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The heterocyclic ring of 4-substituted-1,8-naphthalimides is *NOT* inert to nucleophilic attack, contrary to earlier reports†

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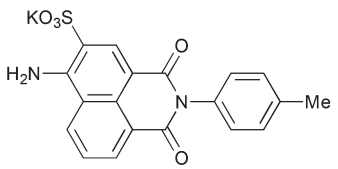
The heterocyclic ring of *N*-aryl-4-chloro-1,8-naphthalimides, reported to be resistant to nucleophilic attack, reacts with primary amine nucleophiles at room temperature to give 4-chloro-*N*-alkyl-1,8-naphthalimides. The reaction is first order in the naphthalimide. The Hammett plot is linear (R^2 0.996) with a large positive slope (+3.0), consistent with substantial negative charge development at nitrogen in the activated complex.

Introduction

The 4-amino-1,8-naphthalimide fluorophore has been widely used in a variety of applications, including fluorescent sensing of cations[1] and anions,[2] fluorescent logic gates and switches,[3] selective staining of live cells,[4] and photochemical welding of tissues with visible light.[5] Part of the importance of this fluorophore arises from its resistance to photochemical bleaching, and part to its chemical stability. In fact, the resistance of the ring system towards nucleophilic attack has become a defining characteristic of this important fluorophore—in his synthesis of Lucifer Yellow anhydride from Brilliant Sulfoflavin (**1**), Stewart[6] established the conventional wisdom that the heterocyclic ring of *N*-arylnaphthalimides is inert to nucleophilic attack except under forcing conditions, or under conditions of unusual electron deficiency, with the following statement: "A striking property of **1** is its extreme resistance to hydrolysis. Prolonged reflux of **1** with aqueous NaOH or H_2SO_4 failed to give the diacid or the corresponding anhydride".



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As a consequence of Stewart's observation, and the experience of three decades of synthetic endeavors in this area,[7] it has become accepted dogma that the heterocyclic ring of the 4-substituted-1,8-naphthalimides, once formed, is unreactive towards nucleophilic and electrophilic reagents alike. We are aware of no reports of nucleophilic displacement in the heterocyclic ring of these compounds.

In contrast to the lack of reactivity of the heterocyclic ring, a halogen or nitro group at the 4-position of the *N*-alkyl-1,8-naphthalimide nucleus has been found to be readily displaced by amine nucleophiles, providing a convenient entry into the highly fluorescent 4-amino-1,8-naphthalimide system.[7,8] Similar copper-catalyzed displacement of the halogen by methoxide anion in a series of *N*-aryl-4-bromo-1,8-naphthalimides has given the corresponding 4-methoxy compounds, without loss of the *N*-aryl group.[9] Thus, confirming Stewart's implications, it has been general experience that the imide ring, once formed, is resistant to attack by heteroatom nucleophiles: *N*-alkyl-4-chloro-1,8-naphthalimides have been found to react with amines in large excess to give products only of displacement of the halogen. To our knowledge, Stewart's synthesis of Lucifer Yellow anhydride represents the only published example of successful nucleophilic attack on the heterocyclic ring of the 4-amino-1,8-naphthalimide nucleus, and in the reactive compound the naphthalimide ring and the *N*-aryl group each carried a pair of strongly electron-withdrawing sulfonyl groups. Because of the apparent high stability of the heterocyclic ring system and its resistance towards nucleophilic attack, reinforcing Stewart's observations, there has been little incentive to study its reactions with nucleophiles, with the result that there has been no systematic study, to date, of these reactions.

In the course of other work, we needed a sulfonylaziridine, which we proposed to prepare by standard methods from the corresponding sulfonamide (**4**) by the approach summarized in Fig. 1. We prepared the *N*-aryl-4-chloroimide **3** by heating sulfanilamide and 4-chloro-1,8-naphthalic anhydride

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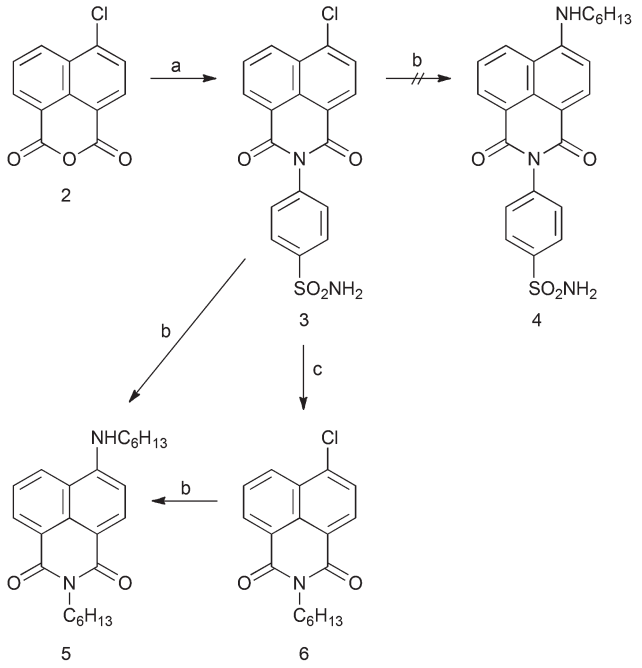
†Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra of imides **3**, **7a–d**, and **11**; data from kinetic runs; Cartesian coordinates of the complex **10**. See DOI: 10.1039/c3ob40639c



a. 4-$H_2NC_6H_4SO_2NH_2$, *o*-$C_6H_4Cl_2$, Δ. b. $C_6H_{13}NH_2$, Δ. c. $C_6H_{13}NH_2$, 25°C.

Fig. 1 Attempted synthesis of the 4-alkylamino-*N*-aryl-1,8-naphthalimide gives unexpected products of substitution in the heterocyclic ring.

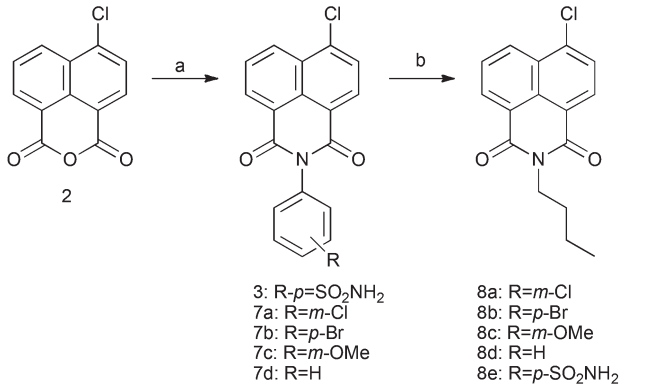
(**2**) in *o*-dichlorobenzene or benzonitrile, and subjected the product to heating in hexylamine in an attempt to effect its transformation into the aziridine precursor **4**. However, the only product isolated from this reaction was *N*-hexyl-4-hexylamino-1,8-naphthalimide, **5**. Even at room temperature, the reaction gave 4-chloro-*N*-hexyl-1,8-naphthalimide (**6**), which showed that the substitution of the aromatic amine is faster than the displacement of the halogen.

These results were entirely unexpected, given three decades of experience that the heterocyclic ring is inert to attack by nucleophiles. Thus—unexpectedly—the combination of a 4-chloro substituent on the naphthalimide ring and an electron-withdrawing substituent on the *N*-aryl ring is clearly sufficient for heterocycle cleavage to occur with primary amine nucleophiles. This then raised the question of just what level of electron deficiency is required for the displacement of the aniline from a 4-substituted-*N*-aryl-1,4-naphthalimide, and just how general this reaction is.

Results and discussion

To assess the requirement for electron-withdrawing groups on the *N*-phenyl substituent, we prepared a series of *N*-aryl-4-chloro-1,8-naphthalimides carrying both electron-withdrawing and electron-releasing substituents on the phenyl ring by standard methods from 4-chloro-1,8-naphthalic anhydride (Fig. 2).

The resultant 4-chloro-*N*-aryl-1,8-naphthalimides were then treated with butylamine at 4 °C. Contrary to our expectations,



a. $ArNH_2$, AcOH, Δ (R=*m*-Cl, *p*-Br, *m*-OMe), or $ArNH_2$, PhCN, Δ (R = SO_2NH_2), or $PhNH_2$, Δ (R = H). b. $BuNH_2$, 25°C

Fig. 2 Synthesis of 4-chloro-*N*-aryl-1,8-naphthalimides and their reactions with butylamine.

we found that every 4-chloroimide underwent some degree of ring cleavage with butylamine at 4 °C to give *N*-butyl-4-chloro-1,8-naphthalimide, although the reaction rate did vary widely with the phenyl substituent; displacement of the chloride became the dominant reaction when the substituent on the *N*-phenyl ring became electron-releasing. Thus, we suggest that in the presence of even a mildly electron-withdrawing substituent at the 4-position (the Hammett σ_p constant for chlorine is 0.23, compared to 0.35 for the sulfonate group and 0.78 for the nitro group[10]), an *N*-aryl group is sufficient to render attack of an amine nucleophile at the imide carbonyl group preferred.

In order to quantify the effects of the phenyl substituent, we determined the kinetics of the displacement of the aromatic amine by butylamine using the nucleophile as solvent; under these conditions, all reactions exhibited excellent pseudo-first order kinetics. Solutions that varied in concentration from 0.06 to 0.6 mM were kept at 25.00 ± 0.02 °C, and aliquots were removed from the reaction flask and quenched with 8 M hydrochloric acid prior to extractive work-up and ^{1}H NMR analysis. The work-up removes both the butylamine solvent and the aniline produced, leaving a mixture of imides for ^{1}H NMR analysis.

The ^{1}H NMR spectra of these compounds (Fig. 3) are especially suited for kinetic studies because the resonances of the naphthalimide ring system are relatively insensitive to changes in substituent at the heterocyclic nitrogen. The proton at position 2 of the naphthalimide ring in chloroimides **7** and chloroimide **3**, regardless of the *N*-aryl substituent, resonates at a chemical shift close to δ 8.5, well separated from the rest of the spectrum, and sufficiently far from the resonance of the same proton in chloroimide **8** (always slightly upfield from the starting imide) to permit its use in quantifying the amount of unreacted starting material in most samples. At the same time, the protons at positions 5 and 7 resonate as a complex multiplet or pair of doublets in the region δ 8.6–8.8 in the spectra of all 4-chloro-1,8-naphthalimides (both *N*-aryl and *N*-butyl) that we have prepared; although this multiplet is

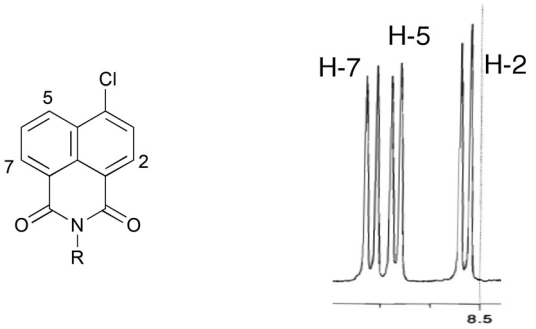


Fig. 3 ^{1}H NMR resonances used in monitoring kinetics (taken from compound **7d**).

sometimes difficult to deconvolute in the mixture of reactant and product, it can be used as an internal integration standard.

The kinetics of the reaction were followed by measuring the disappearance of the resonance of the signal of H-5 of imide **7** (or imide **3**). All reactions were run in triplicate. The reproducibility of the peak integrations was tested by measuring the spectrum of a standard set of samples in quintuplicate. These samples showed less than 0.1% variation in the value of the rate constant and the intercept for the same samples, indicating that there is no substantial error introduced by this method of measurement. The results of the kinetic measurements are gathered in Table 1 (errors are from weighted least squares at the 95% confidence level).

The half-lives of the reactions increased from *ca.* 5 hours when the substituent was *m*-Cl, to more than two days when the phenyl ring was unsubstituted. The chloroimide **3** exhibited a strong propensity to form a solution from which the starting imide would precipitate at different times during the reaction, making any kinetic measurements for this compound unreliable; this compound was therefore omitted from the reaction rate analysis. The reactions of compounds carrying groups less strongly electron-withdrawing than *m*-methoxy (σ_p = 0.12) become very difficult to follow, because displacement of the chlorine becomes the dominant reaction. This problem required that we use a different resonance to monitor the reaction of the parent compound, but fortunately, the resonance of the C-6 proton of the product is well separated from the rest of the resonances. For the same reason, we have restricted this study to substituents with $0.37 > \sigma > 0$.

The pseudo-first order rate constants for reactants with substituents having $0.37 > \sigma > 0$ give the linear Hammett plot in Fig. 4. It is worthwhile noting that there was considerably more scatter in the plots for the *p*-bromo and *m*-methoxy compounds, which we attribute to the much lower solubility of these two compounds in the reaction medium. The Hammett plot is linear (R^2 = 0.996), with a slope of +3.0 ± 1.2, which is comparable to the Hammett ρ values for Hofmann eliminations of quaternary ammonium ions, where computations suggest the development of a formal negative charge of $0.3e^-$ at the β carbon.[5] This is consistent with an increase in the electron density at the heterocyclic nitrogen as the reaction proceeds, with the rate determining step of the reaction being the opening of the heterocyclic ring of **9**, formed in a pre-equilibrium involving addition of butylamine to the imide carbonyl group (Fig. 5).

Table 1 Pseudo-first order rate constants for the reaction of imides **7** with *n*-butylamine at 25.00 °C

R	Rate constant (min^{-1})	R^2
m-Cl	$2.02 \pm 0.04 \times 10^{-3}$	0.995
p-Br	$7.9 \pm 1.2 \times 10^{-4}$	0.994
m-OMe	$3.21 \pm 0.6 \times 10^{-4}$	0.956
H	$1.64 \pm 0.07 \times 10^{-4}$	0.999

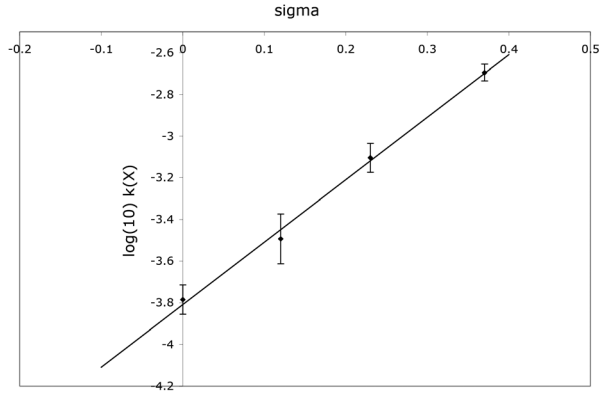


Fig. 4 Hammett plot for the loss of the substituted *N*-phenyl group of the *N*-aryl-4-chloro-1,8-naphthalimides.

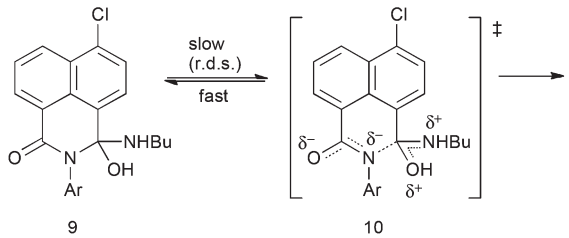


Fig. 5 Rate-determining step of the substitution of *N*-aryl-4-chloro-1,8-naphthalimides by butylamine.

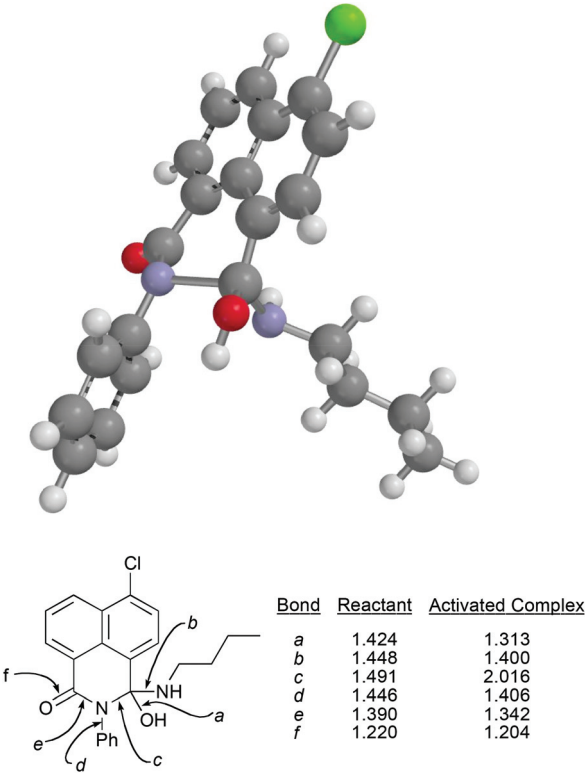
The large slope of the Hammett plot may also reflect the ability of the lone pair on nitrogen to conjugate with the aromatic ring as the ring opens; it is well known that primary alkyl groups bonded to the heterocyclic nitrogen adopt a conformation where the group is orthogonal to the naphthalimide ring system,[7] and substituents on an *N*-phenyl substituent do not interact with the fluorophore.[11] An orthogonal *N*-aryl group would be incapable of conjugating with the lone pair on the imide nitrogen, but rotation about the C–N bond as the ring opens (as in **10**) would allow improved conjugation of the electron density on nitrogen with the phenyl ring. Thus, the large positive ρ value may, in part, reflect this conformational change in the transition state.

In an effort to quantify some of the structural changes occurring during this rate-limiting step, we have carried out

computations, at the MP3/6-31G* level, of the energy profile of intermediate **10** as a function of the C–N bond distance. The geometry of the activated complex was then optimized at the MP3/6-311+G** level.‡ These computations reveal that the energy of the system passes through a maximum when the C–N distance is close to 2.02 Å to give the activated complex model shown in Fig. 6. The major changes in bond lengths of the groups around the heterocyclic ring are also summarized in Fig. 6 for the optimized reactant and product for the ring cleavage. These bond changes are as expected for the formation of the two amide groups: the C–OH bond shortens significantly, from 1.424 to 1.313 Å, as does the C–NHBu bond (from 1.448 to 1.400 Å). The bond between the heterocyclic nitrogen and the phenyl ring shortens by 0.04 Å, and, at the same time, the dihedral angle between the *N*-phenyl ring and the carbonyl group of the incipient amide anion decreases from 92° to 43°. These changes are consistent with **10** as a reasonable model for the activated complex for this reaction. We recognize that these computations omit the hydrogen bonding between **10** and the solvent, and that care must therefore be exercised not to over-interpret the results. Nevertheless, it is gratifying to see that the results of the computations are consistent with the effects implied by the Hammett plot.

The fact that the reaction occurs for *N*-aryl compounds, but not for *N*-(primary)alkyl compounds reaction may be due to either steric or electronic factors. The question of whether or not the aryl substituent is actually necessary for the reaction to occur, or whether any sterically bulky alkyl substituent bonded to nitrogen would suffice, was settled by preparing the *N*-cyclohexyl analogue (**11**) and treating it with butylamine. Only one reaction was observed: displacement of the halogen—there was no evidence for substitution of the heterocyclic nitrogen. Thus, we conclude that the *N*-aryl group is essential for substitution of the heterocyclic nitrogen. We suggest that this may be due to the additional stabilization of the incipient amide anion of **10** by the aromatic ring; similar stabilization is not available to saturated alkyl analogues.

In similar vein, we sought to define the required properties of the substituent at the 4-position by preparing 4-dimethylamino-*N*-(4-aminosulfonylphenyl)-1,8-naphthalimide (**12**), and treating it with butylamine. The synthesis of the imide, which could not be prepared by direct displacement, was effected from the 4-chloronaphthalimide by a modification of Qian's procedure[12] for the synthesis of 4-dimethylamino-1,8-naphthalic anhydride. The reaction provided the 4-dimethylamino-*N*-aryl-1,8-naphthalimide in modest yield. The reaction of this compound with butylamine was extremely slow, and it provided only the 4-butylamino derivative **13**. Thus, we conclude that an electron-releasing group at the 4-position bearing a lone pair and capable of conjugating with the imide carbonyl groups suppresses substitution of the heterocyclic nitrogen; this would account for Stewart's failure to observe hydrolysis in *N*-aryl-4-amino-1,8-naphthalimides.



Bond	Reactant	Activated Complex
a	1.424	1.313
b	1.448	1.400
c	1.491	2.016
d	1.446	1.406
e	1.390	1.342
f	1.220	1.204

Fig. 6 Optimized structure (MP3/6-311+G**) of the activated complex for heterocyclic ring cleavage in the butylamine adduct of *N*-phenyl-4-chloro-1,8-naphthalimide.

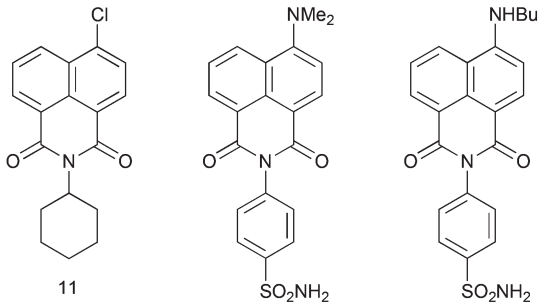
Our efforts to determine the kinetic order of the reaction with respect to butylamine have been complicated by the effects of solvent on the rate of the reaction, which are unexpectedly complex. Thus, while the reactions of **7a** with butylamine using dichloromethane as co-solvent (where hydrogen bonding to the co-solvent is not possible), the observed rate constant decreases with decreasing concentration of the butylamine, but the large amount of scatter in the values obtained does not allow the kinetic order with respect to the amine to be determined. In methanol (which is a strongly hydrogen-bonding cosolvent) on the other hand, changing from butylamine (concentration 10 M) to 5 M butylamine in methanol leads to an *increase* in the rate constant of the reaction despite the decreased nucleophile concentration. We are exploring these solvent effects, and the effects of the structure of the primary amine nucleophile, further.

Conclusions

In conclusion, we report an unprecedented, facile substitution in the heterocyclic ring of *N*-aryl-4-chloro-1,8-naphthalimides by primary amines, in contrast to the conventional wisdom in

‡The calculations were originally carried out using an unrestricted (open shell) calculation. A reviewer pointed out that this system should be a closed-shell system, so the computations were repeated as the closed-shell calculations specified in the body of the text. The changes did not materially affect the outcome of the calculations, with minor differences in equilibrium geometry and energy being noted.

this system. The aromatic ring on the heterocyclic nitrogen appears to be essential for this reaction, and the effects are not simply steric in origin. Electron-donating substituents carrying a lone pair at the 4-position completely suppress the reaction: 4-dimethylamino-*N*-aryl-1,8-naphthalimides undergo only slow substitution at the 4-position, and no substitution in the heterocyclic ring is observed. The Hammett plot for the reaction ($\sigma > 0$) is linear with a large positive slope, consistent with the generation of a substantial partial negative charge on nitrogen, or much improved interaction between the phenyl ring and the lone pair on nitrogen, in the rate-determining step, a conclusion supported by computational results at the B3LYP/6-31G* level of theory.



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Experimental

Melting points were measured using a hot-stage melting point apparatus, and are uncorrected. Butylamine was dried over KOH pellets for at least 24 h prior to use. 4-Chloro-1,8-naphthalic anhydride and the aromatic amines were used as supplied. ^{1}H NMR spectra were recorded at 400 MHz; peaks are reported in ppm (δ) downfield from Me_4Si, and are reported as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz; peaks are reported in ppm (δ) downfield from Me_4Si. Analytical HPLC was carried out using a C-18 reversed-phase column with methanol or 10% water in methanol as the eluting solvent. A blank was run to ensure that artifacts from solvent change were eliminated. High resolution mass spectra were recorded using a dual mode (APCI/ESI) ion source; values of *m*/*z* were calibrated using the isotope cluster of the M or M + H ion from 2,4,6-tribromoaniline ($C_6H_4Br_3N^+$) as internal standards.

Synthesis of chloronaphthalimides

Standard procedure. 4-Chloro-1,8-naphthalic anhydride (1.00 eq.) was mixed with the aromatic amine (1.1–2.0 eq.) and the mixture was dissolved in acetic acid (30–40 mL). The reaction mixture was stirred under reflux for 16–24 hours and allowed to cool to room temperature. The resultant precipitate was collected by vacuum filtration, washed well with water, and recrystallized from acetic acid. The purity of each compound used in the kinetic runs was analyzed by HPLC.

6-Chloro-2-phenyl-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (7d). 4-Chloro-1,8-naphthalic anhydride (3.0147 g, 12.96 mmol) was dissolved in aniline (15 mL, 15.0262 g), and the solution was stirred 24 h under reflux. The solution was poured into 10% HCl (≈ 200 mL), and the solid that precipitated was collected by vacuum filtration and recrystallized from acetic acid, using decolorizing carbon, to give pure 6-chloro-2-phenyl-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione as a pale grey solid (1.8078 g, 45%). HPLC analysis of this material showed it to be >98% pure. Material for use in the kinetics experiments was obtained by a second recrystallization of this imide (0.5045 g) from ethyl acetate–hexane, which gave chromatographically homogeneous imide (0.3902 g, 77% recovery), m.p. 248–249 °C.

^{1}H NMR (δ, CD_3COCD_3): 8.72 (1H, d J = 8.5), 8.67 (1H, d J = 7.3), 8.53 (1H, d J = 7.9), 8.07 (1H, t J = 7.9), 8.05 (1H, d J = 7.9), 7.56 (2H, t J = 7.6), 7.49 (1H, t J = 6.9), 7.46 (2H, d J = 6.9) ppm.

^{13}C NMR (δ, CD_3SOCD_3): 163.3, 163.0, 137.5, 135.8, 131.6, 130.8, 130.1, 129.0, 128.9, 128.64, 128.57, 128.3, 127.7, 123.4, 122.1 ppm.

ν_{max} (KBr): 3070, 1709, 1665 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 308.0462, 310.0416; $C_{18}H_{11}ClNO_2^+$ requires 308.0478, 310.0449.

6-Chloro-2-(3-methoxyphenyl)-1*H*-benz[*de*]isoquinolin-1,3-(2*H*)-dione (7c). This imide was prepared by the standard procedure from 4-chloro-1,8-naphthalic anhydride (2.9535 g, 12.70 mmol) and *m*-anisidine (2.4366 g, 19.78 mmol) in acetic acid (31 mL). The reaction was heated 16 h under reflux. The imide obtained (3.3367 g, 78%), m.p. 273–274 °C, was pure enough for use without a second recrystallization. HPLC analysis showed the material to be >98% pure.

^{1}H NMR (δ, $CDCl_3$): 8.74 (1H, dd J = 0.9, 7.3), 8.69 (1H, dd J = 0.9, 8.6), 8.58 (1H, d J = 7.8), 7.92 (1H, dd J = 7.4, 8.4), 7.89 (1H, d J = 7.8), 7.49 (1H, t J = 8.1), 7.06 (1H, ddd J = 0.7, 2.4, 8.3), 6.93 (1H, ddd J = 0.8, 2.4, 7.7), 6.88 (1H, t J = 2.3), 3.86 (3H, s) ppm.

^{13}C NMR (δ, $CDCl_3$): 163.8, 163.6, 160.5, 139.4, 136.2, 132.4, 131.5, 131.0, 130.1, 129.5, 128.0, 127.5, 123.2, 121.7, 120.7, 114.9, 114.2, 55.4 ppm.

ν_{max} (KBr): 3074, 1709, 1661 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 338.0594, 340.0568; $C_{19}H_{13}ClNO_3^+$ requires 338.0584, 340.0554.

6-Chloro-2-cyclohexyl-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (11). This imide was prepared by the standard procedure from 4-chloro-1,8-naphthalic anhydride (3.1344 g, 13.47 mmol) and cyclohexylamine (20.6550 g, 208.26 mmol) in acetic acid (31 mL). The mixture was stirred 46 h under reflux. The imide was obtained as an off-white solid (3.5927 g, 90%), m.p. 239–240 °C. HPLC analysis showed the material to be ≥95% pure.

^{1}H NMR (d, $CDCl_3$): 8.65 (1H, d J = 7.3), 8.59 (1H, d J = 8.4), 8.49 (1H, d J = 7.9), 7.86 (1H, dd J = 7.5, 8.2), 7.83 (1H, d J = 8.1), 5.03 (1H, tt J = 3.7, 12.2), 2.56 (2H, d J = 3.4 of q J = 12.4), 1.91 (2H, br. d J = 13.2), 1.0–1.8 (6H, complex) ppm.

^{13}C NMR (δ, $CDCl_3$): 164.1, 163.9, 138.6, 131.8, 131.0, 130.2, 129.12, 129.07, 127.8, 127.3, 123.7, 122.2, 53.9, 20.1, 26.5, 25.4 ppm.

ν_{max} (KBr): 3096, 1704, 1661 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 314.0935, 316.0911; $C_{18}H_{17}ClNO_2^+$ requires 314.0948, 316.0918.

6-Chloro-2-(3-chlorophenyl)-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (7a). This imide was prepared by the standard procedure from 4-chloro-1,8-naphthalic anhydride (3.0458 g, 13.09 mmol) and *m*-chloroaniline (2.5843 g, 20.26 mmol) in acetic acid (30 mL). The reaction was heated 20 h under reflux. The imide obtained (4.1885 g, 93%), m.p. 266–267 °C, was pure enough for use without further purification. HPLC analysis showed the material to be >98% pure.

^{1}H NMR (δ, $CDCl_3$): 8.73 (1H, d J = 7.6), 8.71 (1H, d J = 8.4), 8.57 (1H, d J = 7.8), 7.93 (1H, t J = 7.9), 7.90 (1H, d J = 7.9), 7.45–7.55 (2H, complex), 7.36 (1H, br. s), 7.20–7.25 (1H, br. m).

^{13}C NMR (δ, $CDCl_3$): 163.7, 163.4, 139.7, 136.2, 135.0, 132.6, 131.6, 131.2, 130.3, 129.5, 129.4, 129.19, 129.17, 128.0, 127.6, 127.0, 123.0, 121.5 ppm.

ν_{max} (KBr): 3061, 1709, 1665 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 342.0103, 344.0077, 345.9876; $C_{18}H_{10}Cl_2NO_2^+$ requires 342.0089, 344.0059.

2-(4-Bromophenyl)-6-chloro-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (7b). This imide was prepared by the standard procedure from 4-chloro-1,8-naphthalic anhydride (3.0009 g, 12.90 mmol) and *p*-bromoaniline (3.4528 g, 20.07 mmol) in acetic acid (31 mL). The reaction was heated 20 h under reflux. The imide obtained (3.9567 g, 90%), m.p. 296–297 °C, was pure enough for use without further purification. HPLC analysis showed the material to be >98.5% pure.

^{1}H NMR (δ, $CDCl_3$): 8.73 (1H, dd J = 1.1, 7.3), 8.71 (1H, dd J = 1.1, 8.5), 8.57 (1H, d J = 7.9), 7.93 (1H, dd J = 7.3, 8.5), 7.89 (1H, d J = 7.8), 7.70 (2H, AA′ of AA′BB′ system J = 8.7), 7.23 (2H, AA′ of AA′BB′ system J = 8.7) ppm.

^{13}C NMR (δ, $CDCl_3$): 163.9, 163.7, 139.7, 137.1, 132.7, 132.6, 131.7, 131.2, 130.4, 129.5, 129.4, 128.0, 127.6, 123.0, 122.9, 121.5 ppm.

ν_{max} (KBr): 3100, 1704, 1670 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 385.9588, 387.9567, 389.9549; $C_{18}H_{10}BrClNO_2^+$ requires 385.9583, 387.9554, 387.9563, 389.9534.

2-(4-Aminosulfonylphenyl)-6-dimethylamino-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (12). A solution of imide **3** (1.38 g, 3.73 mmol) and copper(II) sulfate pentahydrate (1.69 g, 10.59 mmol) in DMF (25 mL) was stirred 24 h under reflux. The mixture was cooled, and then poured into water (75 mL) to precipitate the crude product. The crude product was collected by vacuum filtration and recrystallized from acetic acid to give the imide **12** (0.46 g, 33%) as a yellow solid, m.p. >300 °C (dec.). HPLC analysis showed the material to be >99.5% pure.

^{1}H NMR (δ, CD_3COCD_3): 8.65 (1H, d J = 8.6), 8.55 (1H, d J = 7.1), 8.45 (1H, d J = 8.4), 8.06 (2H, d J = 8.0), 7.82 (1H, dd J = 8.0, 7.8), 7.62 (2H, d J = 8.0), 7.32 (1H, d J = 7.8), 6.71 (2H, br. s), 3.19 (6H, s) ppm.

^{13}C NMR (δ, CD_3SOCD_3): 163.8, 163.1, 156.8, 143.7, 139.3, 132.4, 131.9, 130.7, 130.2, 129.9, 126.3, 125.0, 124.3, 122.6, 113.3, 112.9, 44.4 ppm.

ν_{max} (KBr): 1691, 1635 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 396.1040; $C_{20}H_{18}N_3O_4S^+$ requires 396.1013.

2-(4-Aminosulfonylphenyl)-6-chloro-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (3). A mixture of 4-chloro-1,8-naphthalic anhydride (3.1076 g, 13.36 mmol) and sulfanilimide (4.6162 g, 26.81 mmol) in benzonitrile (30 mL) was stirred 26 h under reflux. The reaction mixture was allowed to cool, and the crude product was isolated by vacuum filtration. Recrystallization of the crude product from acetic acid gave the imide **3** as an iridescent gold solid (2.9800 g, 53%), exhibiting a sharp m.p. >300 °C (approximately 305–306 °C).

^{1}H NMR (δ, CD_3SOCD_3): 8.70 (1H, dd J = 0.6, 7.9), 8.62 (1H, d J = 7.2), 8.47 (1H, d J = 7.9), 8.10 (1H, d J = 7.9), 8.07 (1H, dd J = 7.6, 7.9), 7.98 (2H, d J = 8.5), 7.63 (2H, d J = 8.5), 7.52 (2H, s) ppm.

^{13}C NMR (δ, CD_3SOCD_3): 172.0, 163.2, 162.9, 144.0, 138.8, 131.6, 130.9, 130.3, 129.8, 128.8, 128.6, 128.5, 127.7, 126.4, 123.2, 121.9 ppm.

ν_{max} (KBr): 3352, 3252, 1713, 1670 cm^{-1}.

HR-APCI-MS (M + H, *m*/*z*): Found: 387.0212, 389.0184; $C_{18}H_{12}ClN_2O_4S^+$ requires 387.0206, 389.0177.

Treatment of imide 2 with hexylamine

The imide **2** (1.00 g, 2.59 mmol) was added to hexylamine (75 mL), and the mixture was stirred 18 h under reflux. The reaction mixture was poured into dilute HCl (10%, 200 mL) and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried and evaporated under reduced pressure to give a yellow solid that was recrystallized from methanol to provide a bright yellow solid (0.70 g, 68%), m.p. 47–50 °C, shown to be identical with 2-hexyl-6-hexylamino-1*H*-benz[*de*]isoquinolin-1,3(2*H*)-dione (**5**) by comparison with an authentic sample.

Kinetics

1. Standardization. All kinetics experiments were run in triplicate in a 30 L water bath thermostated at 25.00 ± 0.03 °C. Temperatures were monitored using two mercury-in-glass thermometers simultaneously immersed in the bath for the duration of the experiment; temperature readings of the two thermometers did not differ by more than 0.01 °C at any time during the runs. Monitoring of the temperature during the run showed that the temperature remained constant to within ±0.01 °C throughout the run. The variability of the ^{1}H NMR integrations was determined by running the same sample five times, and recording the integrations of the peaks used. The results showed that the ratios of the integrated areas of the critical peaks varied by less than ±0.1%.

2. Solution preparation and kinetic data collection. The samples were prepared by adding dry 1-butylamine (≈12 mL) to an accurately weighed quantity of the chloronaphthalimide (≈12 mg), and stirring briefly to dissolve as much of the solid

as possible. The resultant homogeneous solution was transferred to a volumetric flask (10.00 mL), and the unused solution was evaporated under reduced pressure to provide the mass of undissolved imide. The flask was placed in the thermostated water bath, and aliquots (≈0.5 mL) were withdrawn periodically and quenched with 20% aqueous HCl (≈10 mL). The acidified solution was extracted with dichloromethane (2 × 20 mL), and the combined organic layers were washed with water (20 mL), dried (Na_2SO_4), and evaporated. The composition of the sample was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$ solution.

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