

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

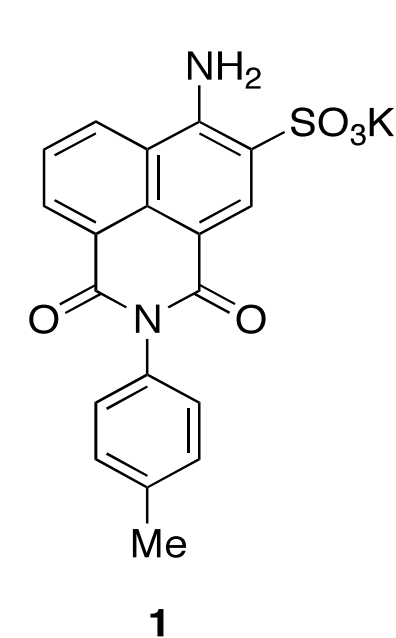


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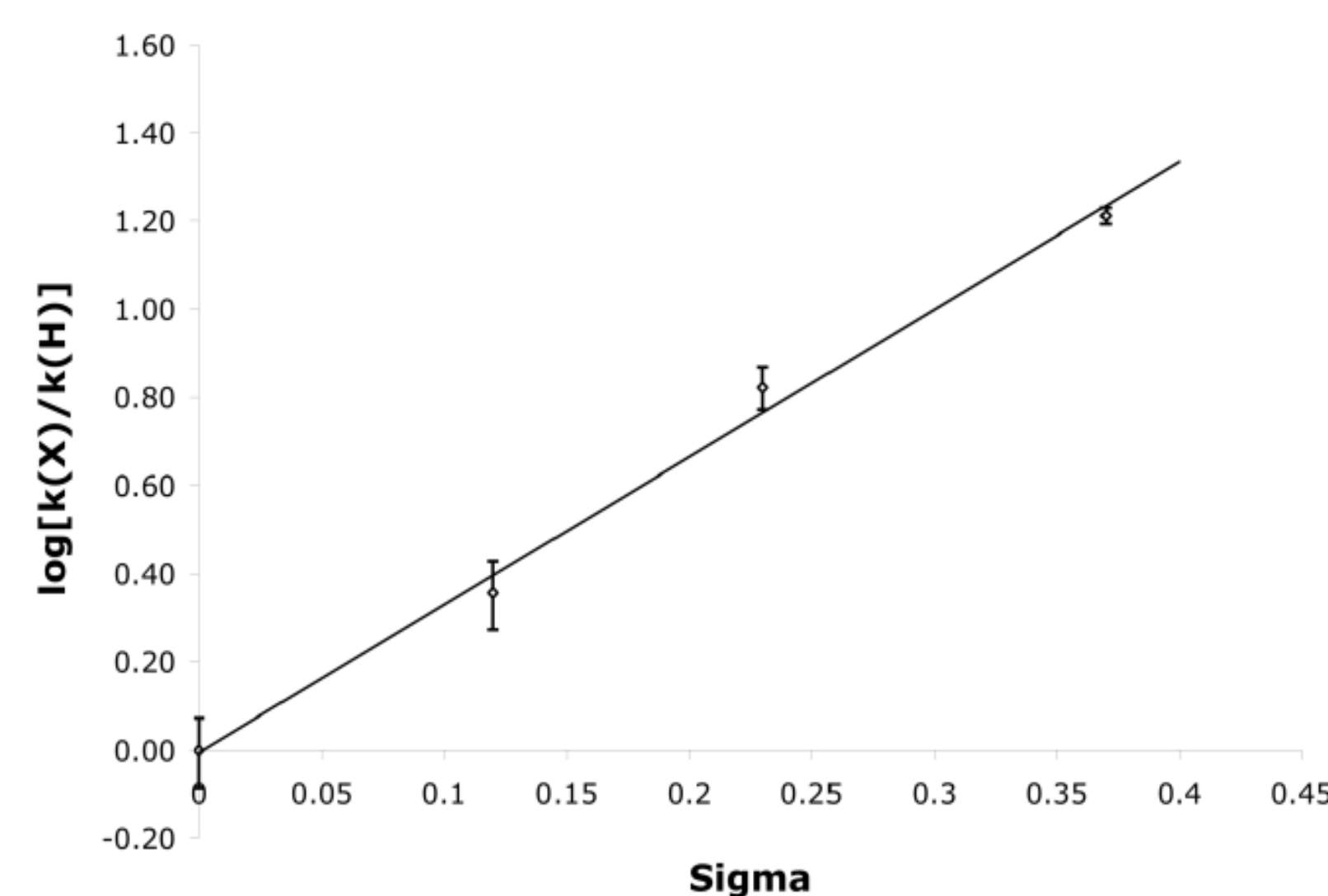
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Conventional Wisdom



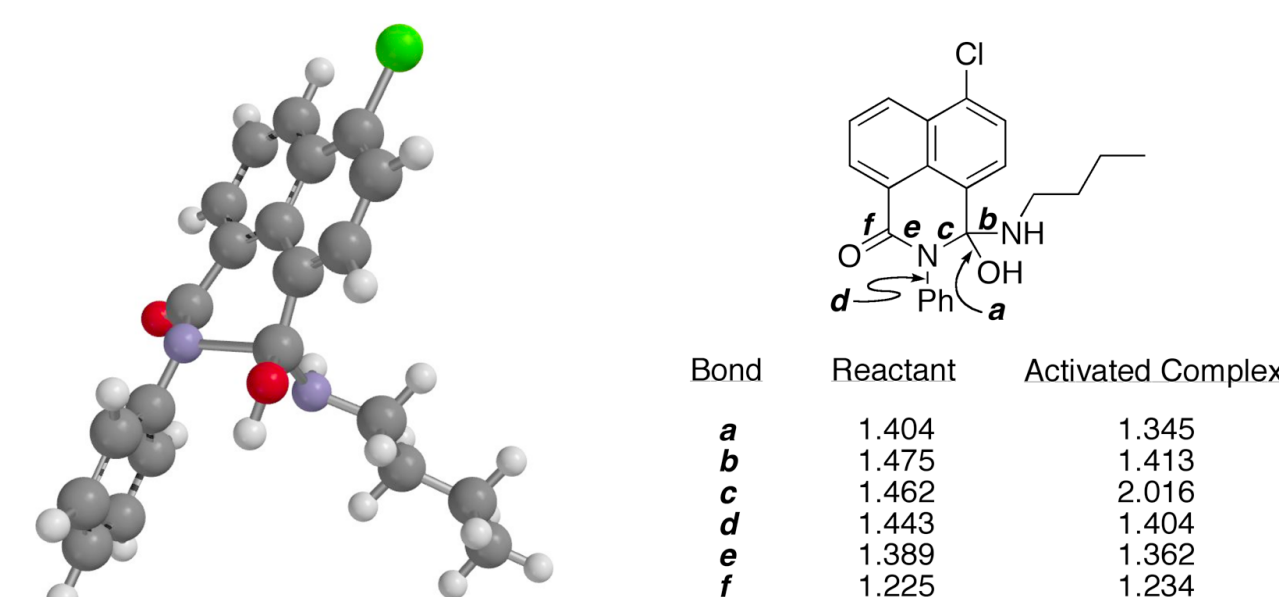
- The conventional wisdom is that the heterocyclic ring of *N*-arylnaphthalimides is resistant to nucleophilic attack (Stewart, Lucifer Yellow anhydride, 1981).
- Nucleophilic attack on the heterocyclic ring was successful only when both the naphthalimide ring and the *N*-aryl group carried two strongly 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.

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



Deductions from Kinetic Data

- Hammett ρ constant = +3.3
 - significant negative charge development at N
 - comparable to Hofmann elimination (E1cb-like E2)



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.

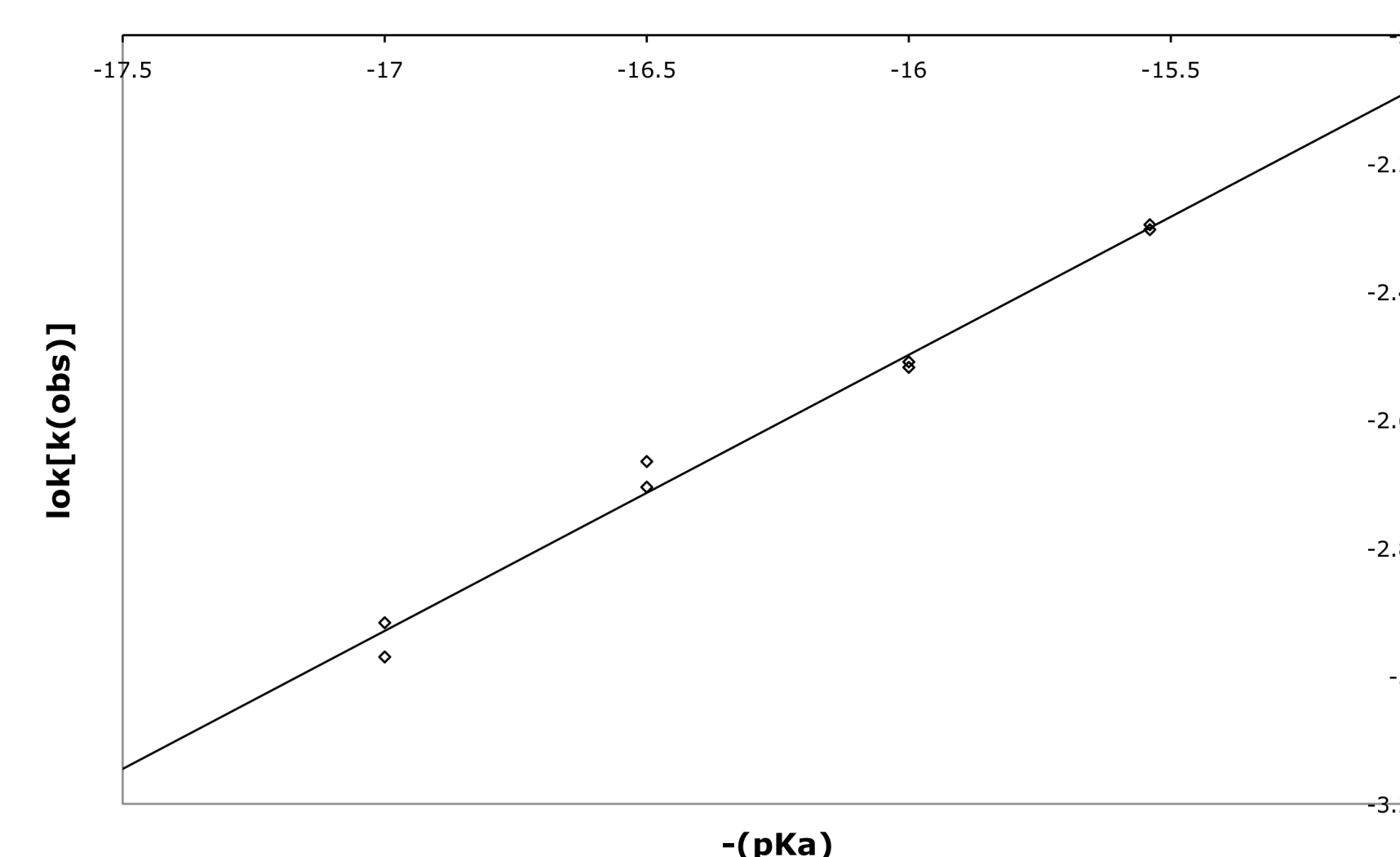
Attempts to Determine Kinetic Order with Respect to Butylamine

- Reactions were to be carried out at 7.5 M, 5.0 M, and 2.5 M butylamine (all pseudo-first order conditions)
- Using dichloromethane (dielectric constant close to that of butylamine) as a cosolvent gave very complex kinetics
- Using methanol as cosolvent resulted in an *increase* in the value of the observed rate constant
 - hydrogen bonding?
 - something else?
- Used a series of alcohols as cosolvents
- Tested results using a Brønsted Law plot: $\log(k_{\text{obs}}) = C - \alpha(pK_a)$

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 for Alcohol Cosolvents



Kinetic data for alcohol solvents

| pK_a of Alcohol | k_{obs} (min^{-1}) | $\log_{10} k_{\text{obs}}$ |
|-------------------|--|----------------------------|
| 15.54 | 4.97×10^{-3} | -2.304 |
| 15.54 | 5.06×10^{-3} | -2.296 |
| 16.5 | 1.97×10^{-3} | -2.706 |
| 16.5 | 2.16×10^{-3} | -2.666 |
| 16 | 3.03×10^{-3} | -2.519 |
| 16 | 3.09×10^{-3} | -2.510 |
| 17 | 1.07×10^{-3} | -2.971 |
| 17 | 1.21×10^{-3} | -2.917 |

Brønsted Law Results

- Specific Acid Catalysis
 - $\alpha = 1$
- General Acid Catalysis
 - $0 < \alpha < 1$
- Our results:
 - Slope = +0.43
 - $R^2 = 0.993$
 - Consistent with General Acid Catalysis*

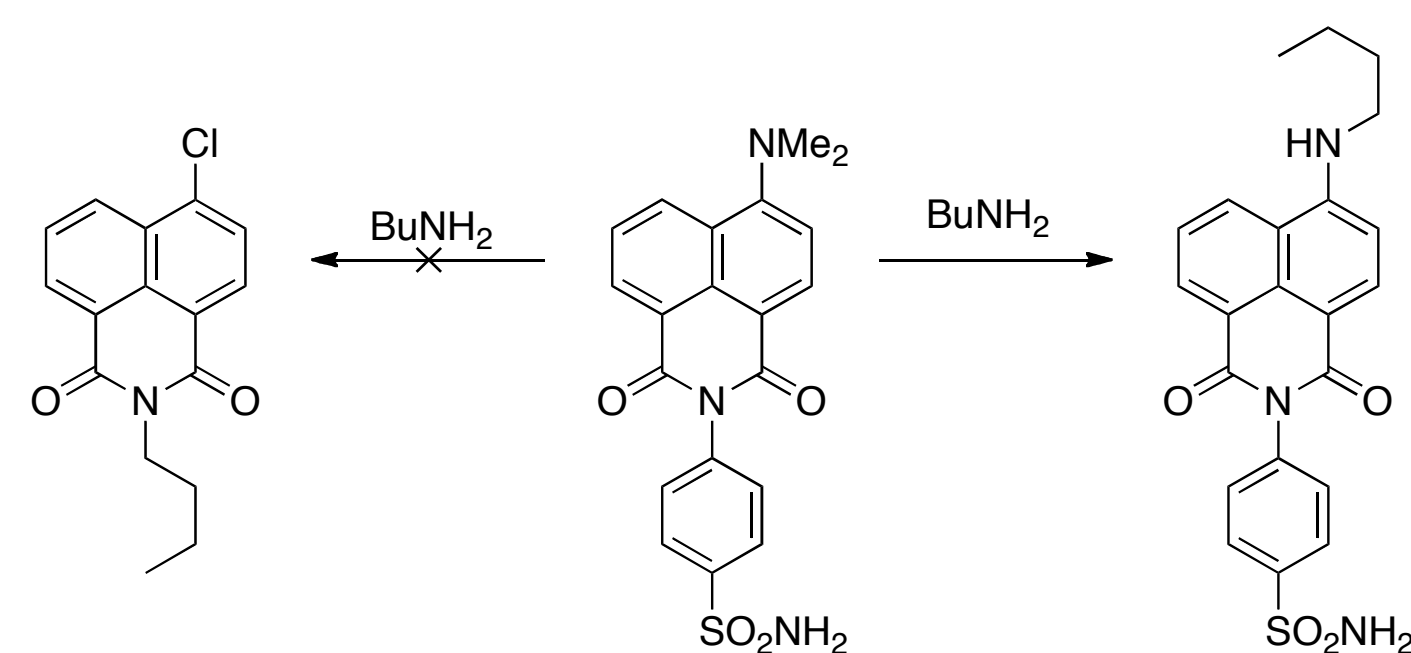
Conclusions

- 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.

Acknowledgments

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 - Leah L. Groess

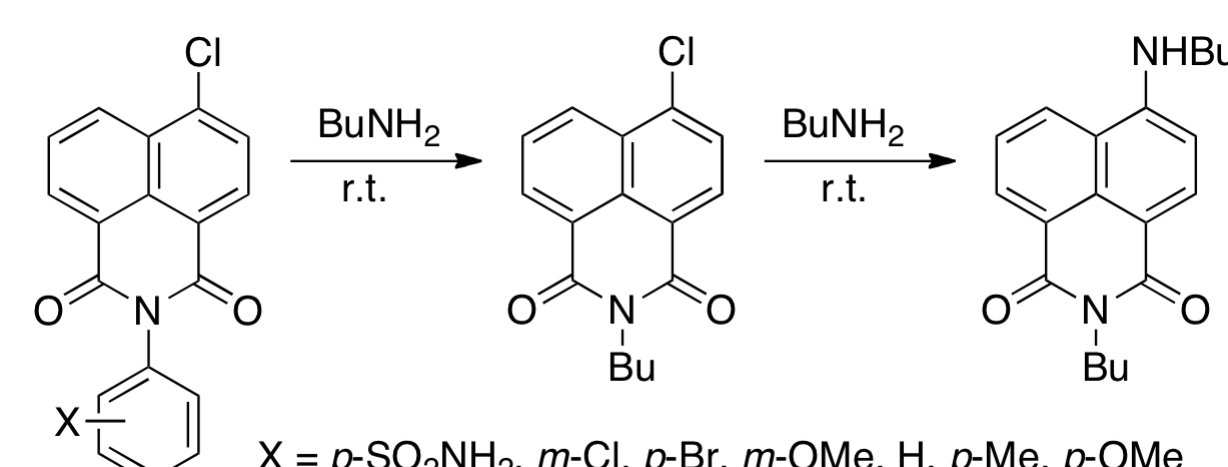
But... Conventional Wisdom is not always right



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.

What is the Scope of this Reaction?



- Displacement of arylamine is faster for electron-withdrawing substituents
- Displacement of halogen becomes competitive with displacement of the arylamine for electron-releasing substituents
- Even with electron-releasing substituents, displacement of the arylamine precedes halogen displacement