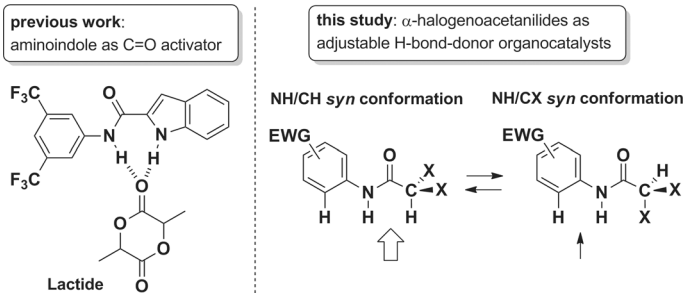
Abstract: α-Halogenoacetanilides (X = F, Cl, Br) were examined as H-bonding organocatalysts designed for the double activation of C=O bonds through NH and CH donor groups. Depending on the halide substituents, the double H-bond involved a nonconventional C–H···O interaction with either a H–CX_n (n = 1–2, X = Cl, Br) or a H–C_{Ar} bond (X = F), as shown in the solid-state crystal structures and by molecular modeling. In addition, the catalytic properties of α-halogenoacetanilides were evaluated in the ring-opening polymerization of lactide, in the presence of a tertiary amine as cocatalyst. The α-dichloro- and α-dibromoacetanilides containing electron-deficient aromatic groups afforded the most attractive double H-bonding properties towards C=O bonds, with a N–H···O···H–CX_2 interaction.

Introduction

Hydrogen-bonding catalysis has developed considerably over the last decade, as demonstrated by the numerous reviews dealing with the topic.[1] In particular, activation of carbonyl bonds by hydrogen-bond (H-Bond) donor compounds is a blossoming field of research, due to the extended scope of asymmetric transformations (Michael type additions, cycloadditions, radical cyclization, Baylis–Hillman reaction, cyanosilylation) and because of the current challenges in the controlled polymerization of cyclic esters.[2] Thus, conventional H-bond donor groups have been exploited to activate C=O bonds, using more or less complex structures based on thiourea, alcohol, phenol, amide, sulfonamide, protonated amine, guanidine and amidine, and phosphoric acid moieties. However, the search for alternative H-bond donor groups that better activate the substrate (increased electrophilicity) or enhance a selective activation towards a unique substrate in the presence of several reactants, is still valuable. Indeed, recent interest in one-pot reactions involving H-bonding catalysts[3] and the need for dual H-bonding systems in polymerization[4, 2d] (H-bond donor and acceptor) has spurred on the emergence of new, adjustable H-bond donor structures that are compatible with other catalysts and reactants.

We previously demonstrated that an amidoindole platform efficiently activates the C=O bond in the ring-opening polymerization (ROP) of lactide, as a model reaction (Scheme 1).[5]



Scheme 1. H-Bonding amide catalysts with two donor groups.

The mechanism relied on the formation of a double H-bond between the C=O of the monomer and the two NH groups of the catalyst. The acidity of the amide proton was enhanced by electron-withdrawing groups on the aromatic group, and the presence of two H-bond donor groups was necessary to better complex the lactide unit, as demonstrated by comparative catalytic properties. However, some disadvantages were ob-

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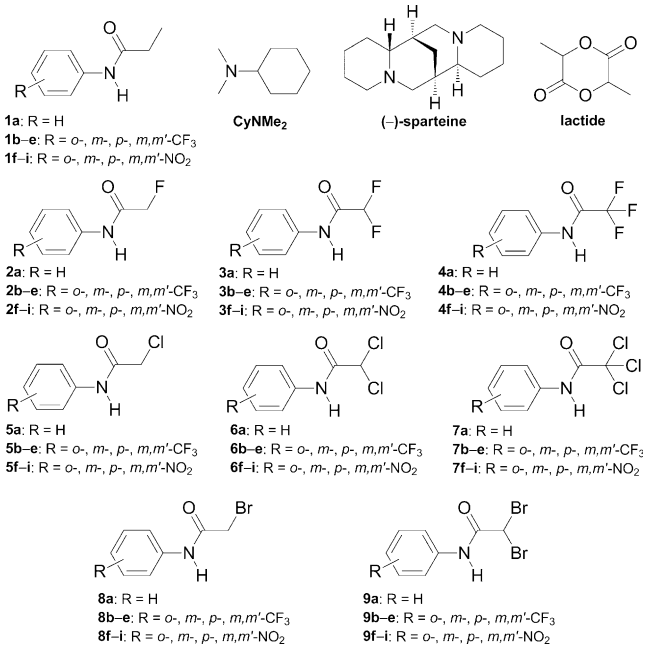
served: i) indole as a second H-bond donor was poorly adjustable thus limiting the scope of activated substrates, and ii) some amide catalysts tended to interact with the cocatalyst (tertiary amine) employed in ROP of cyclic esters, rather than with the substrate. This undesired phenomenon led to poor conversions.[5b]

Weak nonconventional C–H···O interactions were recently highlighted in natural and artificial systems that offer complementary interactions useful for structure and function (protein folding, enzyme activity, advanced materials, organic synthesis).[6] Concerning their contribution to organocatalysis, the N^+–CH moiety within quaternary ammonium groups has been exploited in asymmetric C–C bond formations[7] and ROP,[8] whereas less activated CH groups were reported in a few examples as probable participants in the stereocontrol of such reactions.[9]

Taking advantages of the H-bonding properties of anilides and keeping in mind the need for an adjustable activation of C=O bonds even in the presence of a cocatalyst or a second substrate,[3,4] we envisioned that α-halogenoacetanilides possessing a second activated H-bond donor group such as H–CX_n (n = 1–2), should be attractive catalysts (Scheme 1). If the H–CX_n bond is not available for the substrate (steric hindrance, unfavored conformation), then a secondary but less activated H-bonding site could be the H–C_{Ar} bond on the electron-deficient aromatic substituent (Scheme 1). All the NH and CH acidities could be easily modulated, depending on the electronic nature of the substituents. In addition, both NH and CH groups can be positioned in a geometry that is similar to those of thioureas, which are known to be efficient double H-bonding catalysts. We therefore decided to investigate acetanilides **1** and α-halogenoacetanilides **2**–**9** (Scheme 2), with a range of aromatic substituents (R=H, CF_3, NO_2) and X_nCH_{3-n} groups (n = 1–3; X = F, Cl, Br) of different electron-withdrawing nature.[10] Catalysts **1**–**9** were evaluated in a model reaction, that is, the ROP of lactide. In this reaction, cyclohexyldimethylamine ($CyNMe_2$) and (−)-sparteine (Sp) were chosen as cocatalysts, taking into account their different strength in H-bond formation, to activate the initiator and the growing chain, which both hold an alcohol function.[2] Thus, the potential inhibition of the H-bond donating properties of **1**–**9** towards the substrate was evaluated in the presence of a tertiary amine.

It is worth noting that α-halogenoacetanilides have, to the best of our knowledge, never been described as organocatalysts. α-Chloroacetanilides have been employed as herbicides, pesticides, bioactive compounds[11] as well as synthetic precursors of molecules intended for pharmaceutical or biomedical purposes (β-lactams, oxindoles, MRI contrast agents).[12] Sigman et al. studied the H-bonding behavior of oxazolines provided with an alcohol and halogenated acetamide groups in an enantioselective hetero Diels–Alder reaction.[13] For these alkyl-NH-CO-$CH_{3-n}X_n$ derivatives, the acidity of the amide proton ($CF_3 > CCl_3 > CHCl_2 > CH_2F > CH_2Cl$) was shown to directly impact both the reaction rate and the enantioselectivity. In particular, the most acidic oxazolines induced higher conversions. Herein, α-halogenoacetanilides **2**–**9** were more acidic than aliphatic acetamides and their structures were simpler.



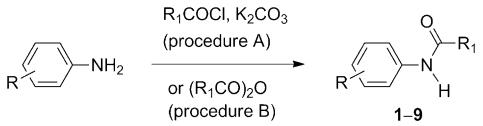
Scheme 2. Acetanilides **1**–**9** investigated as H-bonding organocatalysts, cocatalysts and lactide.

Their properties were also found to be governed by parameters other than acidity. Indeed, O'Hagan and others[14] studied α-monofluoroamides and their particular arrangement for which the C–F bond prefers *anti* and *syn* conformations versus the carbonyl and the NH bond, respectively, mainly as a result of the interaction between fluorine lone pairs and the N–H σ* orbital. These results were exploited to control peptide folding and asymmetric induction.[14d] Smith et al. showed that difluoroacetanilides could form an intramolecular double H-bond with the C=O bond of their carbamate moiety, thus inverting the C–F bond towards a pseudo-conformation *anti* to the NH bond.[15] This conclusion was based on the X-ray structure of compounds and quantum calculations. Consequently, dihalogenated acetanilides can be considered as promising original candidates for C=O activation in organocatalysis. In this context, the role of the $CH_{3-n}X_n$ group in α-halogenoacetanilides can be limited to an electron-withdrawing group and/or be extended to an H-bonding moiety, the properties of which are still unknown. To explore the H-bonding properties of compounds **1**–**9**, the present study encompasses solid-state studies, molecular modeling in the gas phase, and an investigation of catalysis in solution.

Results and Discussion

Synthesis of α-halogenoacetanilides

The preparation of organocatalysts **1**–**9** was achieved in high yields (84–98%) from commercial reagents (Scheme 3). According to classical procedures (A or B depending on the availability of reactants),[16] acetanilides **1** and α-halogenoacetanilides **2**–**9** were obtained from the condensation of the correspond-



Scheme 3. Synthesis of α-halogenoacetanilides **1**–**9**.

ing anilines (R=H, CF_3, NO_2) and freshly distilled acid chlorides or acyl anhydrides (R_1=$CH_{3-n}X_n$) in dichloromethane. Among the series **1**–**9**, the new compounds were fully characterized (see the Supporting Information). It should be noted that several α-tribromoacetanilides with electron-withdrawing groups were also prepared (not shown) but were too unstable in solution to be properly evaluated as organocatalysts.

Molecular interactions in solution

Host/guest titrations were conducted on three model acetanilides to assess their binding ability towards lactide in $CDCl_3$ (see the Supporting Information). Compounds with a trifluoromethyl substituent on the aromatic group were selected to better evaluate the impact of CX_3 and CHX_2 groups. A binding constant (K_{ass}) of 4 M^{-1} was determined between trifluorinated compound **4e** and lactide, showing that the N–H bond was accessible to lactide, even with a bulky substituent ($COCF_3$). Dichlorinated catalysts **6e** and **6d** also associated with lactide, showing binding constants of 2 and 1 M^{-1}, respectively. Because these binding constants were very low, no valid comparison between the K_{ass} values and the catalyst structures could be made. However, previous studies demonstrated that even weak H-bonds could trigger ROP reactions.[4b,5b,17] Thus, despite the low values of K_{ass}, the data support the possible activation of a C=O bond by the aforementioned acetanilides in solution.

X-Ray diffraction

Whereas reports of α-chloroacetanilides in the solid-state are common because of their attractive properties,[11,12] no X-ray structure of α-bromoacetanilide and only a few of α-fluoroacetanilides have been described. Thus, only the crystal structures of monochlorinated **5a**[18] and **5h**,[19] dichlorinated **6a**[20] and **6h**,[21] and trichlorinated **7a**[22] and **7h**[23] acetanilides have been reported. Interestingly, the authors focused on strong intermolecular H-bonds between the NH and the carbonyl groups stabilizing the packing of α-chloroacetanilides into polymeric chains (N–*H*···*O*=C distances ranging from 2.04 to 2.23 Å and NHO angles of 155–178°). No comments were made on possible interactions between the acidic X_nCH group and the carbonyl, even though most structures present parallel alignments of NH and X_nCH bonds. Recently, compound **3a** was fully described with a N–H···O···H–C interaction involving short distances (d(N–*H*···*O*=C) = 2.0 Å and d(F_2C–*H*···*O*=C) = 2.5 Å).[15] In general, the range of distances for short C–H···O interactions are d(C–*H*···*O*) = 2.1–2.5 Å and d(*C*–H···*O*) = 3.1–3.5 Å and their angles are between 150 and 180°, as expected for interactions governed by electrostatics.[6c]

To extrapolate the potential activity of double H-bonding organocatalysts, a selection of dihalogenated compounds with electron-withdrawing aromatic substituents were crystallized and submitted to X-ray analysis. Monocrystals of **3h** (X = F), **3i** (X = F), **6d** (X = Cl), **6i** (X = Cl), and **9i** (X = Br) were grown in dichloromethane by slow diffusion of pentane. Selected interactions (length and angle) and torsion angles are listed in Table 1 (for detailed crystallographic data see the Supporting Information).

Table 1. Hydrogen bonds and torsion angles in **3h**, **3i**, **6d**, **6i**, and **9i** monocrystals.[a]

	3h	**3i** (50/50)[c]	**6d**	**6i**	**9i**
R	*p*-NO_2	*m*,*m*′-NO_2	*p*-CF_3	*m*,*m*′-NO_2	*m*,*m*′-NO_2
R^1	CHF_2	CHF_2	$CHCl_2$	$CHCl_2$	$CHBr_2$
C=O···H–N	2.15 (165)	2.07 (168)	2.01 (167)	2.11 (162)	2.10 (165)
C=O···H–CX	none	none/2.88 (140)	2.46 (148)	2.31 (146)	2.26 (145)
N–H···X–C	2.22 (110)	2.31 (106)/3.00 (83)	none	none	none
<HN–CO>	178	180	−179	−171	−171
<OC–CH>	74	73/160	176	−164	−166
<H–N/C–A>[b]	14 (F)	9 (F)/−19 (H)	−3 (H)	24 (H)	22 (H)

[a] Length of H-bonds in Å and angles in degrees (bracket). [b] Angle of the conformational tweezer pointing at the O=C bond, either single H-bond donor (A = F) or double H-bond donor (A = H). [c] Data for two conformers are shown: NH/CF *syn* conformation followed by NH/CH *syn* conformation.

tion). All crystals are packed through strong intermolecular H-bonds between amides, displaying usual distances and angles: d(N–H···O=C) = 2.01–2.15 Å and (NHO) = 162–168°. Aromatic groups are arranged in more or less ordered layers depending on the geometry of H-bonds and steric hindrance. Noticeable differences appear between difluorinated and other dihalogenated acetanilides. Interestingly, difluorinated amide **3h** (Figure 1a) adopts a different conformation to that described for **3a**:[15] one fluorine atom interacts with the adjacent N–H group (d(F···H–N) = 2.55 Å), as already seen with monofluoroacetanilides.[14a–b] The N–H and C–F bonds are almost parallel (HN/CF) = 14°. The C=O bond also interacts with the NH group (d = 2.15 Å) and the aromatic proton (d(C=O···H–C_{Ar}) = 2.56 Å and (OHC) = 110°.

As a result of disorder in the crystal, difluoroacetanilide **3i** is observed in NH/C–F *syn* and NH/C–H *syn* conformations in equal proportion (Figure 1b and c, respectively). In the NH/C–F *syn* conformation (Figure 1b), the NH bond is almost parallel with the C–F bond (HN/CF) = 9° and then close to the fluorine atom (d(F···H–N) = 2.31 Å). A single intermolecular H-bond between the N–H and C=O bonds is observed (d = 2.07 Å). In contrast to **3h**, no interaction between C=O and the acidic aromatic proton is seen in **3i**, despite similar conformations. In the NH/CH *syn* conformation ((HN/CH) = −14°, Figure 1c), a double H-bond to carbonyl is composed of the same strong NH···O=C (d = 2.07 Å) and weak F_2C–H···O=C interactions (d = 2.88 Å). However, due to the weakness of this secondary interaction involving the CHF_2 group, it could be considered that compound **3i** mainly interacts with the second molecule

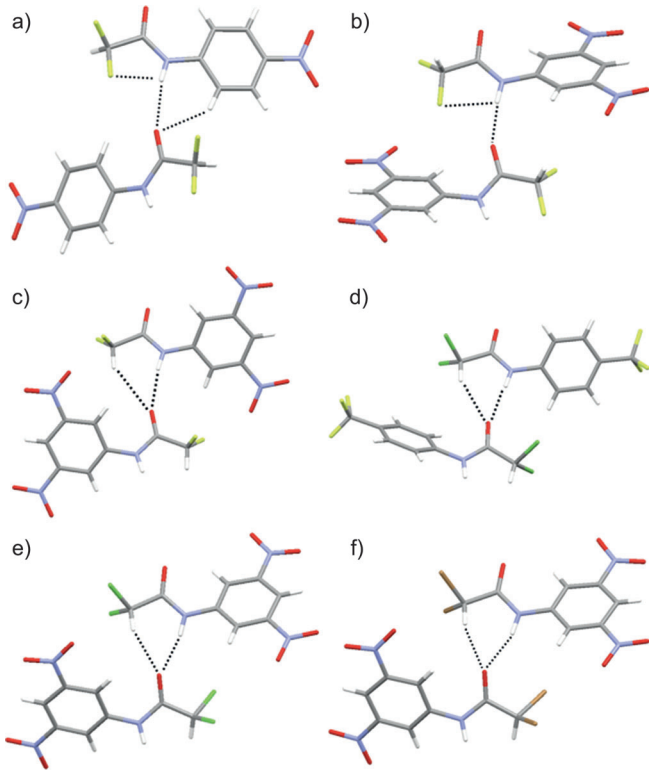


Figure 1. Hydrogen-bonded α-dihalogenoacetanilides in the crystal: a) **3h**, b) **3i** in NH/CF *syn* conformation, c) **3i** in NH/CH *syn* conformation, d) dichlorinated **6d**, e) dichlorinated **6i**, f) dibrominated **9i**.

through a sole NH···O=C interaction, but experience two conformations of equal probabilities for the CHF_2 group.

Dichlorinated compounds **6d** and **6i** as well as dibrominated **9i** form intermolecular double H-bonds between the carbonyl group and the NH/CH bonds (Figure 1 d, e and f, respectively). These nonconventional X_2C–H···O=C interactions are quite strong, with distances of 2.46, 2.31, and 2.26 Å, respectively and similar CHO angles (145–148°). The NH and CH bonds are almost parallel (HN/CH) = −2 to +22°. Finally, when compounds **3i**, **6i**, and **9i**, with identical aromatic groups (*m*,*m*′-NO_2), are compared, the length of the NH···O=C H-bond is slightly shorter for **3i** (single interaction, 2.07 Å) than for **6i** (double interaction, 2.11 Å), and **9i** (double interaction, 2.10 Å).

These results indicate that, in the solid-state, α-dihalogenoacetanilides provided with electron-deficient aromatics interact strongly through intermolecular single or double H-bond(s), depending on the nature of the halide: α-difluoroacetanilides present classical N–H···O=C interaction (and possibly a C_{Ar}–H···O=C interaction), whereas α-dichloro- and α-dibromo- acetanilides show an original N–H···O···H–CX_2 interaction. Importantly, this nonconventional H-bond is particularly strong (*d* = 2.26–2.46 Å).

Molecular modeling

To the best of our knowledge, intermolecular H-bonding of α-halogenated acetanilides towards a substrate has never been modeled. To better predict the activation of the C=O bond, geometry optimizations at the B3LYP/6-31+G** level were achieved on L-lactide, a selection of catalysts, and mixtures of both species, in vacuum.[24] Herein, the most favorable complexes are presented, however, complexes of similar energy could be present in solution and also activate the substrate. A series of six α-acetanilides provided with a *p*-nitrobenzene substituent were chosen to compare the effect of halide atom(s) on H-bonding: **10** ($R^1 = CH_3$), **2h** (CH_2F), **3h** (CHF_2), **4h** (CF_3), **6h** ($CHCl_2$), and **9h** ($CHBr_2$). A compound with an *m*,*m*′-dinitrobenzene group (**2i**; CH_2F) was also considered to assess the impact of a *m*,*m*′-NO_2 substituent. Although the simulations are not fully representative of the experimental conditions of the reaction (solvent, cocatalyst, growing chain), they provide information on the geometry and energy of the lactide complexes (Figure 2, Table 2) and thus allow the H-bonding properties of several catalysts towards the same substrate to be compared. To better assess the existence of weak interactions, some complexes were analyzed through their electron density, using the NCIPLOT program developed by Yang et al.[25] The gradient surfaces obtained within the complexes indicate the location and the strength of any noncovalent interactions,

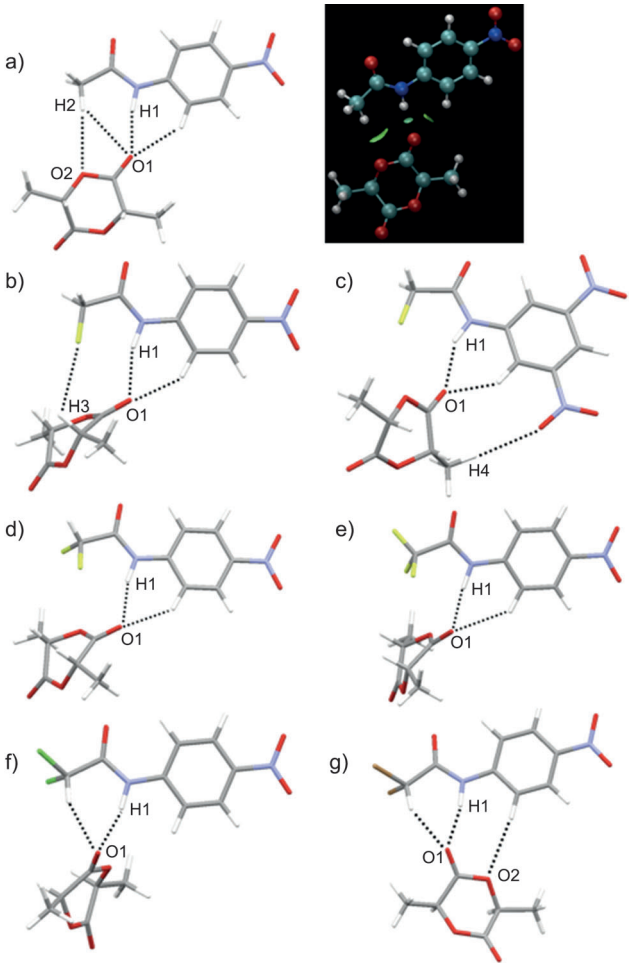


Figure 2. Molecular modeling at the B3LYP/6-31+G** level of complexes between L-Lactide and a) **10** (left) with the NCI analysis (right), b) **2h**, c) **2i**, d) **3h**, e) **4h**, f) **6h**, and g) **9h**.

Table 2. Hydrogen bonds and energy of interaction in modeled complexes between L-Lactide and **1h**, **2h**, **3h**, **4h**, **6h**, and **9h**.[a]

	1h	**2h**	**3h**	**4h**	**6h**	**9h**
R^1	CH_3	CH_2F	CHF_2	CF_3	$CHCl_2$	$CHBr_2$
C=O···H–N	2.09 (171)	2.13 (164)	2.04 (170)	1.96 (176)	2.00 (169)	2.02 (170)
C=O···H–C	2.97 (139)	none	none	none	2.39 (135)	2.37 (144)
C=O···H–C_{Ar}	2.58 (141)	2.44 (143)	2.49 (141)	2.66 (136)	none	none
N–H···X–C	–	2.22 (F)	2.33 (F)	2.58 (F)	2.16 (H)	2.12 (H)
<H–N/C–A>[b]	0.9 (H)	2.1 (F)	27.3 (F)	50.8 (F)	23.5 (H)	13 (H)
ΔE_{int}[c]	−6.15	−5.42	−6.84	−7.58	−8.66	−8.47

[a] Length of H-bonds in Å and angles in degrees (bracket). [b] Angle of the conformational tweezer pointing at the O=C bond, either single H-bond donor (A = F) or double H-bond donor (A = H). [c] Energy of interaction in kcal mol^{-1}.

using a color code (blue for strong noncovalent interaction, green for weak interactions, and red for nonbonded overlap).

The optimized structures of catalysts (without lactide) showed that all amide moieties are coplanar to the aromatic ring and in *trans* conformation. All fluorinated compounds (**2h**, **2i**, **3h**, **4h**) and the dibrominated compound **9h** adopt a NH/C-X *syn* conformation, whereas dichlorinated **6h** has a NH/CH *syn* conformation. In the complexes with L-lactide, the conformations of acetanilides are identical, except for dibrominated **9h**, which adopts a NH/CH *syn* conformation. The cost of the latter geometry change is +4.00 kcal mol^{-1}. The calculated deformation is +1–2 kcal mol^{-1} for all other complexes (see the Supporting Information). All the NH groups of α-acetanilides are strongly H-bonded[26] to L-lactide (d(N–H···O=C) = 1.96–2.13 Å and (HNO) = 164–176°).

Firstly, as seen in Figure 2a, nonhalogenated compound **10** interacts with the C=O group of L-lactide through its N–H bond (d(N–H···O=C) = 2.09 Å) and a C_{Ar}–H bond (d(C_{Ar}–H···O=C) = 2.58 Å), whereas the C–H2 bond is parallel with the NH bond and weakly H-bonded to the intracyclic oxygen O2 of lactide (d(C–H···O2) = 2.90 Å and (CHO2) = 176°). The energy of interaction (ΔE_{int}) was calculated to be −6.15 kcal mol^{-1}. The noncovalent interaction (NCI) analysis of the **10**/lactide complex reveals the same interactions as those detected from the atomic distance measurements. Logically, the blue-green gradient isosurfaces involving NH and C_{Ar}H bonds are typical of weak H-bonds, whereas the bright-green isosurface involving the methyl group is characteristic of weaker Van der Waals interactions.

Secondly, α-fluoroacetanilides **2h**, **3h** and **4h** (Figure 2b and d–e) exhibit a double H-bond with the carbonyl of lactide, involving their N–H group (d(N–H···O=C) = 2.13, 2.04 and 1.96 Å, respectively) and a C_{Ar}–H bond (d(C_{Ar}–H···O=C) = 2.44, 2.49 and 2.66 Å, respectively). Due to the NH/CF conformation, no interaction between the H–CF_n bond and the C=O bond of lactide was observed. The strength of the main N–H···O=C H-bond between fluorinated catalysts and lactide increases with the number of fluorine atoms, whereas the strength of secondary NH···H–C_{Ar} and NH···F–C interactions decrease. The values of the interaction energy also became more negative when the number of fluorine atoms were increase while keeping the same aromatic substituent: −5.42, −6.84, and −7.58 kcal mol^{-1} for **2h**, **3h**, and **4h**, respectively.

Thirdly, dichlorinated and dibrominated **6h** and **9h**, respectively, both adopt a NH/CH *syn* conformation ((NH/CH) = 23° and 13°, respectively, Figure 2f and g) to complex the carbonyl group of L-lactide through a double H-bond, as seen in the crystal structures of **6i** and **9i**. Both lengths are short (C=O···H–N distances are 2.00 and 2.02 Å for **6h** and **9h**, respectively) and nonconventional C=O···H–CX_2 distances were 2.39 and 2.37 Å, respectively. Concerning the **9h**/lactide complex, an additional weak interaction was observed between the acidic aromatic proton of acetanilide and the intracyclic oxygen O2 of lactide (d(C_{Ar}–H···O_2) = 2.86 Å and (CHO2)161°). The latter weak binding between C_{Ar}–H and an intracyclic oxygen atom was also observed by Schreiner between a thiourea provided with *m*,*m*′-CF_3 groups and a lactone.[27] The energies of interaction are stronger for dichloro- and dibromoacetanilides complexes than the previous complexes: −8.66 kcal mol^{-1} (for **6h**/lactide) and −8.47 kcal mol^{-1} (for **9h**/lactide). Thus, the lowest negative energies of interactions were calculated for trifluorinated, dichlorinated, and dibrominated compounds **3h** > **6h** ≈ **9h**, respectively, indicating that these molecules could be the most attractive activators of C=O bonds.

Concerning the *m*,*m*′-NO_2 derivative (Figure 2c), the calculated **2i**/lactide complex was found to interact through a slightly shorter double H-bond than **2h**/lactide, with d(N–H···O=C) = 2.15 Å ((NHO) = 156°) and d(C_{Ar}–H···O=C) = 2.20 Å ((HCO) = 146°). Importantly, the *meta*-NO_2 group displays a secondary H-bond with the methyl group of lactide (d(C–H_4···O–NO) = 2.79 Å and (HCO) = 165°). The distance between the lactide methyl group and the acidic aromatic proton was calculated to be 2.98 Å. The NCI analysis confirms the existence of H-bonds between the carbonyl and the NH/CH tweezer and Van der Waals forces for the secondary interaction due to the *meta*-NO_2 group (see the Supporting Information). The interaction energy **2i**/lactide is more negative than **2h**/lactide (−6.56 vs. −5.42 kcal mol^{-1}, respectively), showing the impact of a *m*,*m*′-NO_2 group compared with a *para*-substituent.

For the modeled α-fluoroacetanilides complexes (Figure 2b and d–e), the C–F bonds point toward the acidic intracyclic protons of the lactide without making realistic H-bonds (distances greater than 3.00 Å: d(C–F···H_3–C) = 3.09, 3.51, and 3.45 Å for **2h**, **3h**, and **4h**, respectively). This effect results in the unparallel positioning of the lactide plane towards acetanilides, and an eclipsed conformation (H–N/C–F = 51°) appears in the **4h**/lactide complex. In addition, the unusual preferred approach of lactide can also account for the interaction energy of **2h**/lactide, which is less negative (−5.42 kcal mol^{-1}) than one of the **10**/lactide complex (−6.15 kcal mol^{-1}). Thus, the geometry of these lactide complexes is affected by very weak C–F···H–C interactions.[28] Notably, no C–X···H–C interactions were observed with chlorinated or brominated catalysts that were designed for double H-bonding a carbonyl group through H–CX_n groups.

Finally, B3LYP/6-31+G** calculations on α-halogenoacetanilide/L-lactide complexes in vacuum predict that the C=O activation occurs through different H-bonds depending on the nature of the halide; α-dichloro- and α-dibromoacetanilides adopt a NH/CH *syn* conformation that favor a strong double H-bond with C=O group, whereas α-fluoroacetanilides display a double H-bond involving the NH group and an aromatic proton. According to the calculations, weak secondary interactions (C–F···H–C or ON–O···H–CH_2) can influence the geometry of the complex. Modeling confirms the solid-state study revealing the favored conformations of α-halogenoacetanilides towards C=O bonds and also supports the binding experiments in solution, highlighting the C=O bond activation even with trihalogenoacetanilides. Although the calculations do not take into account the complexity of the reaction medium (solvent, other H-bonding compounds), a catalytic activity for the α-halogenoacetanilides can be envisioned in the ROP of lactide in dichloromethane.

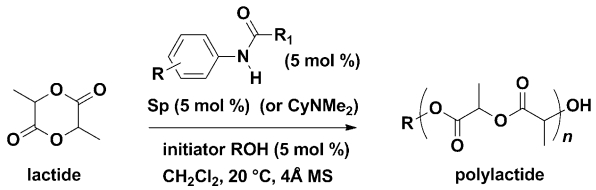
H-Bonding catalysis

In contrast to the solid-state and modeling studies, the catalytic activity of α-halogenoacetanilides was also evaluated for the lactide in the presence of a tertiary amine as a cocatalyst. Thus, two factors can influence the outcome of the reaction: i) The H-bonding properties of **1**–**9** towards the substrate, and ii) the acid-base interactions between **1**–**9** and the cocatalyst. The following discussion will take into account both influences.

The ROP of lactide was undertaken under classical conditions with lactide (0.7 M) in dichloromethane, at 20 °C, in the presence of 4-biphenylmethanol as the initiator, $CyNMe_2$ or (−)-sparteine (Sp) as activator of the initiator/polymer growing chain, and 4 Å molecular sieves.[5,8,17] Preliminary experiments indicated that each component of the system (initiator, catalyst, and 4 Å MS) did not trigger the polymerization independently. Only Sp allowed a 10–15% of conversion in the presence of an initiator and in the absence of H-bond donor.[5b] The H-Bond donor/H-Bond acceptor/initiator system was employed in 5:5:5 mol% ratio versus the monomer to initiate and propagate the reaction in a controlled fashion.[17b] The crude polyesters were analyzed by ^{1}H NMR (% conv.), size-exclusion chromatography [molar mass (M_n), Dispersity (Đ)], and MALDI-TOF (chain-end fidelity, distribution) (see the Supporting Information). In accordance with a living-like mechanism, the average molar masses were close to the theoretical values and the dispersity was very narrow (Đ < 1.1). The percentage conversion for acetanilides **1**, α-fluoroacetanilides **2**–**4**, α-chloroacetanilides **5**–**7**, and α-bromoacetanilides **8**–**9** are presented in Table 3.

As a first general observation (Table 3), all reactions conducted in the presence of *ortho*-substituted catalysts by a CF_3 (**1b**, **2b**, **3b**, **4b**, **5b**, **6b**) or a NO_2 group (**1f**, **2f**, **3f**, **4f**, **5f**, **6f**), display low conversions (13–36%) irrespective of which cocatalyst was used, compared with the corresponding *meta*- and *para*-substituted catalysts (27–100% conv.). Strong intramolecular H-bonds are proposed to disable the activation of lactide for all *ortho*-substituted acetanilides. Indeed, some acetanilides provided with accepting *ortho*-substituents (NO_2, CO_2R, SO_2NR_2) were shown to present an intramolecular H-bond between the NH amide and its aromatic substituent.[29] This is the first time that a CF_3 group has been reported as an intramolecular accepting group in compounds **1b**, **2b**, **3b**, **4b**, **5b**, and **6b**. Furthermore, the impact of *meta*- versus *para*- substituents on the conversion yield was similar, with a ±5–10% difference (within the range of experimental error), except for **1g** versus **1h** (42 vs. 67%). The reason for the large difference in catalytic activity of the latter is not yet clear. Because acetanilides **1** are less efficient catalysts, we focused on the halogenated compounds and will present this case later. However, a detailed

Table 3. Catalytic properties of acetanilides **1**–**9** in the ROP of DL-Lactide; percentage of conversion in the presence of Sp (or $CyNMe_2$).[a,b]



R/R^1	CH_2Me	CH_2F	CHF_2	CF_3	CH_2Cl	$CHCl_2$	CH_2Br	$CHBr_2$
H	**1a**, 29	**2a**, 36	**3a**, 62 (20)	**4a**, 29 (10)	**5a**, 58	**6a**, 88 (36)	**8a**, 73	**9a**, 84 (28)
o-CF_3	**1b**, 25 (14)	n.d.[c]	**3b**, 23 (19)	n.d.[c]	**5b**, 22	**6b**, 36 (28)	**8b**, n.d.[c]	**9b**, n.d.[c]
m-CF_3	**1c**, 27	**2c**, 44	**3c**, 96 (37)	n.d.[c]	**5c**, 87 (49)	**6c**, 98 (62)	**8c**, 96	**9c**, 97 (53)
p-CF_3	**1d**, 29	**2d**, 37	**3d**, 95 (27)	n.d.[c]	**5d**, 81 (24)	**6d**, 99 (40)	**8d**, 93	**9d**, 97 (51)
m,*m*′-CF_3	**1e**, 56	**2e**, 94	**3e**, 100 (46)	**4e**, 15 (10)	**5e**, 100 (40)	**6e**, 100 (66)	**8e**, 100 (50)	**9e**, 100 (85)
o-NO_2	**1f**, 25 (13)	n.d.[c]	**3f**, 19 (15)	n.d.[c]	**5f**, 22	**6f**, 32	**8f**, n.d.[c]	**9f**, n.d.
m-NO_2	**1g**, 42	**2g**, 59	**3g**, 97 (49)	n.d.[c]	**5g**, 91 (61)	**6g**, 100 (87)	**8g**, 97	**9g**, 100 (65)
p-NO_2	**1h**, 67	**2h**, 51	**3h**, 96 (44)	n.d.[c]	**5h**, 92 (59)	**6h**, 100 (90)	**8h**, 97	**9h**, 100 (65)
m,*m*′-NO_2	**1i**, 100 (34)	**2i**, 100 (40)	**3i**, 100 (79)	**4i**, 10 (15)	**5i**, 100 (82)	**6i**, 100 (100)	**8i**, 100 (90)	**9i**, 100 (100)

[a] Conditions of ROP: DL-Lactide (0.7 M in dichloromethane), H-bond donor catalyst (5 mol%), Sp (or $CyNMe_2$) cocatalyst (5 mol%), 4-biphenylmethanol as initiator (5 mol%), 4 Å molecular sieves, 20 °C, 24 h. [b] Determined by ^{1}H NMR spectroscopic analysis; percent conversion in the presence of $CyNMe_2$ is given in parenthesis. [c] n.d.: not determined.

analysis of *m*- versus *p*-substituted compound conversions indicates that for the moderately activated compounds (among **2c**–**6d**), *m*-substituted catalysts induce slightly higher conversion than the corresponding *p*-substituted derivatives, in a systematic manner: thus, in the presence of Sp, **2c** versus **2d** (44 vs. 37%), **2g** versus **2h** (59 vs. 51%), and **5c** versus **5d** (87 vs. 81%). The phenomenon is clear in the presence of $CyNMe_2$, with **3c** versus **3d** (37 vs. 27%), **5c** versus **5d** (49 vs. 24%), and **6c** versus **6d** (62 vs. 40%). Although, in some cases, the difference in percent conversion was within the range of the experimental error, repeated experiments (eight times) confirmed the same tendency (*m*- > *p*-) was found for the quoted compounds. This interesting phenomenon could be attributed to i) a slight difference in amide pK_a between *m*- and *p*- derivatives, as reported for a thiourea,[30] which might result in slightly different H-bonding properties, or ii) to secondary interactions between *m*-NO_2/CF_3 and the methyl group of lactide, as seen in the computed **2i**/lactide complex (Figure 2c). Further experiments are in progress to explain and exploit the H-bond accepting properties of *m*-substituted catalysts with appropriate substrates, which has been poorly documented so far.

As a second general remark, based on conversion, the electron-withdrawing properties of CF_3 and NO_2 groups followed the expectations ($CF_3 < NO_2$). In both cases, two electron-withdrawing groups on the aromatic function (instead of only one group) are required to reach the highest catalytic activities. However, the effect of halide atoms is more subtle (see below). The unique general tendency is that dihalogenated acetanilides are more active than the monohalogenated acetanilides.

As a third general point, the activating power of Sp is known to be higher than that of $CyNMe_2$, thus leading to higher conversions under the same conditions. An exception was found when Sp interacts with the H-bond donor catalyst (thus inducing lower conversion than with $CyNMe_2$) or when the H-bond donor catalyst is not active.[5b] Interestingly, trifluorinated **4b–i** and trichlorinated **7a–i** catalysts (see the Supporting Information) undergo 5–15% conversion irrespective of which cocatalyst was used. As shown by modeling and the binding constant, these catalysts can activate the C=O bond of lactide. Consequently, steric hindrance or electronic factors do not account for the lack of activation. Here, the acidity of the trihalogenoacetanilide NH protons is the highest among **1**–**9** and, accordingly, is proposed to induce a preferential interaction with the cocatalyst, thus significantly reducing its catalytic properties (see below). In summary, acidic α-trihalogenated acetanilides poorly activate carbonyl groups in the presence of a H-bond acceptor cocatalyst.

Catalysis with α-fluoroacetanilides

Firstly, aryl-propionamides **1a**–**h** are moderately active (25–67% conv.) in the presence of Sp, except when they are provided with the most powerful electron-withdrawing group (*m*,*m*′-NO_2). Compound **1i** with Sp undergoes 100% conversion, compared with *m*,*m*′-CF_3 compound **1e** with Sp, which only leads to 56% conversion. As mentioned above, *m*-NO_2 and *p*-NO_2 substituted **1g** (42% conv.) and **1h** (67% conv.) exhibit a large difference in catalytic activity in the presence of Sp. This point is not yet clearly understood and requires further investigations that are out of the scope of the present study.

Secondly, the H-bonding behavior of α-fluoroacetanilides **2**–**4** is dependent on the number of fluorine atoms. The catalytic properties of monofluorinated compounds **2a**–**g** with Sp (36–94% conv.) are slightly higher than the corresponding nonhalogenated compounds **1a**–**g** with Sp (25–56% conv.), which, in connection with the electron-withdrawing properties of fluorine, better activates the amide bond, despite the less advantageous NH/CF *syn* conformation. The **2i**/Sp system induced the highest conversion in the series (100% conv.) but **2i**/$CyNMe_2$ was far slower (40% conv.) under the same conditions.

Concerning α-difluoroacetanilides **3**, their catalytic properties follow the expected electronic effects: by increasing the electron-withdrawing power of R^1 (CHF_2 vs. CH_2F) and R (NO_2 vs. CF_3) substituents, the percentage of lactide conversion increased. Thus, difluorinated catalysts **3** are more efficient than monofluorinated **2**, and compound **3i** is the most forceful H-bond donor of the series: 100% in the presence of Sp and 79% when associated with $CyNMe_2$.

α-Trifluoroacetanilides **4** were inefficient irrespective of which cocatalyst was used (10–29% conv.). As discussed in the general comments, an extra H-bond between the donor and acceptor catalysts is probably responsible for these low conversions. This hypothesis is corroborated by the fact that the less acidic compound **4a** (R=H), provided with a phenyl group, is the best activator (29% conv.) of the series (10–15% for **4b**–**i**).

Catalysis with α-chloro- and α-bromoacetanilides

Concerning the monochlorinated **5a**–**h**/Sp systems, the conversions range from 58 to 100% (except for *ortho*-substituted compounds), whereas monofluorinated **2a–h**/Sp trigger 36–59% conversion. Monobrominated **8a–h**/Sp is able to convert 73–100% lactide. With similar derivatives, the following order of efficiency was found: $CH_2F < CH_2Cl < CH_2Br$. The same comparisons in efficiency can be made with the dihalogenated systems: difluorinated **3a**–**h**/Sp (62–96% conv.) < dichlorinated **6a**–**h**/Sp (88–100% conv.) ≈ dibrominated **9a**–**h**/Sp (84–100% conv.). Again, the catalysts provided with the strongest electron-withdrawing groups (*m*,*m*′-CF_3, *m*,*m*′-NO_2) undergo the best conversions: 100% with **6i** or **9i** irrespective of the cocatalyst. These unprecedented total conversions obtained in the presence of $CyNMe_2$ are remarkable, because the latter tertiary amine is recognized as a moderate H-bond acceptor. As predicted by molecular modeling (Figure 2f and g), the geometry and stability of the **6h**/lactide and **9h**/lactide complexes are in the same range, revealing comparable catalytic properties. As already observed for trifluorinated compounds **4**, trichlorinated derivatives **7a–i** are ineffective when associated with Sp (5–15% conv.) or $CyNMe_2$ (10–23% conv.; see the Supporting Information). Again, the electron-withdrawing power of the $COCX_3$ group on the amide is probably too high, inducing pre-

ferred interactions with the cocatalyst that hampers the H-bonding catalysis.

The living-like aspect of the reaction is controlled by running chain extension experiments with **6i**/Sp (see Table S5 in the Supporting Information). Indeed the catalytic activity of the H-bonding system is maintained after three successive additions of monomer (100% conv., 24 h after each loading). Compared with the most popular catalytic system for ROP of lactide, that is, thiourea TU/Sp,[2] which allows full conversion in 24 h under the same conditions, the presented systems based on **3i**, **6i** and **9i** are at least as efficient. Importantly, the H-bond donor catalysts **6i** and **9i** are the first to allow full conversion of lactide in 24 h in the presence of $CyNMe_2$. Interestingly, the use of $CyNMe_2$ has two advantages compared with classical amine-based cocatalysts: a) a lower basicity ($pK_a \approx 18$ in CH_3CN) than Sp ($pK_a = 21.6$), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) ($pK_a = 24.3$), and TBD ($pK_a = 26$), and b) a lower nucleophilicity than 4-(*N*,*N*-dimethylamino)pyridine (DMAP), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO). Accordingly, α-dihalogenoacetanilides with *m*,*m*′-NO_2 substituents opens new perspectives on organocatalyzed reactions relying on $CyNMe_2$ as a cocatalyst.

Finally, the conversion obtained in the presence of $CyNMe_2$ is informative regarding comparative catalytic activity as most of activate catalysts led to total conversion in the presence of Sp. Except for *ortho*-substituted compounds and trihalogenated acetanilides, a classification depending on aromatic substituents for the H-bonding catalysts in this ROP reaction with $CyNMe_2$ emerges: i) for *m*,*m*′-CF_3 dihalogenated compounds, **3e** < **6e** < **9e** (46, 66, 85% conv.); ii) for *m*,*m*′-NO_2 monohalogenated catalysts, **2i** < **5i** < **8i** (40, 82, 90% conv.), and iii) for *m*,*m*′-NO_2 dihalogenated compounds, **3i** < **6i** = **9i** (79, 100, 100% conv.). The impact of aromatic and halide substituents on the conversion is strong. The most important information for the powerful α-dihalogenoacetanilides/cocatalyst systems in the ROP of lactide is the following classification: $CHF_2 < CHCl_2 < CHBr_2$.

H-Bonding and lactide activation

To rationalize the halide dependent conversions observed in the ROP of lactide ($CHF_2 < CHCl_2 < CHBr_2$), two hypotheses are proposed: i) due to their increasing acidity ($CHF_2 > CHCl_2 > CHBr_2$),[13] the catalysts interact with both the substrate and the basic cocatalysts with different strengths, or ii) the interaction between catalysts is minor and the scale of reactivity is linked to another phenomenon, such as different modes of H-bonding, as suggested by solid-state packing and modeling.

Indeed, all the acetanilides interact with the cocatalysts with differing strengths depending on their acidity. For instance, the most acidic trifluorinated **4** and trichlorinated **7** compounds were shown to be inactive in C=O activation due to strong interaction with the cocatalysts. To evaluate the dihalogenated structures, we modeled the complexes between one of the more efficient catalysts (i.e., **6h**) and the basic cocatalyst Sp (Figure 3). It was found that **6h**/Sp forms a strong complex with an interaction energy of -8.28 kcal mol^{-1}, which is slightly

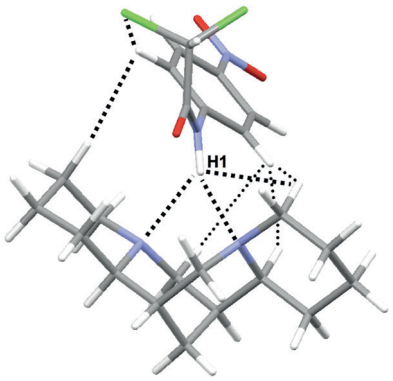
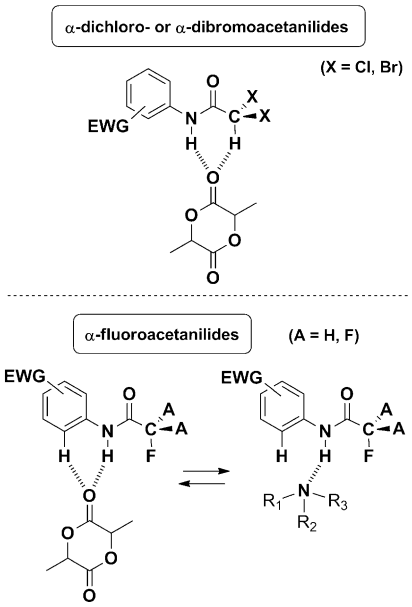


Figure 3. Molecular modeling at the B3LYP/6-31+G** level of **6h**/Sp.

less negative than those of **6h**/lactide ($E_{int} = -8.66$ kcal mol^{-1}). Multiple short distances were measured between the substrates: a double H-bond in which the NH group is pinched between the two nitrogen atoms of Sp (d(N–H···N) = 2.12 and 2.55 Å) and the acidic aromatic protons are in short contact with CH groups in proximity to the Sp nitrogen atoms (d(C_{Ar}–H···H–CN) = 2.24, 2.64 and 2.70 Å). However, to better fit its host, dichloroacetanilide **6h** adopts an unusual conformation in which the amide group is not coplanar with the aromatic ring ($<$(O)CN$C_{Ar}C_A> = 43°$) and C=O and N–H bonds are in *syn* conformation. The calculated energy of deformation for **6h** to fit Sp is $+9.13$ kcal mol^{-1} compared with $+1$–2 kcal mol^{-1} for the other complexes (see the Supporting Information). Thus, despite a strong energy of interaction, this complex would not be favored in solution due to the high cost in energy required to move from the stable *trans* C(O)–NH bond coplanar with the aromatic ring, which is observed in the solid and calculated for all the previous complexes. Catalyst **6h** therefore appeared to interact poorly with the Sp cocatalyst. This assumption can be reasonably extended to the other dihalogenated catalysts. Concerning the weaker H-bond donor $CyNMe_2$, some acid-base interaction between catalysts are revealed but to a lesser extent.

Based on solid-state and molecular modeling, we propose that the H-bonding mode of α-halogenoacetanilides towards the C=O bond of lactide depends on the nature (and the number) of halide substituents (Scheme 4): i) α-mono- and α-di-fluoroacetanilides provide a preferred H-bond to lactide through the amide group and the acidic C_{Ar}–H bond, and interact with the cocatalyst, in a larger propotion than less acidic chlorinated and brominated catalysts, and ii) α-dichloroacetanilides and α-dibromoacetanilides display a remarkable double H-bond to a C=O group through their activated and available NH and X_2CH groups, whereas their acid-base interaction with the cocatalyst is weak. Therefore, as a result of preferential conformations and appropriate acidities, adjustable α-dichloro- and α-dibromoacetanilides are efficient H-bonding catalysts that act through double H-bonds involving a nonconventional X_nC–H···O interaction, even in the presence of tertiary amines as cocatalysts.



Scheme 4. Two different binding modes of α-halogenoacetanilides depending on the nature of the halide.

Conclusion

For the first time, α-halogenoacetanilides have been shown to be efficient activators of carbonyl bonds. Electron-withdrawing properties of the substituents and their number are found to be crucial. In the ROP of lactide, organocatalysts provided with electron-deficient aromatic (*m*,*m*′-NO_2) substituents induce the highest conversion, irrespective of which H-bond acceptor co-catalyst was used (Sp or $CyNMe_2$). The effect of the halide substituents is more subtle; due their differing electron-withdrawing nature and their impact on the acidity of compounds, the catalytic properties increase in the following order: F < Cl < Br. Importantly, X_nCH halogenomethyl groups ($n = 1$–2; X = Br, Cl) are shown to be modular and complementary binding groups to NH. For α-dichloro and α-dibromoacetanilides, we have demonstrated the utility of nonconventional X_nC–H···O interactions in the activation of C=O bonds even in the presence of tertiary amines (Sp and $CyNMe_2$). Halogenated acetanilides are under investigation as organocatalysts in other reactions.

Experimental Section

Materials

DL-Lactide was recrystallized three times in toluene and freshly sublimed. Dichloromethane was dried over calcium hydride and distilled. 4-Biphenylmethanol was purified by precipitation in pentane. $CyNMe_2$ was dried over CaH_2 and distilled under argon before use. Commercially available (−)-sparteine was used as received.

Synthesis of H-bonding catalysts

Depending upon the commercial availability of the reactants, two procedures of condensation were undertaken. All reactions were performed under an inert atmosphere.

Procedure A: A mixture of the corresponding acyl chloride (4.0 mmol), potassium carbonate (4.0 mmol), corresponding aniline derivative (2.0 mmol), and CH_2Cl_2 (10 mL) was stirred at RT for 2–12 h under nitrogen, then poured into water (30 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were successively washed with aqueous saturated $NaHCO_3$ (2×10 mL), water (2×10 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was washed with pentane and dried under vacuum.

Procedure B: A mixture of the corresponding acyl anhydride (5.5 mmol), corresponding aniline derivative (5.0 mmol), and CH_2Cl_2 (10 mL) was stirred at RT for 1–2 h under nitrogen, then poured into water (30 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were successively washed with aqueous saturated $NaHCO_3$ (2×10 mL), water (2×10 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was washed with pentane and dried under vacuum.

Polymerization reactions

Under nitrogen, in a dry Schlenk tube, were successively introduced organocatalyst (35 μmol), initiator (4-biphenylmethanol, 35 μmol), lactide (700 μmol), 4 Å molecular sieves (five beads), anhydrous dichloromethane (1 mL), and cocatalyst ($CyNMe_2$ or (−)-sparteine, 35 μmol). The reaction mixture was stirred at 20 °C under nitrogen for 24 h, then filtered and concentrated in vacuo. Conversion was determined by ^{1}H NMR spectroscopic analysis, by integrating the signals of the methine proton in the residual lactide and the polymer. Polymer molar masses and the dispersity index were measured by size-exclusion chromatography (SEC) with a PL-GPC50 Plus apparatus equipped with RI and UV detectors and Tosoh G4000HXL, G3000HXL and G2000HXL columns (eluent: THF; flow rate 1.0 mL min^{-1}; temperature: 40 °C; calibrated with polystyrene standards). MALDI-TOF analysis was conducted on the same samples.

X-ray crystallography

Single-crystals of **3h**, **3i**, **6d**, **6i**, and **9i** were grown by slow diffusion of pentane in a solution of dichloromethane, containing each catalyst. Detailed crystal structures, cell parameters, and R values are reported in the Supporting Information. CCDC-944150 (**3h**), 944151 (**3i**), 944147 (**6d**), 944148 (**6i**), and 944149 (**9i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Molecular modeling

The structures of all compounds were optimized at the B3LYP level[31] in conjunction with the 6–31+G** basis set,[32] and the lanl2dz potential[33] was used for the bromide atoms. Vibrational frequency calculations were then performed at the same level of calculation by using the standard approximations: rigid rotator and harmonic approximation and we checked that all the frequencies were positive, confirming the fact that theses structures are minima of the potential energy surface. All the calculations were performed by using Gaussian09.[34] Interaction energies were also computed by using the counterpoise method and the values indicated in the text are all corrected from BBSE (basis set superposition error).[35]

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