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The Uncatalyzed Direct Amide Formation Reaction – Mechanism Studies and the Key Role of Carboxylic Acid H-Bonding

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Calorimetric studies of the mixing of a series of carboxylic acids and amines have been carried out to measure heat output, which has been compared with their ability to react to form carboxylate ammonium salts and amides. In order to identify which species (salt or H-bonded species) were formed, ^{1}H NMR studies were also carried out by mixing carboxylic acids and amines in [D_8]toluene and monitoring the resulting reactions. These experiments were also compared to DFT computational studies, from which the relative merits of different mechanistic schemes for direct amide formation could be assessed. A reaction mechanism involving zwitterionic intermediates could be eliminated on the basis of calculated energies in toluene, however, a neutral intermediate pathway, involving carboxylic acid dimerization by mutual hydrogen bonding was found to be accessible and may explain how the direct amide formation reaction occurs. Such a mechanism is not inconsistent with kinetic modelling of direct amide formation under different reactions conditions.

Introduction

Amide bond formation between amines and carboxylic acids is generally promoted by the use of stoichiometric coupling reagents such as carbodiimides, or by the use of other activated carboxylic acid derivatives such as acid chlorides or anhydrides.[1] However, the use of condensing and activating agents is increasingly undesirable as environmentally benign alternatives to standard chemical transformations are sought.[2] In particular, catalytic solutions to many chemical reactions are being developed, aiming for high yielding processes coupled with high atom efficiency and minimising the associated E-factor for the transformation.[3] To that end, the most desirable way to construct an amide bond would be the direct condensation of an amine with a carboxylic acid. However, despite the fact that direct amide formation was reported as early as 1858,[4,5] there have been relatively few reports in the literature referring to direct condensation[5,6] and it remains an understudied and misunderstood reaction. These misconceptions largely derive from early reports of relatively forcing conditions[4,5] and the commonly taught assumption that the lack of reaction between an amine and carboxylic acid is the result of unreactive ammonium carboxylate salt formation as in Equation (1).

(1)

A rennaisance in the direct reaction of an amine with a carboxylic acid has been triggered by the discovery of a number of catalysts (Figure 1), which allow direct amide formation to proceed at lower temperatures[7–12] making the more general synthetic application much more appealing. However, it has not always been appreciated to what extent the direct amide formation competes with the catalyzed reaction, though it is known that certain combinations of carboxylic acid and amine can provide the corresponding amide in good yield in the absence of catalysis.[10] In addition, relatively little is understood regarding the kinetics and mechanistic details of the direct amide formation reaction.[13] Mechanistic investigations into the spontaneous formation of lactams from *ortho*-aminophenylpropionic acids under aqueous conditions have been carried out,[14] however, the mechanism described in this type of intramolecular reaction does not necessarily provide a suitable basis for explaining how intermolecular direct amide formation occurs, particularly under nonpolar and nonaqueous reaction conditions. In order to advance the development of amide bond formation reactions, a comprehensive under-

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standing of the mechanism(s) operating is essential. In this paper, we report our investigations into the mechanistic aspects of this reaction.

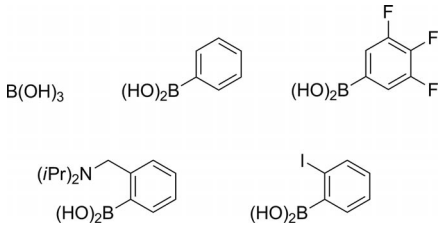

Figure 1. Boron based catalysts for direct amide formation.

Results and Discussion

Reaction Calorimetry

In order to establish whether ammonium carboxylate salt formation occurs upon mixing carboxylic acids and amines in a *nonpolar*, *aprotic solvent*, the heat output of several combinations of amines and carboxylic acids were followed over time in toluene solution. The range of amines and carboxylic acids used was selected on the basis of their pK_a values in water (it has been claimed that there is not a direct relationship between amine and carboxylic acid pK_a values and their ability to undergo direct amide formation)[15] and solubility in toluene. The total heat outputs were also determined (Table 1) and direct amide formation reactions were carried out under both thermal and catalytic conditions to determine if there was a correlation between the propensity for amide formation and experimentally determined heat output (see Table 1).

The results shown in Table 1 demonstrate that the highest heat outputs were derived from the reactions of bromoacetic acid (pK_a 2.69) with the different amines and the rate of heat output was also similarly rapid for each amine reaction. In contrast, phenylbutyric acid (pK_a 4.76) gave a much reduced heat output with benzoic acid (pK_a 4.19) giving intermediate heat output with the different amines, together with gradation of the heat output. It is clear, and not surprising, that heat output is strongly related to pK_a, which is demonstrated by the relative order of reactivity of the three carboxylic acids. Bromoacetic acid also interacts with all the amines examined in an exothermic manner and, interestingly, fails to react under either thermal or the standard boronic or boric acid catalyzed reaction conditions. Phenylbutyric acid in contrast is more reactive and amide formation occurs to some extent with all the amines examined, whereas benzoic acid shows reactivity intermediate between that of the other two carboxylic acids. This shows that there is some level of correlation between the carboxylic acid pK_a and the ability to undergo direct amide formation, i.e. higher pK_a equates to higher reactivity, which contrasts with previous claims.[15]

Examining the amine reactivity is similarly intriguing. There was no major difference in heat output between the amines, with the exception of aniline (ammonium pK_a 4.63), which was universally considerably less reactive with all three carboxylic acids. This lower reactivity clearly results from the lower basicity of aniline in comparison to the other amines, resulting in diminished susceptibility towards protonation. However, and in stark contrast, lower basicity does not extrapolate to lower reactivity towards direct amide formation. In fact, the least reactive amine was *tert*-butylamine (ammonium pK_a 10.83), which failed to react with any of the carboxylic acids under any of the reaction conditions. These results show that the amine reactivity contribution to amide formation is not a simple function of amine basicity; steric and electronic effects must play a part. This conclusion is reinforced by examining the reactivity of benzylamine (ammonium pK_a 9.33) compared with other amines, which is the most reactive amine under all conditions with the two reactive carboxylic acids, despite being

Table 1. Results from calorimetry and yields for direct amide formation.

Carboxylic acid	Amine	Total heat output [kJ/mol]	Yields [%] of direct amide formation Uncat.[a]	Cat.[b]	Cat.[c]
Bromoacetic acid	benzylamine	79[d]	0	0	0
	tert-butylamine	75[d]	0	0	0
	2-methoxyethylamine	79	0	0	0
	piperidine	74[d]	0	0	0
	aniline	43[d]	0	0	0
Phenylbutyric acid	benzylamine	24	64	89	76
	tert-butylamine	30[d]	< 1	3	< 1
	2-methoxyethylamine	21	54	70	49
	piperidine	19	24	80	1
	aniline	0	4	74	16
Benzoic acid	benzylamine	60[d]	14	86	2
	tert-butylamine	56[d]	0	0	0
	2-methoxyethylamine	65[d]	5	24	5
	piperidine	51	10	49	0
	aniline	0	0	35	20

[a] Uncatalyzed in toluene at 120 °C with Dean–Stark water removal over 48 h. [b] Boric acid catalyzed in toluene at 120 °C with Dean–Stark water removal over 48 h. [c] *o*-Iodophenylboronic acid catalyzed in toluene at 50 °C using 3 Å molecular sieves over 48 h. [d] Crystallization of salt occurred on mixing carboxylic acid and amine.

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neither the most basic (see proton affinities below in a simulated nonpolar solvent) nor the least sterically hindered amine. We[10] and others[15] have observed this enhanced reactivity of benzylamine previously, and hence, understanding this "benzylic effect" (with respect to amine reactivity) would be an important consequence of studying how direct amide formation works.

Ammonium Carboxylate Salt Formation and Solution NMR Studies

The high heat output from certain carboxylic acid–amine combinations (Table 1) leads to the obvious conclusion that this results from exothermic salt formation. However, solid products were not always produced, and in cases where heat output was lower, it was not immediately obvious which resulting species are likely to be responsible for the lower exothermicity. In order to probe this question further, it was necessary to establish exactly what species were produced

Table 2. Yields of ammonium carboxylate salt precipitated from combinations of carboxylic acids and amines (all precipitates were confirmed by CHN analysis).

Carboxylic acid	Amine	Analysis	Yield [%] precipitate
Bromoacetic acid	benzylamine	CHN	50
	tert-butylamine	CHN	48
	2-methoxyethylamine	NMR	–
	piperidine	CHN	13
	aniline	CHN	46
Phenylbutyric acid	benzylamine	NMR	–
	tert-butylamine	CHN	100
	2-methoxyethylamine	NMR	–
	piperidine	NMR	–
	aniline	NMR	–
Benzoic acid	benzylamine	CHN	64
	tert-butylamine	CHN	100
	2-methoxyethylamine	CHN	72
	piperidine	NMR	–
	aniline	NMR	–

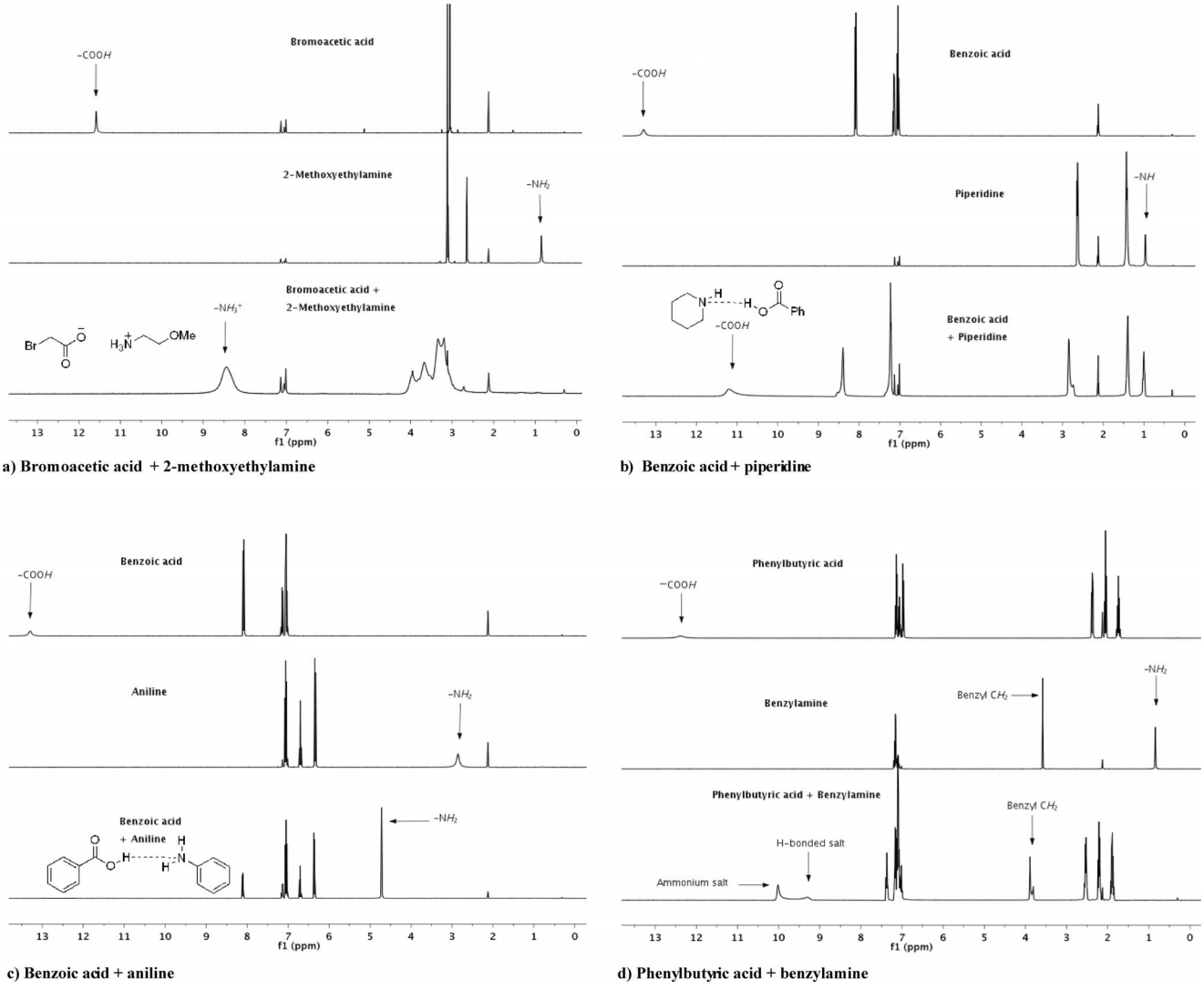

Figure 2. ^{1}H NMR spectra obtained from mixing selected carboxylic acids and amines.

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upon mixing the carboxylic acids and amines. Hence, each carboxylic acid and amine was mixed at room temperature in toluene, and for those combinations that produced a precipitate (Table 2), this was removed by filtration and analysed to confirm that ammonium carboxylate salt formation had taken place. For those combinations that failed to produce a precipitate (Table 2), the solutions (in [D_8]toluene) were examined by NMR up to 24 h after mixing in order to identify what species were present in solution and how they changed.

For the combinations of amines and carboxylic acids that remained in solution upon mixing, the solutions remained homogeneous and it was reasonably straightforward to follow the reactions over time. NMR revealed the presence of three different types of species being formed: 1) complete salt formation (for example Figure 2, a); 2) H-bonding between ammonium and carboxylate (for example Figure 2, b); 3) and H-bonding between amine and carboxylic acid (for example Figure 2, c). In contrast, in the case of phenylbutyric acid with benzylamine (Figure 2, d), the spectrum obtained just after mixing showed the presence of an ammonium salt, however, H-bonding between ammonium and carboxylate was also observed in a 2:1 ratio. The benzyl CH_2 peak was also split (2:1) suggesting the presence of two different species. It is noteworthy that this combination of carboxylic acid and amine seems to be one of the most reactive for direct amide formation, with or without a catalyst (see Table 1) and hence, presumably this association observed between the ammonium and carboxylate, and association between the free amine and carboxylic acid, are important for assisting direct amide formation is some way. In order to ensure that all of the reactions carried out in the NMR tube had finished, each sample was re-examined after 24 h. The results from this second set of NMR spectra showed that, for the three combinations of different amines reacting with phenylbutyric acid (i.e., benzylamine, 2-methoxyethylamine and piperidine), the presence of ammonium salt, H-bonded salt or just H-bonding became less clear. These samples were, therefore, heated at 50 and 85 °C to see if this resulted in simplification of the spectra, which it did. In all three cases the ammonium salt was the only species present after this process. It should also be noted that for all three cases, increasing the temperature from 50–85 °C resulted in a higher field shift ammonium salt formation, though notably at different rates depending the amine–carboxylic acid combination. Rerunning the same NMR samples after cooling to room temperature showed the presence of the ammonium salt in all three cases, with broad ammonium N–H peaks observed at δ = 7.58 (3 H) for phenylbutyric acid + benzylamine, δ = 8.32 (3 H) for phenylbutyric acid + 2-methoxyethylamine and δ = 9.72 (2 H) for phenylbutyric acid + piperidine. Hence, from the evidence obtained from calorimetry, NMR studies and the yields of direct amide formation it can be concluded that several factors influence the reactivity of carboxylic acid–amine partners for direct amide formation, i.e. 1) the stability of the ammonium carboxylate salt, 2) the pK_a of the carboxylic acid, and 3) the nucleophilicity vs. basicity of the amine, tuned by steric vs. electronic (conjugation) effects. In order to understand exactly how the direct amide formation actually occurs, a detailed computational study was carried out.

Calculated Proton Affinities

In order to get a measure of the relative basicity or acidity of the substrates used throughout the study, proton affinities were obtained in the gas phase and using an approximate (polarization continuum model, PCM) solvation model for toluene by DFT calculations. This study was carried out in order to ascertain that calculated proton affinities reflected experimental pK_a values and, more importantly, to provide a better picture of the susceptibility of the different amine derivatives towards protonation by carboxylic acids in a simulated nonpolar solvent. The values obtained using a B3LYP functional, 6-31G** and 6-31+G** basis sets are given in Table 3.

Although the calculated proton affinity values are consistently slightly higher than the experimental values, these results provide a useful trend showing relative basicity, which enables us to compare one compound with another. The trend for five experimentally known affinities is exactly reproduced, and a plot of experimental vs. calculated affinities yields a straight line fit with an R^2 coefficient of 0.998. Hence, the DFT results can be used to provide a reasonable estimate for the unknown bases (including the conjugate bases of the three acids in this study). It should be noted that none of the bases used in Table 1 are predicted to be as basic as triethylamine.

The calculated proton affinities are in good agreement with the five experimentally measured affinities in Table 3 at the 6-31G** level (mean error of 2%). With the further addition of diffuse functions using 6-31+G** basis sets (which give a better representation of soft anions), the predicted values improve further to a mean error of 0.2%. The proton affinities were also estimated in toluene using an approximate PCM solvation treatment. Here, as expected, proton affinities for the neutral bases in toluene are slightly higher because of the dielectric effects of the solvent stabilizing the charged conjugate acid. Although the trend in proton affinities does not change with solvation, the range of values is significantly reduced by the presence of the solvent. However, the dielectric effect of the solvent is fairly weak (compared to more polar solvents) and the basicity of the three carboxylic acid anions is such that we do not expect salt formation in toluene for any of the combinations in Table 1, at least without an additional contribution from the lattice energy assisting precipitation, and/or interactions with water (or water molecules) stabilising an ion pair. These results are intriguing especially in contrast to the results reported in Table 1 and Table 2. From the pK_a values and energy differences calculated, we do not expect proton transfer to form salts to be enthalpically favored. It is, therefore, likely that the heat output measured (Table 1) in many of the amine–carboxylic acid reactions results from

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Table 3. Proton affinities in the gas phase and in the toluene solvation model.

		Gas phase		Toluene solution	
	Exp. affinity (kJ/mol)[a]	Calcd. (6-31G**) Affinity (kJ/mol)	Calcd. (6-31+G**) Affinity (kJ/mol)	Calcd. (6-31G**) Affinity (kJ/mol)	Calcd. (6-31+G**) Affinity (kJ/mol)
Ammonia	854	873	849	1050	1019
Aniline		900	879	1043	1006
Methylamine	896	916	896	1076	1049
2-Methoxyethylamine		923	901	1072	1040
Ethylamine		931	910	1084	1057
Dimethylamine	923	941	925	1085	1065
Benzylamine		946	924	1085	1052
tert-Butylamine		955	934	1089	–[b]
Trimethylamine	942	957	942	1086	1072
Diethylamine		967	942	1099	1074
Piperidine		969	951	1106	1077
Triethylamine	972	991	976	1110	1090
Bromoacetic acid ion		1439	1386	1313	1263
Benzoic acid ion		1469	1412	1344	1283
Phenylbutyric acid ion		1495	1428	1359	1298
Bromoacetic acid		803	777	947	891
Benzoic acid		854	828	977	937
Phenylbutyric acid		830	807	958	–[b]

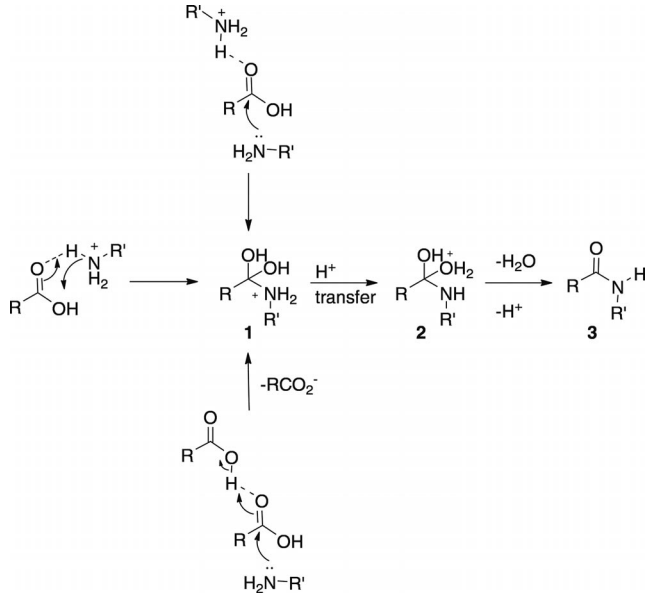
[a] For experimental proton affinities, see ref.[16] [b] Convergence not obtained for 6-31+G** basis set with PCM.

precipitation of the ammonium carboxylate salt rather than proton transfer from acid to amine. In solution, where there is no precipitation, but where NMR studies indicate formation of the ammonium carboxylate salt, we expect the formation of solvent stabilized ion pairs. However, the latter is difficult to model without the use of explicit solvent molecules.

Kinetic Evidence for Acid or Base Catalysis in Direct Amide Formation

Having examined proton affinities and how these are reflected in the observed interactions and reactions between carboxylic acids and amines, we turned to investigate the viability of possible alternative mechanisms for direct amide formation with the aim of establishing the viability of different intermediates and transition states along different reaction pathways. To start, a mechanism analogous to the acid-catalyzed esterification reaction was investigated, i.e. where the electrophilicity of the carboxylic acid is increased by protonation of the carbonyl oxygen atom, facilitating attack of an amine. If direct amide formation can be catalyzed by a general acid, then the acid source could derive from an ammonium salt NH or from excess carboxylic acid as shown in Scheme 1. In order to investigate this possibility, direct amide formation reactions between phenylbutyric acid and benzylamine in the presence of either a 20% excess of carboxylic acid or a 20% excess of amine were followed over time. The results are shown in Figure 3.

The addition of excess carboxylic acid or amine produced very similar results (Figure 3) and indeed, both show only a slight rate enhancement in comparison to the equimolar reaction (for further experiments see Supporting Information). This slight increase in rate for the excess amine and acid reactions is very close to the calculated ranges,



Scheme 1. Initial proposed mechanism for direct amide formation based on acid-catalyzed esterification.

hence, although this difference may be a real effect, it is clearly not significant, and we can therefore conclude that it is unlikely that direct amide formation is particularly amenable to either acid or base catalysis. If it was amenable to such general catalysis, a more significant increase in rate would have been expected.

In light of the direct amide formation reaction not being enabled by general acid or base catalysis (vide supra), a second reaction mechanism requiring consideration could involve attack of an amine directly on the carboxylic acid as outlined in Scheme 2. Such a mechanism appears to be plausible when looking at the yields of direct amide formation (Table 1), as carboxylic acids attached to electron-with-

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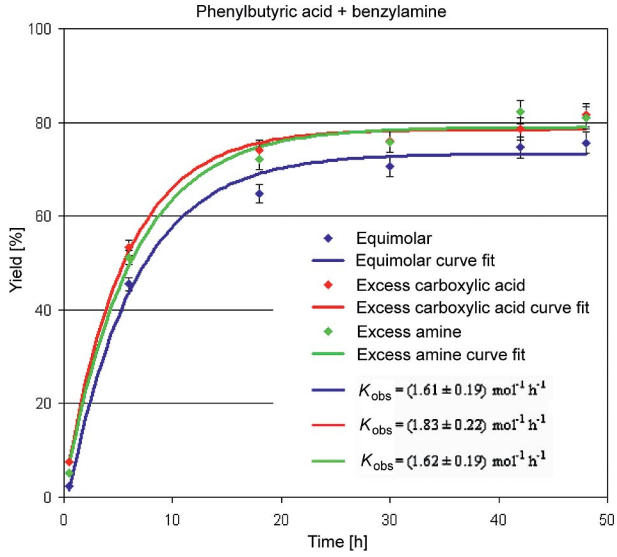
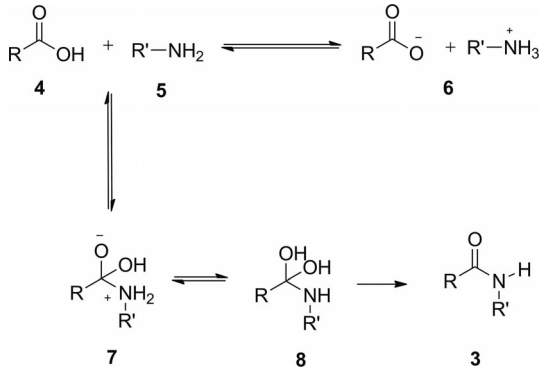


Figure 3. Results following the reaction between phenylbutyric acid and benzylamine over time.

drawing groups are likely to be largely in the form of the ammonium salt due to their lower pK_a values. Considering the amine, electron-donating groups stabilize ammonium salt formation, and this would explain why the combination of bromoacetic acid with *tert*-butylamine does not undergo direct amide formation because the only species present in solution is the carboxylate salt. If direct amide formation were to proceed by the direct attack of the amine on the carboxylic acid (Scheme 2) then an amine that is a good nucleophile is required, followed by formation of a stable zwitterionic intermediate species (**7** in Scheme 2). Carboxylic acid–amine combinations that form stable carboxylate ions, where the ammonium salt cannot reprotonate the carboxylate back to the neutral acid form, are predicted to be unreactive. In order to probe this mechanistic theory further, additional computational studies were carried out.

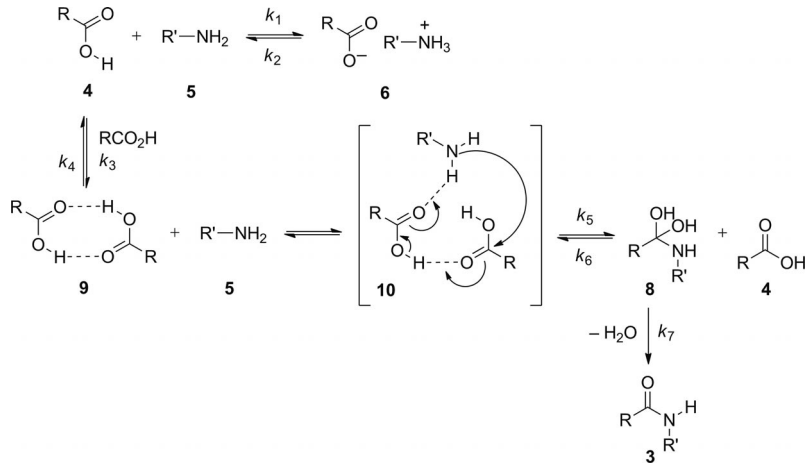


Scheme 2. Alternative proposed mechanism for direct amide formation through zwitterion **7**.

Computational Studies on Possible Direct Amide Formation Mechanisms

Initially, DFT calculations were used to investigate the structure and energies of possible intermediate compounds as outlined in Scheme 2. Calculations were carried out for all combinations of carboxylic acids and amines that were used in the calorimetry and NMR studies (see above and Supporting Information). These investigated the possibility of various species being either stable intermediates (energy minima) or transition states on the reaction surface in a simulated toluene solvent. The results clearly showed that the zwitterion **7**, formed from the attack of the free amine on a free carboxylic acid, was unstable in all cases and would rapidly dissociate to give back the starting materials. Species **7** (Scheme 2) is, therefore, not involved as a transition state or intermediate in direct amide formation and can be discounted from Scheme 2. However, in the process of investigating plausible intermediates, neutral species **8** was found to be stable in all cases (see Supporting Information), which raises the question as to how such an intermediate could be generated. If **8** is formed, it clearly does not result from zwitterion **7** by deprotonation; therefore, what other mechanism could be operating to account for its formation?

Mutual dimerisation of carboxylic acids through intermolecular hydrogen bonding (to give **9**, Scheme 3) is well documented.[17,18] Indeed, not only are such dimerisations



Scheme 3. New proposed mechanism for direct amide formation supported by DFT calculations.

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particularly efficient in nonpolar solvents (such as toluene), but these dimers can be observed at elevated temperatures and even persist into the gas phase, where they compete with linear hydrogen-bonded dimers. We, therefore, theorized that such species might be important as the potentially reactive form of the carboxylic acid, which might be sufficiently activated to enable a nucleophilic attack by an amine. Examining this possibility by DFT showed that the mechanism for direct amide formation could proceed through a carboxylic acid dimer **9**, which could form readily in toluene. Subsequent attack on this species by the amine results in the formation of a transition state **10** as shown in Figure 4, in which the reacting amine is able to attack one carboxylic acid of the carboxylic acid dimer **9** and the second carboxylic acid acts as the proton acceptor (see Supporting Information). The result of a concerted proton transfer from amine to acid and release of the second carboxylic acid is the neutral intermediate **8**, from which water is readily lost (see Scheme 3). Importantly, a mechanism that proceeds in this manner avoids the formation of zwitterion **7**, which had been shown to collapse back to the starting materials from previous calculations (vide supra). An overall calculated energy profile using benzoic acid and benzylamine is shown in Figure 5.

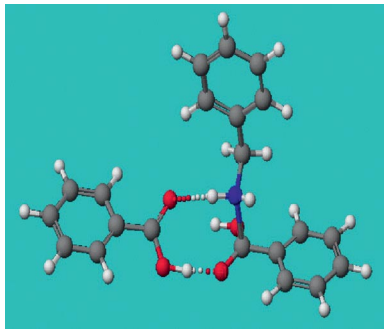

Figure 4. Structure of proposed transition state supported by DFT calculations in simulated toluene. The transition state shown is formed from the attack of benzylamine on a carboxylic acid dimer.

In order to achieve efficient direct amide formation, the removal of water from the reaction is essential, typically by azeotropic distillation at higher temperature[11] or using activated molecular sieves under more ambient conditions.[12] Without efficient water removal, direct amide formation is markedly slowed but does not stop.[11] If direct amide formation does indeed proceed by carboxylic acid dimers of type **9**, why is it necessary to remove water? This can be explained by observations that the addition of even small amounts of water causes hydration of the mutually H-bonded cyclic carboxylic acid dimer (i.e. **9**), resulting in the incorporation of the water molecules into the dimer structure leading to water separated structures. Quantum chemical calculations[18] carried out on acetic acid, for example, show that with the addition of even one molecule of water to **9** causes the hydrogen bonds to break. Addition of a second water molecule will break the second hydrogen bond of the dimer and as more water molecules are added, more water separated complexes of the acetic acid dimer are

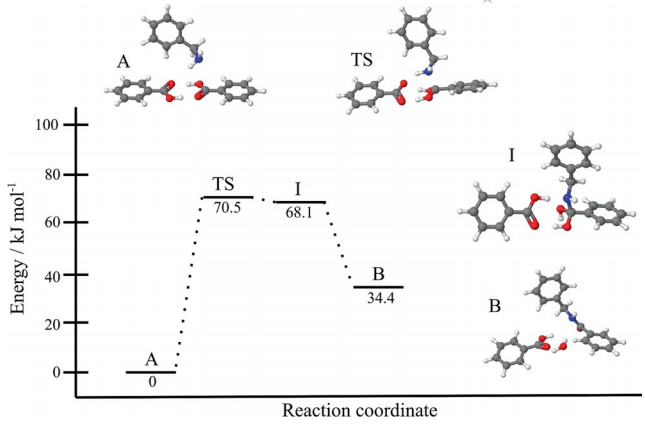

Figure 5. Calculated energy profile for species contributing to direct amide formation by a hydrogen bonded acid dimer, for the reaction of benzoic acid with benzylamine. Relative energies obtained from gas phase DFT calculations (B3LYP/6-31g**). Calculated relative energies are shown as an approximate guide to the suggested reaction pathway and are quoted as the sum of uncorrected electronic and zero point energies in the absence of solvent. (A = amine **5** + carboxylic acid dimer **9**, TS = transition state **10**, I = dihydroxy intermediate **8** hydrogen-bonded to acid **4**, B = amide **3** + acid **4** + water.).

formed.[18] Hence, active water removal becomes essential in order to maintain a sufficient dimer **9** concentration to enable carboxylic acid activation and hence, amine nucleophilic addition.

In further support of the new mechanistic proposal outlined in Scheme 3, it is worth noting that investigations carried out by Kirby et al.[14] on the kinetics and mechanism of intramolecular direct amide formation discussed the importance of the formation of a similar neutral intermediate to **8**. Although this work differs from our investigations (due to aqueous conditions and intramolecularity), the role of the carboxylic acid dimer **9** necessarily orchestrates the intermolecular reaction, especially under nonaqueous conditions (in toluene for example). In many other respects, the mechanism in Scheme 3 is similar and one can explain this on the basis of how, for example, acids with low pK_a values prevent direct amide formation due to forcing the equilibrium betweeen acid **4** and amine **5** fully in the direction of ammonium carboxylate salt **6** and hence, direct amide formation kinetics are most heavily influenced by this equilibrium. In addition, one can understand the possible origin of the "benzylic effect" of amine reactivity (vide supra) in terms of the balance required between amine nucleophilicity (to enable formation of **8**) and to minimise competing salt **6** formation by the amine not being too basic. If the mechanistic analysis in Scheme 3 is correct, then it would be expected that the addition of either excess carboxylic acid **4** or excess amine **5** would have only a small effect on the rate of direct amide formation as addition of excess of either would cause increased salt **6** formation. However, compared with the equimolar reaction, if the step from **9** + **5** to give **8** through **10** were rate determining, then one would expect some sign of an increased rate of reaction. Indeed, Figure 3 does suggest that this might be the case. Hence, in addition

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to these data, the direct amide formation reaction of phenylacetic acid and benzylamine was carried out with much greater (and varying) excesses of amine and carboxylic acid. When Micromath Scientist® software was employed to model the mechanism represented in Scheme 3, it was found to reproduce the observed data (see Supporting Information), and hence, did not contradict the potential viability of the mechanism as represented in Scheme 3.

Conclusions

We previously postulated[10] the intervention of anhydrides from the thermolysis of carboxylic acids as the mechanism by which direct amide formation might occur. However, we have no direct evidence that this process occurs in the presence of amines to result in amide formation. The studies reported herein clearly show that amines and carboxylic acids generally do react to some extent to give ammonium carboxylate salts. However, this reaction only seems to proceed to completion with combinations involving acids with lower pK_a values and basic amines, and completion of the reaction is likely to be driven by the formation of a salt precipitate. NMR studies clearly show that a number of species can be formed in solution upon mixing carboxylic acids and amines, ranging from hydrogen-bonded amine–acid species, through to hydrogen-bonded ammonium carboxylate species, and essentially noninteracting ammonium carboxylate ions. These types of species most likely act to diminish (to varying extents) the potential for direct amide formation, which explains the very low of reactivity of α-amino acids on direct amide formation.[19] The process of amide formation is likely to proceed through another equilibrium species, i.e. the carboxylic acid hydrogen-bonded dimer **9**, especially under nonaqueous and nonintramolecular circumstances.[14] There is little evidence for general acid- or base-catalyzed direct amide formation under these conditions, though as hydrogen bonding and proton transfer processes are key to this reaction, it not surprising that there is only a minor effect from the addition of excess acid or amine (though it not clear at this point exactly how this occurs). More importantly, it is clear that highly charged zwitterionic species are not involved in the direct amide formation reaction, and indeed, this may even extrapolate to the boronic acid-catalyzed reaction variants.[20] DFT calculations suggest that a plausible mechanism for intermolecular direct amide formation proceeds through the existence of carboxylic acid hydrogen-bonded dimers, which are not only known to persist even at elevated temperatures but are likely to be highly favourable in nonpolar solvents. The role of such hydrogen-bonded dimers, as demonstrated in Scheme 3, is to enable both carboxylic acid activation towards nucleophilic attack by the amine, and to allow the reaction to proceed through to a neutral intermediate such as **8**, which, according to the calculations, is energetically accessible. This new mechanistic proposal has important similarities with kinetic and mechanistic studies carried out on the intramolecular amide formation reaction[14] in that the formation of a similar neutral intermediate is required for the direct amide formation reaction in aqueous conditions, from which water loss is rapid to give the amide. In our current proposed mechanism, the reaction in organic solvents of course differs considerably, and especially with respect to the likelihood that carboxylate ammonium salt formation may well have the greatest effect upon the rate of direct amide formation.

Further studies are underway to examine direct amide formation in more detail and to develop improved catalysts for carboxylic acid–amine combinations that are less reactive.

Experimental Section

Calorimetry Studies: Microcalorimetry was carried out at using an Omnical reaction calorimeter and Omnical WinCRC 2000 for MS Windows software. The appropriate carboxylic acid (2 mL of a 1 M solution in toluene) was added to a calorimetry vial equipped with a stirrer bar. This was placed inside the calorimeter, which was set at 30 °C and once the heat flow had stabilised the appropriate amine was added (2 mL of a 1 M solution in toluene). Once the heat flow had stabilised following an exotherm the vial was removed from the calorimeter and the heat output recorded. The data were processed using Excel. Due to the solubility of benzoic acid in toluene, a 0.5 M solution was made and all amines used in combination with benzoic acid were diluted to achieve 0.5 M solutions keeping the combination equimolar.

NMR Studies: Solutions of the amines and carboxylic acids in [D_8]-toluene were mixed in an NMR tube and submitted for ^{1}H NMR immediately. After 24 h the same sample was resubmitted.

Procedure for Following Reactions Over Time: 4-Phenylbutyric acid (3 mmol or 3.6 mmol) was weighed into each reaction vessel, followed by the addition of naphthalene (0.35 mmol) and assembly of a micro-Soxhlet apparatus loaded with activated molecular sieves (3 Å) under argon. Toluene (10 mL) and benzylamine (3 mmol or 3.6 mmol) were then added to each reaction vessel. Reactions were sampled (50 μL) at 6 h intervals (48 h reaction time). Samples were diluted once (50 μL in 450 μL MeCN) mixed and analysed by HPLC [gradient MeCN (0.05% TFA)/water (0.05% TFA) 50:50 over 15 min; 1 mL min^{-1}]. Naphthalene was used as an internal standard. Data was analysed using Micromath Scientist® version 2.01.

General Procedure for the Preparation of Amides at 120 °C: The appropriate carboxylic acid (3.05 mmol) was dissolved in toluene (30 mL) and amine (1 equiv.) was added, followed by the addition of catalyst (5 mol-%). The reaction mixture was heated to 120 °C and azeotropic removal of water was performed using a Dean–Stark condenser. The mixture was allowed to stir with heating to reflux for 48 h before being concentrated in vacuo. The residue was then redissolved in ethyl acetate (25 mL), washed with brine (25 mL), 5% HCl (25 mL), brine (25 mL), 5% NaOH (25 mL), brine (25 mL), dried ($MgSO_4$) and the solvent evaporated.

General Procedure for the Preparation of Amides at 55 °C: The appropriate carboxylic acid (3.05 mmol) was dissolved in toluene (30 mL) and amine (1 equiv.) was added, followed by the addition of catalyst (5 mol-%) and activated 3 Å molecular sieves. The reaction mixture was heated to 55 °C and allowed to stir at this temperature for 48 h before being filtered and concentrated in vacuo. The residue was then redissolved in ethyl acetate (25 mL), washed

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with brine (25 mL), 5% HCl (25 mL), brine (25 mL), 5% NaOH (25 mL), brine (25 mL), dried ($MgSO_4$) and the solvent evaporated.

Quantum Chemical Calculations: The quantum chemical calculations used DFT, employing Becke's three-parameter hybrid exchange functional (B3)[21] combined with the correlation functional of Lee, Yang and Parr (LYP),[22] together with 6-31G** or 6-31+G** basis sets for all atoms within the Gaussian 03 program.[23] Single-molecule calculations were fully optimized at this level of theory, with stationary points confirmed by vibrational analysis. Some calculations employed an implicit solvation model for toluene provided by a PCM.[24]

***N*-Benzyl-4-phenylbutyramide:** The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.69 g (89%), yield in the presence of *o*-iodophenylboronic acid: 0.59 (76%), yield in the absence of catalyst: 0.49 g (64%) as a white solid. Spectroscopic details were the same as those reported in the literature.[7,8]

***N*-(*tert*-Butyl)-4-phenylbutanamide:** The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.017 g (3%) as a yellow oil. $\tilde{\nu}_{max}$ (ATR): 696, 1221, 1543, 1644, 2927, 3301 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.3 (s, 9 H, 3CH_3), 1.93–1.99 (m, 2 H, CH_2), 2.09 (2 H, J = 7 Hz, CH_2), 2.63–2.68 (m, 2 H, CH_2), 5.19 (s, 1 H, N*H*), 7.17–7.21 (m, 3 H, 3Ar*H*), 7.26–7.30 (m, 2 H, 2Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (*C*H_3), 20.9 (*C*H_2), 21.4 (*C*H_2), 28.8 (*C*H_2), 60.3 [*C*$(CH_3)_3$], 125.3 (Ar*C*), 128.2 (Ar*C*), 128.3 (Ar*C*), 128.5 (Ar*C*), 129 (Ar*C*), 137.8(Ar*C*), 171.1 (*C*=O) ppm. HRMS: calcd. for $C_{14}H_{24}NO$ $[M + H]^+$ 220.1701; found 220.1704.

***N*-(2-Methoxyethyl)-4-phenylbutanamide:** The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.47 g (70%), yield in the presence of *o*-iodophenylboronic acid: 0.33 g (49%), yield in the absence of catalyst: 0.36 g (54%) as a pale yellow oil. $\tilde{\nu}_{max}$ (ATR): 700, 1132, 1542, 1550, 2942, 3289 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ = 1.94–1.98 (m, 2 H, CH_2), 2.17 (t, 2 H, J = 7.7 Hz CH_2), 2.64 (t, 2 H, J = 7.7 Hz, CH_2), 3.33 (s, 3 H, CH_3), 3.43 (m, 4 H, 2CH_2), 5.82 (s, 1 H, N*H*), 7.16–7.18 (m, 3 H, 3Ar*H*), 7.25–7.72 (m, 2 H, 2Ar*H*) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 27.1 (*C*H_2), 35.1 (*C*H_2), 35.8 (*C*H_2), 39.1 (O*C*H_3), 58.7 (*C*H_2), 71.2(*C*H_2), 126.9 (2 Ar*C*), 128.2 (Ar*C*), 128.3 (Ar*C*), 128.5 (Ar*C*), 141.5, 172.7 (*C*=O) ppm. HRMS: calcd. for $C_{13}H_{20}O_2N$ $[M + H]^+$ 222.1489; found 222.1490.

1-(4-Phenylbutanoyl)piperidine: The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.56 g (80%), yield in the presence of *o*-iodophenylboronic acid: 0.008 g (1%), yield in the absence of catalyst: 0.17 g (24%) as a colourless oil. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 24.5 (*C*H_2), 26.5 (*C*H_2), 26.6 (*C*H_2), 26.8 (*C*H_2), 32.5 (*C*H_2), 36.4 (*C*H_2), 42.6 (*C*H_2), 46.6 (*C*H_2), 125.8 (2 Ar*C*), 128.3 (Ar*C*), 128.5 (2 Ar*C*), 141.8, 170.9 (C=O) ppm. All other spectroscopic details were consistent with those reported in the literature.[25]

4-Phenylbutyranilide: The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.54 g (74%), yield in the presence of *o*-iodophenylboronic acid: 0.12 g (16%), yield in the absence of catalyst: 0.030 g (4%) as a white solid. Spectroscopic details were the same as those reported in the literature.[26]

***N*-Benzylbenzamide:** The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.56 g (86%), yield in the presence of *o*-iodophenylboronic acid: 0.011 g (2%), yield in the absence of catalyst: 0.092 g (14%) as a white solid. Spectroscopic details were the same as those reported in the literature.[7]

***N*-(2-Methoxyethyl)benzamide:** The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.13 g (24%), yield in the presence of *o*-iodophenylboronic acid: 0.027 g (5%), yield in the absence of catalyst: 0.028 g (5%) as a pale yellow oil. $\tilde{\nu}_{max}$ (ATR): 694, 1018, 1299, 1533, 1638, 2927, 3309 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, CH_3), 3.56 (t, 2 H, J = 5.6 Hz, CH_2), 3.65 (m, 2 H, CH_2), 6.54 (s, 1 H, N*H*), 7.43 (m, 2 H, 2Ar*H*), 7.49 (m, 1 H, Ar*H*), 7.79 (d, 2 H, J = 7 Hz, 2Ar*H*) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 39.7 (*C*H_2), 59.8 (O*C*H_3), 71.2 (*C*H_2), 126.9 (2 Ar*C*), 128.5 (2 Ar*C*), 131.4 (Ar*C*), 134.5, 167.4 (C=O) ppm. HRMS: calcd. for $C_{10}H_{14}O_2N$ $[M + H]^+$ 180.1019; found 180.1020.

***N*-Benzoylpiperidine:** The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.28 g (49%), yield in the absence of catalyst: 0.058 g (10%) as a white solid. Spectroscopic details were the same as those reported in the literature.[27]

Benzanilide: The general procedure for the preparation of amides was followed. Yield in the presence of $B(OH)_3$: 0.21 g (35%), yield in the presence of *o*-iodophenylboronic acid: 0.12 g (20%) as a white solid. ^1H NMR: (400 MHz, $CDCl_3$): δ = 7.14–7.19 (m, 1 H, Ar*H*), 7.35–7.40 (m, 2 H, Ar*H*), 7.46–7.52 (m, 2 H, Ar*H*), 7.54–7.58 (m, 1 H, Ar*H*), 7.64 (m, 2 H, Ar*H*), 7.82 (br., 1 H, N*H*), 7.86–7.89 (m, 2 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.2 (2 Ar*C*), 124.6 (Ar*C*), 127.0 (2 Ar*C*), 128.8 (2 Ar*C*), 129.1 (2 Ar*C*), 131.9 (Ar*C*), 135.1 (Ar*C*CO), 137.9 (Ar*C*NH), 165.7 (*C*=O) ppm. Other spectroscopic details were the same as those reported in the literature.[26]

Supporting Information (see footnote on the first page of this article): General experimental, experimental, calorimetry data, computational chemistry experimental, amide formation reactions, NMR data, computational chemistry data.

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