

Kinetics of competing reactions of *N*-aryl-4-chloro-1,8-naphthalimides with primary amines



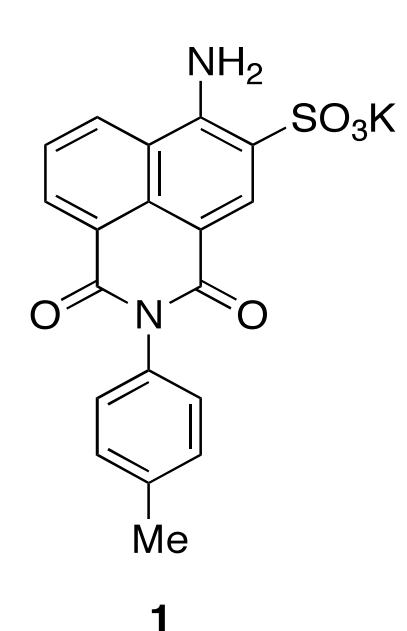
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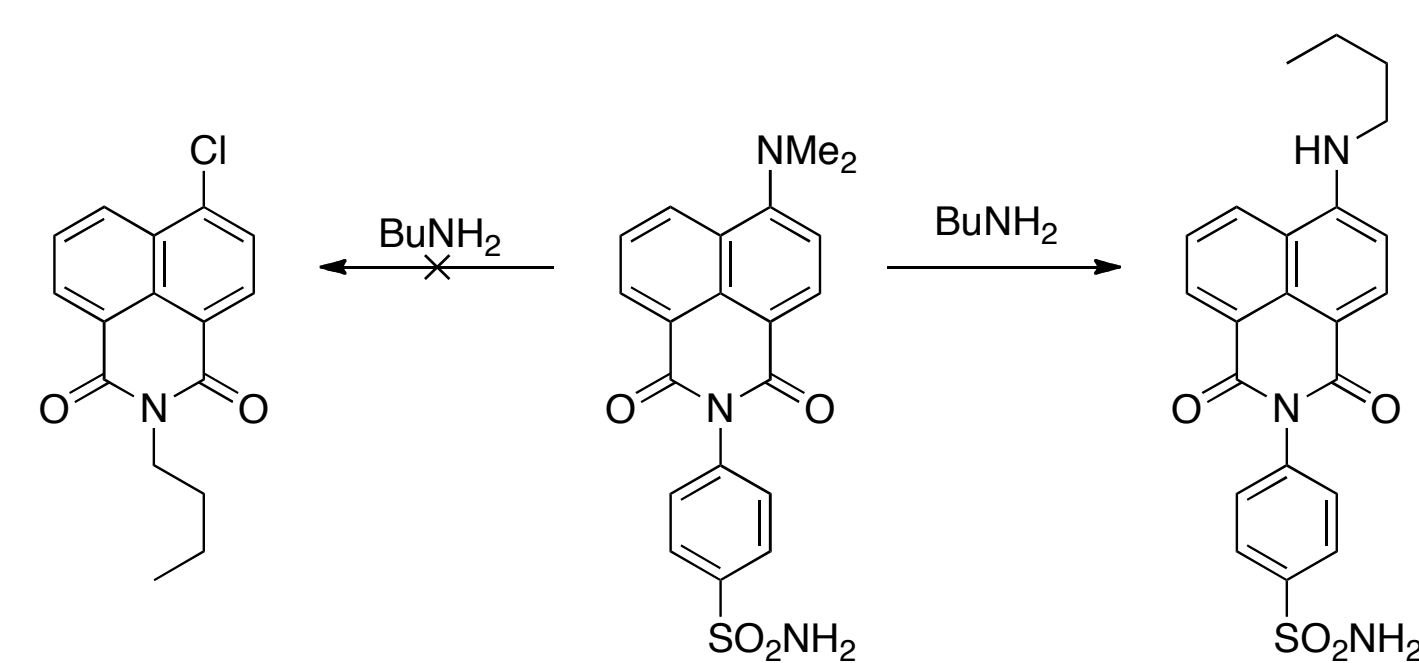
Conventional Wisdom



- The conventional wisdom is that the heterocyclic ring of *N*-arylnaphthalimides is resistant to nucleophilic attack (Stewart, Lucifer Yellow anhydride, 1981).
- Nucleophilic attack on the heterocyclic ring was successful only when both the naphthalimide ring and the *N*-aryl group carried two strongly electron-withdrawing sulfonyl groups.
- Subsequent finding that a halogen at the 4-position of the *N*-alkyl-1,8-naphthalimide is readily displaced by amine nucleophiles.

Preparation of Dye and Unexpected Reactivity with Primary Amines

- We prepared the *N*-aryl-4-chloroimide **3** by heating sulfanilamide and 4-chloro-1,8-naphthalic anhydride (**2**) in benzonitrile.
- When imide **3** was heated in hexylamine, the product isolated was *N*-hexyl-4-hexylamino-1,8-naphthalimide (**5**).
- Even at room temperature, the reaction gave 4-chloro-*N*-hexyl-1,8-naphthalimide (**6**).
- This shows that the substitution of the aromatic amine is faster than the displacement of the halogen.



Acknowledgments

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Rate Constants

R	Rate Constant (min ⁻¹)
<i>m</i> -Cl	2.65±0.11 × 10 ⁻³
<i>p</i> -Br	1.08±0.12 × 10 ⁻³
<i>m</i> -OMe	3.7±0.6 × 10 ⁻⁴
H	1.6±0.4 × 10 ⁻⁴

- A Hammett plot of the rate constants for reactants with substituents having 0.37 > σ > 0 is given in Figure 2.
- It is linear ($R^2=0.994$), with a slope $\rho=+3.35$.
- This is consistent with an increase in the electron density at the heterocyclic nitrogen as the reaction proceeds.

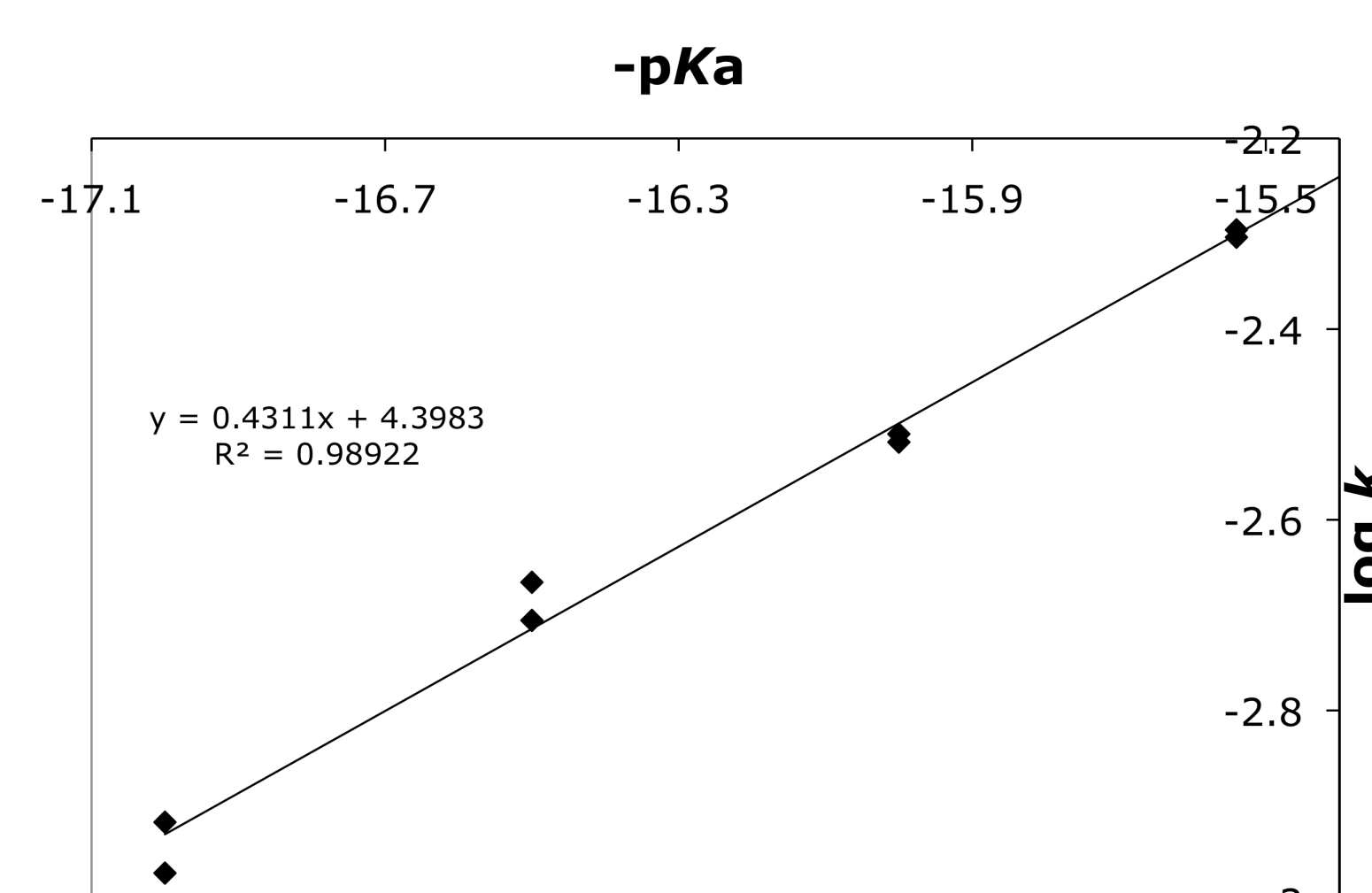
Minimum Structural Requirement

- The combination of a 4-chloro substituent on the naphthalimide ring and an electron-withdrawing substituent on the *N*-aryl ring is sufficient for heterocycle cleavage to be effected by primary amine nucleophiles

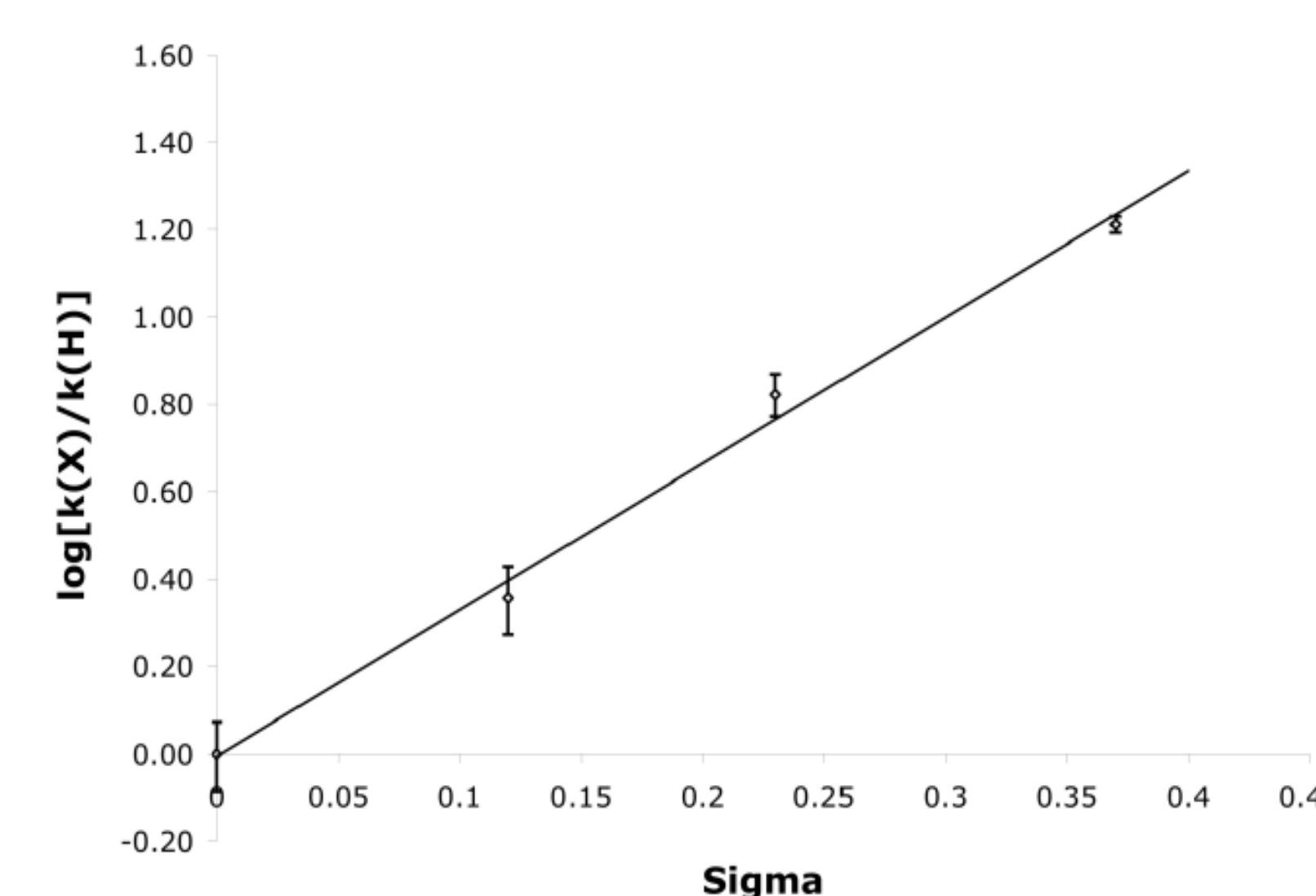
Effects of Solvent

- Attempts to explore effect of the concentration of the amine using alcohol cosolvents resulted in *acceleration* of the displacement reaction.
- We studied four alcohols to examine the solvent effects:
 - methanol (pK_a 15.54)
 - 1-propanol (pK_a 16.0)
 - 2-propanol (pK_a 16.5)
 - tert*-butyl alcohol (pK_a 17.0)
- The trend in reaction rates appears to correlate with the alcohols' ability to act as a hydrogen bond donor.

Brønsted Law Plot



Hammett Plot for Reaction ($\sigma \geq 0$)



Is the Effect of the *N*-Phenyl Ring Simply Steric?

- The *N*-cyclohexyl analogue was prepared
- It was treated with butylamine.
- The displacement of the halogen was the only reaction that occurred.
- Thus, the *N*-aryl group is essential for substitution of the heterocyclic nitrogen. Replacement by a similar bulky alkyl group is not sufficient.

What About the Substituent at the 4-Position?

- The reaction of the 4-dimethylamino derivative at right with butylamine was extremely slow, and it gave only the product of displacement of the dimethylamino group.
- No displacement of the phenyl ring was observed
- 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.

Brønsted Plot

- Brønsted catalysis law: $\log_{10} k = \alpha \log_{10} K_a + C$
 - $\alpha=0$: no acid catalysis
 - $\alpha=1$: specific acid catalysis
 - $0 < \alpha < 1$: general acid catalysis
- The plot of $\log_{10} k$ vs. against ($-pK_a$) for the alcohol is linear (slope=0.43, $R^2=0.99$), a clear indication of general acid catalysis during the activated step.

Brønsted Plot Summary

- The $-pK_a$ of the alcohols was plotted versus the $\log k$ to explore the possibility of acid catalysis by the alcohols.
- The plot is linear (slope=0.43, $R^2=0.99$), a clear indication of general acid catalysis during the activated step.
 - A slope of 1.0 would indicate specific acid catalysis and 0.0 would indicate no acid catalysis.

Conclusions

- The aromatic ring on the heterocyclic nitrogen is essential for this reaction (not steric in origin)
- Electron-donating (amine) substituents at the 4-position completely suppress the reaction.
- The large positive slope of the Hammett plot is consistent with the generation of a substantial partial negative charge on the nitrogen.
- When the same reaction takes place with an alcohol as a co-solvent the kinetic data clearly demonstrate general acid catalysis of the reaction.