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Kinetics and Thermodynamics of Amine and Diamine Signaling by a Trifluoroacetyl Azobenzene Reporter Group

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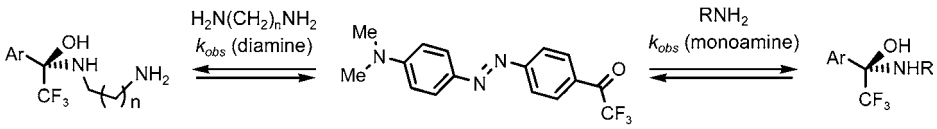
ABSTRACT



k_{obs} (diamine) >> k_{obs} (monoamine)

(Trifluoroacetyl)azobenzene dyes were previously employed as amine reporter groups (chemosensors) in a dendrimer-based monomolecular imprinting system. Kinetic and binding studies with a range of amines and diamines show that the highly selective signaling observed for alkane diamines by these imprinted dendrimers arises from a kinetic effect due to intramolecular general base-catalyzed carbinolamine formation with the dye itself. The relationship between diamine structure and carbinolamine stability and rate of formation is described.

Azo-dye (**1a**) was developed by Mohr and co-workers as a polymer-bound reporter group for the detection of amine analytes.[1] As a result of its distinct color change upon exposure to amines (50 nm blue-shift) and the extensive studies of trifluoroacetophenone−amine interactions by Richie and others,[2] it was proposed that **1a** signals amine binding by forming carbinolamine **2a**. Recently, we integrated **1b** into our monomolecular imprinting method.[3,4] Thus, dendrimer **3** was synthesized, cross-linked via the ring-closing metathesis (RCM) reaction, and cored to give host **4**.[4,5] Despite the small size of the two dendrons linking the butane diamine template in **3** and the correspondingly small number of cross-links formed in the imprinting step, **4** proved to be a remarkably selective chemosensor for alkane diamines. In particular, 1,3-diaminopropane (**5**) and 1,4-diaminobutane (**6**) gave strong color changes.[6]

Key control experiments suggested that the selective signaling of **5** and **6** actually resulted from faster and tighter binding. Herein we report the first combined spectroscopic, kinetic, and thermodynamic study on carbinolamine formation from simple alkyl diamines that quantifies the contribution played by the second amino group as a function of the diamine length. The results rule out aminal formation between diamines and **1b** and further indicate a general base-catalyzed pathway to carbinolamine **2b**, which is stabilized by intramolecular hydrogen bonding. Prior to kinetic studies with **1b**, evidence for formation of **2b**[7] was sought. ^{1}H NMR studies were carried out by adding neat butylamine (**7**) to solutions of **1** in $CDCl_3$, whereupon new peaks between 7.70 and 7.90 ppm appeared alongside peaks for **1b** (Figure 1).

(1) (a) Mohr, G. J.; Demuth, C.; Spichiger-Keller, U. E. *Anal. Chem.* **1998**, *70*, 3868−3873. (b) Mohr, G. J.; Tirelli, N.; Lohse, C.; Spichiger-Keller, U. E. *Adv. Mater.* **1998**, *10*, 1353−1357. (c) Mohr, G. J.; Citterio, D.; Demuth, C.; Fehlmann, M.; Luzi, J.; Lohse, C.; Moradian, A.; Nezel, T.; Rothmaier, M.; Spichiger, U. E. *J. Mater. Chem.* **1999**, *9*, 2259−2264.

(2) Ritchie, C. D. *J. Am. Chem. Soc.* **1984**, *106*, 7187−7194 and references therein.

(3) Mertz, E.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2003**, *125*, 3424−3425.

(4) Zimmerman, S. C.; Wendland, M. S.; Rakow, N. A.; Zharov, I.; Suslick, K. S. *Nature* **2002**, *418*, 399−403.

(5) Wendland, M. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1999**, *121*, 1, 1389−1390. Zimmerman, S. C.; Schultz, L. G.; Zhao, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1962−1966.

(6) Recent reports of hosts with azobenzene reporter groups: Hayashita, T.; Teramae, N.; Kuboyama, T.; Nakamura, S.; Yamamoto, H.; Nakamura, H. *J. Inclusion Phenom.* **1998**, *32*, 251−265. Lee, D. H.; Lee, K. H.; Hong, J.-I. *Org. Lett.* **2001**, *3*, 5−8. Ward, C. J.; Patel, P.; Ashton, P. R.; James, T. D. *Chem. Commun.* **2000**, 229−230.

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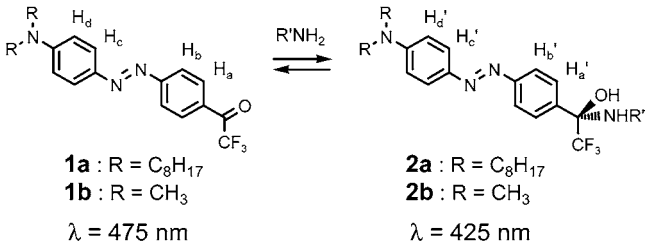
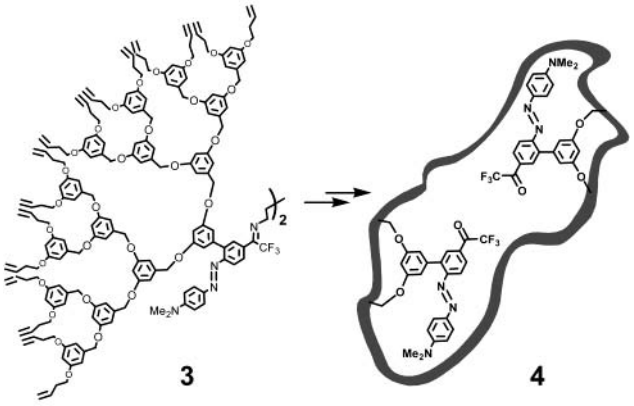
Scheme 1. Amine Signaling Reaction



Scheme 2. Monomolecular Imprinting of Butanediamine



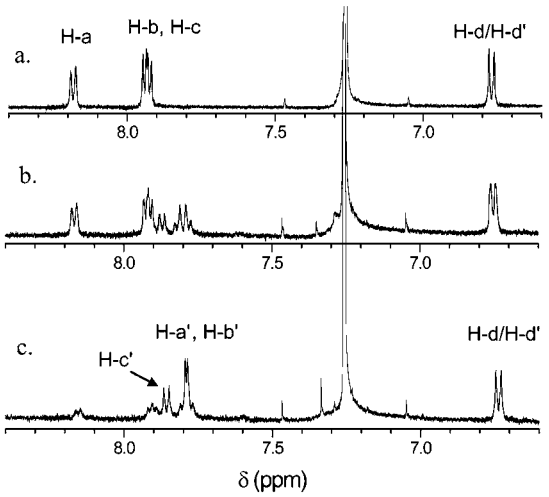


Figure 1. ^{1}H NMR of carbinolamine formed between **1b** and butylamine (**7**) in $CDCl_3$. Partial spectra of **1** equilibrated with (a) [**7**] = 0 M, (b) [**7**] = 0.14 M, and (c) [**7**] = 0.26 M.

The doublet at 7.88 ppm was assigned to proton H-c′ and the multiplet at 7.80 to H-a′ and H-b′. The presence of peaks from both **1b** and **2b** indicates that carbinolamine−dye exchange is slow on the NMR time scale. The upfield shift in protons H-a, H-b, and H-c on **1** is consistent with adduct formation. A slight change in chemical shift and appearance of the H-a′/H-b′ peak was observed with an increase in the concentration of **7**. This observation can be explained by (1) the carbinolamine−dye interconversion rate being faster than but still comparable to the NMR time scale, (2) higher order **2b**·**7** complexes, or (3) a buffer effect where excess **7** removes traces of acid present in the $CDCl_3$.

Additional characterization of the adduct formed from **1** and amines was provided by ^{13}C and ^{19}F NMR. In THF-d_8, the trifluoromethyl group of unbound **1** (1.9 mM) appeared at −71.8 ppm in the ^{19}F NMR (Figure 2). Addition of 2 equiv of butylamine caused appearance of a new peak at −82.3 ppm, consistent with a $-CF_3$ group attached to a carbinolamine carbon atom.[8] The change in shift of the carbonyl carbon in the ^{13}C NMR spectra upon adduct formation was most informative and effectively ruled out aminal formation from both mono- and diamines. Thus, a ca. 0.1 M solution of **2b** in THF showed a quartet ($^2J_{F^{19}C13}$) at 179 ppm, which upon addition of 2 equiv of **7**, ethylenediamine (**8**), or *N*,*N*-dimethyl ethylenediamine (**9**) disappeared and was replaced by a quartet for the carbinolamine carbon at 86 ppm. Each spectrum showed a 1:1 ratio of free amine to adduct and other peaks fully consistent with formation of **2b**. The ^{1}H and ^{19}F NMR spectra of **2b**·**6** were similar to those obtained for **2b**·**7** and consistent with a carbinolamine not an aminal.

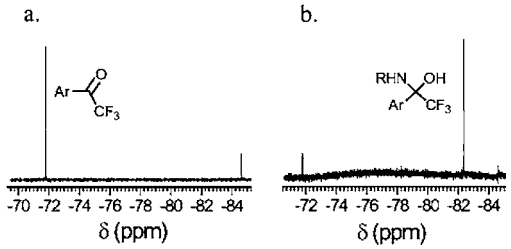


Figure 2. ^{19}F NMR spectra of dye **1b** with butylamine (**7**) in THF-d_8. Partial spectra of **1** upon addition of (a) [**7**] = 0 mM and (b) [**7**] = 3.78 mM.

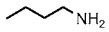
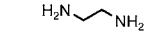
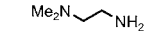
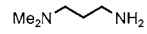
Equilibrium constants (K_{eq}) for the **1b** to **2b** interconversion with amine guests in THF were determined by spectrophotometric titrations. As the amine concentration increased, the main band blue-shifted from λ_{max} = 475 nm (**1b**) to $\lambda_{max} \approx 420-425$ nm (**2b**). Plotting the decrease in absorbance at 475 nm (ΔA_{475}) vs [amine] gave a binding isotherm that fit a 1:1 complexation model, giving the K_{eq} values in Table 1. The reversible nature of the binding was demonstrated by diluting solutions of **2b**, whereupon the peak shifted back to 475 nm.

From the data in Table 1, it appears that a second amino group contributes up to 1.5 kcal/mol to the stability of **2b**. The stabilization is greatest for **8** and slightly reduced for **9**. Little or no effect is seen for **6**, whose K_{eq} is identical to that for **7** once the statistical correction is applied. These

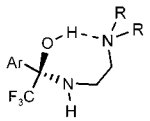
(7) Compound **2b** was prepared using the procedure reported by Mohr (ref 1b) with *N*,*N*-dimethylaniline in the diazonium coupling reaction.

(8) Tamborski, C.; Prabhu, U. D. G.; Eapen, K. C. *J. Fluorine Chem.* **1985**, *28*, 139−150. Saloutin, V. I.; Burgart, Y. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin, O. N. *J. Fluorine Chem.* **2000**, *103*, 17−23.

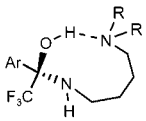
Table 1. Equilibrium Constants (K_{eq}) with Standard Deviations for Carbinolamine Formation between **1b** and Amines

compd no.	guest	K_{eq} (M^{-1})
7		790 ± 210
8		28,000 ± 6,000
9		11,600 ± 3,600
10		8,600 ± 3,300
6		4,200 ± 2,600

data suggest that the stabilization arises from an intramolecular hydrogen bond as in **11**. The shorter diamines are expected to provide more stabilization due to a preference for the 6.5-membered hydrogen bonded ring in **11** vs the 8.5-membered ring in **12**.[9a]



11



12

Thus, for alkane diamines, Aue reported the highest proton affinity for **6** and suggested that its 6.5-membered ring allowed for a linear hydrogen bond. However, the relative stability of such rings in both ground and transition states is a balance of numerous effects.[9b,c]

The rate of conversion of **1b** to **2b** upon addition of 17 different amines and diamines in THF was measured by observing the disappearance of **1b** at λ_{max} = 475 nm over time. As seen in Figure 3, the rates were qualitatively quite different for some of the compounds examined. In general,

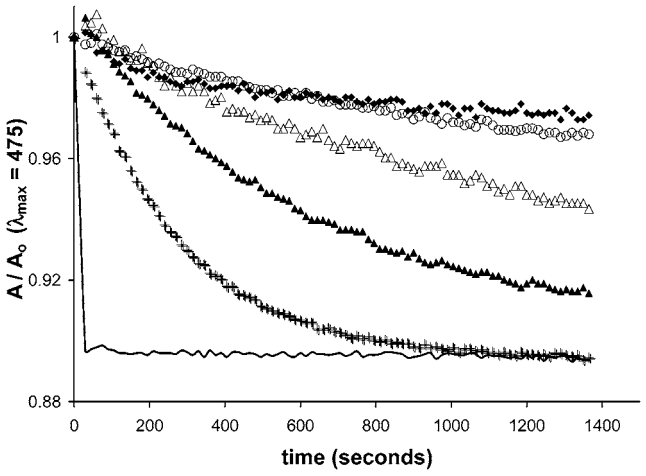
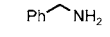
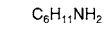
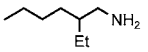
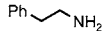
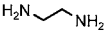
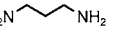
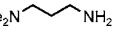
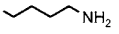
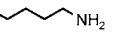
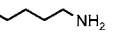
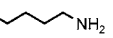
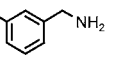
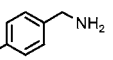
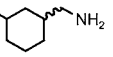
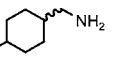
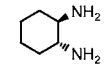


Figure 3. Plots showing decreased absorbance at λ_{max} = 475 nm (**1b**) upon addition of 33 equiv of (◆) benzylamine (**13**), (○) butylamine (**7**), (△) cis/trans 1,4-bis(aminomethyl)cyclohexane (**23**), (▲) 1,8-diaminooctane (**19**), (+) 1,6-diaminohexane (**18**), and (−) 1,4-diaminobutane (**6**) to a 3 μM THF solution of **1b** at 22.5 °C.

Table 2. Pseudo-first Order Rate Constants (k_{obs}) for Formation of **2b** from **1b** and Amines

compd no.	guest	k_{obs} (10^{-3} s^{-1})[a]	k_{obs} (s^{-1})[b]
Monoamines			
7		1.0	1.4
13		0.69	
14		0.69	
15		0.69	
16		1.2	
Diamines			
8		3.6	
5		*c*	23.8
10		*c*	10.4
6		*c*	15.5
17			7.9
18		2.9	
19		1.6	
20		1.0	
21		1.3	
22		1.3	
23		1.2	
24		1.4	

[a] See text and Figure 3 legend for details on conditions and methods used to determine k_{obs} values. [b] Determined by stopped-flow method with addition of 10 mM amine solution to 12.5 μM solution of **1b** in THF. [c] Data were collected, but reaction was too fast for accurate k_{obs} determination.

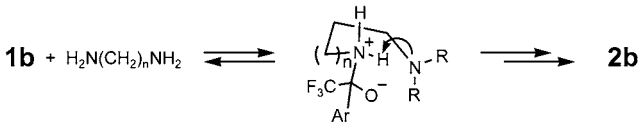
with diamines **5**, **6**, and **10**, formation of **2b** proceeded very rapidly with the reaction being nearly complete within 15−30 s. Reaction of **1b** with other diamines (e.g., **8**, **18**) was slower, requiring 10−20 min to reach completion. Monoamines **13**−**15** reacted the slowest, taking over 30 min to achieve equilibrium.

Under conditions described in the legend to Figure 3, pseudo-first-order rate constants (k_{obs}) could be calculated for 13 of the 17 amines studied. The rate of reaction of **5**, **6**, and **10** were too fast, so these rates, as well as that of 1,5-pentanediamine (**17**), were determined using a stopped-flow spectrophotometric method (Table 2). For the other 13 amines examined using a standard spectrophotometer, plots of $\log(-(A_{475\infty} - A_{475t}))$ versus time (t) were linear over several half-lives, and the slopes afforded the k_{obs} values given in Table 2.[10] The measured equilibrium constants for carbinolamine formation were sufficiently large that correcting for the back reaction (k_r) was not necessary.

In looking at the data in Table 2, it is clear that the rate of carbinolamine formation for the monoamines is nearly independent of the structure. Thus, α- and β-branching and

phenyl substituents have little effect on the amine reactivity. There is considerably more variation in the k_{obs} values for the diamines. Linear, unbranched diamines react with **1** at a faster rate than monoamines and other diamines. Linear diamines with three or four intervening methylene groups achieve the most significant rate enhancement.

To distinguish the alkane diamine rates from one another and quantify their advantage over butylamine (**7**), a stopped-flow spectrophotometric method was used to determine the k_{obs} values for **5**−**7**, **10**, and **17** (Table 2). Because these measurements required much higher concentrations of both **1** and diamine, the k_{obs} values are not directly comparable to those conventionally determined for **7**, **8**, **13**−**16**, and **18**−**24**. Relative to the k_{obs} value for butylamine (**7**), there is a ca. 6- to 17-fold rate enhancement seen in the alkane diamines. The order of reactivity observed in Table 2 closely matches that reported by Page and Jencks in the aminolysis of acetylimidazole by alkane diamines.[11] Although those rate enhancements were somewhat larger (15- to 75-fold), it is likely that the kinetic advantage observed here also originates in a general base-catalyzed amine addition reaction. Thus, high-energy intermediate **25** is either trapped or avoided altogether by intramolecular proton transfer to the second amino group.[12]



25

In summary, we obtained spectroscopic evidence for the formation of carbinolamine **2b** in the reaction of dye **1b** and several mono- and diamines. The rate of formation of **2b** is generally insensitive to the amine structure, but simple alkane diamines with between three and five methylene groups react more rapidly most likely as a result of an intramolecular proton transfer. In our previous work,[3] this kinetic advantage initially disguised itself as an example of highly selective monomolecular imprinting.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM61067) for support and Christopher McGinley and Wilfred A. Van der Donk for assistance with stopped-flow kinetics experiments.

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(9) (a) We use the ring size nomenclature introduced by R. P. Bell (see ref 9c for an overview). (b) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 2699−2701. (c) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183−279.

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