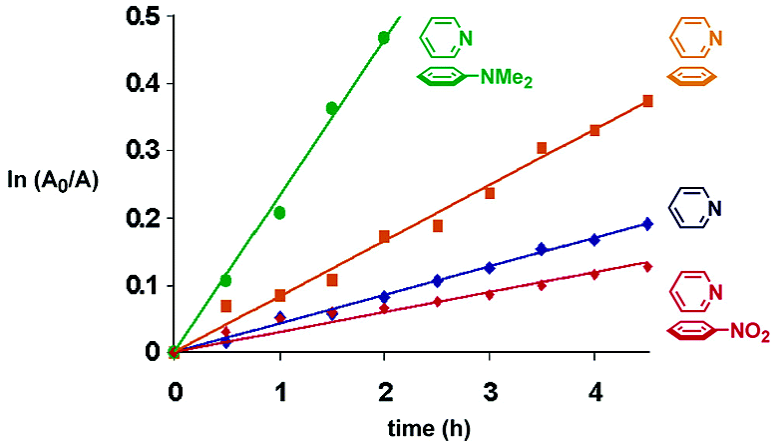
Communication

Quantification of Functional Group Interactions in Transition States

Christopher A. Hunter, Caroline M. R. Low, Jeremy G. Vinter, and Cristiano Zonta

J. Am. Chem. Soc., **2003**, 125 (33), 9936-9937• DOI: 10.1021/ja034767d • Publication Date (Web): 23 July 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 07/23/2003

Quantification of Functional Group Interactions in Transition States

Christopher A. Hunter,*,† Caroline M. R. Low,‡ Jeremy G. Vinter,‡ and Cristiano Zonta*,†

Centre for Chemical Biology, Krebs Institute for Biomolecular Science, Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK, and James Black Foundation, 68 Half Moon Road, London SE24 9JE, UK

Received February 20, 2003; E-mail: c.hunter@shef.ac.uk

The astonishing rate accelerations and the specificity achieved by enzymes is due to a combination of factors that conspire to stabilize the activated complex relative to the reactant.[1] Attempts to mimic these properties in synthetic systems have met with limited success.[2] One reason is the difficulty in quantifying the contributions of individual functional groups to catalysis in complex systems which complicates both the analysis of efficient catalysts and incremental approaches to catalyst design.

We have been using chemical double mutant cycles to quantify functional group interaction energies in simple H-bonded complexes in chloroform solution.[3] We recently found that interactions between the edge of a pyridinium cation and the face of an aromatic ring can be up to 5 kJ mol^{-1} more favorable than the corresponding pyridine−aromatic interaction.[4] This suggests that it might be possible to catalyze the alkylation of pyridine using the π-electron density on the face of a nearby aromatic ring (Figure 1). Indeed, Dougherty reported catalysis of quinoline alkylation by macrocylic aromatic receptors in water.[5] A remarkable feature of the Dougherty results is that the transition state is more strongly bound than either the starting material or the product, so that the system is catalytic. The explanation proposed is that the high polarizability of the aromatic side walls of the receptor could preferentially stabilize the charge redistribution taking place in the transition state relative to the fully developed positive charge in the product. The double mutant cycle approach allows us to test such hypotheses by directly quantifying the contributions of individual functional group interactions as a function of polarizing substituents. Here we demonstrate that the method can be applied to transition-state as well as ground-state interactions.

Preliminary ^{1}H NMR experiments showed that addition of **4** does indeed accelerate the reaction of **1** with methyl iodide in chloroform and that the accelerated reaction is first order with respect to the concentration of the **1**·**4** complex (Figure 1).[6] In 10% DMSO, the rate of reaction was unaffected by the presence of **4** which shows that disruption of the H-bonding interactions responsible for complex formation is sufficient to abolish any rate acceleration. These experiments demonstrate that formation of the **1**·**4** complex leads to an increase in the rate of methylation of the pyridine.

Moreover, the electronic properties of the aromatic ring that is in close proximity to the pyridine in the complex have a dramatic effect on the rate constant (Figure 2). An electron-donating group, X = NMe_2, increases the rate of reaction, and an electron-withdrawing substituent, X = NO_2, reduces the rate.

The association constants for each of the complexes were determined by ^{1}H NMR titration experiments, and these values were used to calculate the fraction of bound **1** (α) in the kinetic experiments. Since the rate constant for methylation of free **1** (k_f) can be measured directly, the rate constants for the reaction of bound

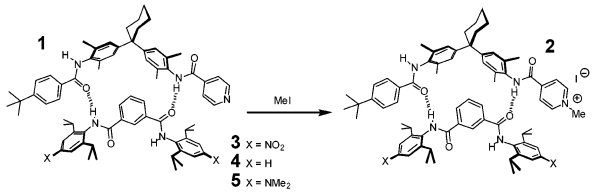


Figure 1. Complex formation changes the rate of methylation of **1**.

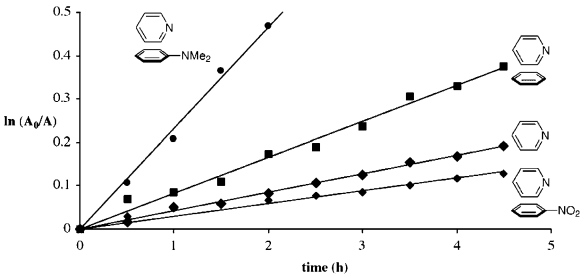


Figure 2. Time courses for the methylation of **1** (10 mM) with MeI (1 M) in the presence of **3**, **4** and **5** (1−20 mM) in deuteriochloroform solution at 30 °C. Under these conditions, **1** is 40−70% bound.

Table 1. Results of the Kinetic and Binding Experiments[7]

complex	X	k (M^{-1} s^{-1})	$\Delta G^{\ddagger}$(kJ mol^{-1})	K (M^{-1})	ΔG (kJ mol^{-1})
1		140 ± 10	81.6 ± 0.2		
1·**3**	NO_2	72 ± 4	83.6 ± 0.2	79 ± 5	−10.6 ± 0.2
1·**4**	H	540 ± 70	78.3 ± 0.3	103 ± 7	−11.3 ± 0.2
1·**5**	NMe_2	1660 ± 70	75.4 ± 0.1	76 ± 5	−10.6 ± 0.1
1·**6**		216 ± 4	80.6 ± 0.1	24 ± 3	−7.7 ± 0.3

1 with methyl iodide (k_b) can easily be determined using eq 1.[6] The results are summarized in Table 1.

$$k_{obs} = \alpha k_b + (1 - \alpha)k_f \quad (1)$$

The rate of reaction in the complex changes by more than an order of magnitude as X is varied. However, there are several interactions that may be involved in changing the energy of the transition state. For example, differences in H-bond strength may contribute to the rate differences. To dissect out the contribution of the aromatic interaction to the change in the rate of reaction, we need to construct the double mutant cycle shown in Figure 3.[7]

The double mutant cycle in Figure 3 contains binding constants for transition states that cannot be determined directly (ΔG_A and ΔG_C). However, the free energy of complexation for a transition state can be derived from the association constant for formation of the ground-state complex and the rates of reaction in the free and bound states as illustrated in Figure 4.[5,8]

Thus, the association constants and rate constants in Table 1 can be used to construct double mutant cycles to evaluate the influence of the aromatic interaction on the rate of methylation of bound **1**.

† University of Sheffield.
‡ James Black Foundation.

10.1021/ja034767d CCC: $25.00

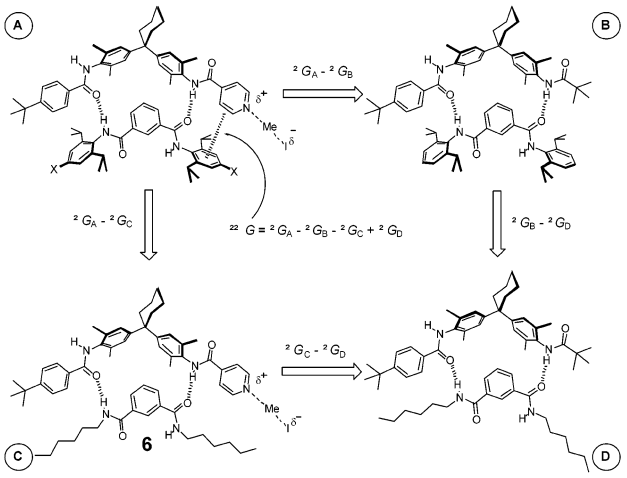


Figure 3. Chemical double mutant cycle used to measure the interaction in the transition state for the *N*-methylation of **1** in complex A.

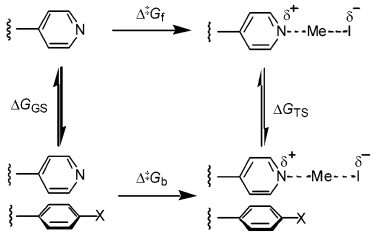


Figure 4. Thermodynamic cycle used to evaluate the binding constant for the transition state complexes ($\Delta G_{TS} = \Delta G_{GS} + \Delta G^{\ddagger}_{b} - \Delta G^{\ddagger}_{f}$).[7]

Table 2. Functional Group Interaction Energies (kJ mol^{-1})[9]

X			
NO_2	+2.1 ± 0.4	+5.2 ± 0.5	+2.3 ± 0.6
H	-2.2 ± 0.4	-4.6 ± 0.6	-2.5 ± 0.6
NMe_2	-3.6 ± 0.5	-8.6 ± 0.6	-7.8 ± 0.8

In addition, thermodynamic double mutant cycles can be used to evaluate the magnitude of the corresponding aromatic interactions in the reactant and product complexes.[4,9] The energies for the nine different double mutant cycles are summarized in Table 2.

There are some clear trends. The X = NMe_2 interactions are the most favorable, followed by X = H, and the X = NO_2 interactions are repulsive. This trend can be explained on the basis of electrostatic interactions between the positive hydrogens on the edge of the pyridine/TS/pyridinium ring with the π-electron density on the face of the aniline π-system. As the aniline π-electron density increases, the magnitude of the aromatic interaction increases. One might therefore expect that as the charge on the pyridinium ring increases on going from reactants to TS to products, the aromatic interaction would increase.[10] However in all cases, the interactions in the transition state are larger than the interactions in either the reactant or product. This could be caused by polarization effects that preferentially stabilize a more polarizable TS.[5] However, polarization does not account for the behavior of the X = NO_2 system, where the aromatic interaction is unfavorable and becomes even more unfavorable in the TS. This result implies that electrostatic effects are important as well. However, the pyridine/pyridinium hydrogens are less positive in the TS than in the product.[11] The electrostatic effects could be due to the strongly dipolar nature of the TS and the change in the position of the leaving group between the TS and product.

This approach represents a general method for the quantification of weak noncovalent interactions in transition states. The results show that the mechanism by which aromatic rings catalyze pyridine alkylation is through electrostatic stabilization of the developing positive charge. The interactions in the transition state are stronger than in the product and depend strongly on substituents. The double mutant cycle approach could also be applied to enzyme catalysis to determine the contribution of individual functional group interactions to transition-state stabilization, if the enzyme and substrate were both mutated.[12]

Acknowledgment. This work was supported by the University of Sheffield and the James Black Foundation (C.Z.).

References

(1) Kraut, J. *Science* **1988**, *242*, 533−540. Schramm, V. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 556−563. Bruice, T. C. *Acc. Chem. Res.* **2002**, *35*, 139−148.
(2) Corey, M. J.; Corey, E. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 11428−11434.
(3) Adams, H.; Carver, F. J.; Hunter, C. A.; Morales, J. C.; Seward, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1542−1544. Carver, F. J.; Hunter, C. A.; Livingstone, D. J.; McCabe, J. M.; Seward, E. M. *Chem. Eur. J.* **2002**, *13*, 2848−2859. Chessari, G.; Hunter, C. A.; Low, C. M. R.; Packer, M. J.; Vinter, J. G.; Zonta, C. *Chem. Eur. J.* **2002**, *13*, 2860−2867.
(4) Hunter, C. A.; Low, C. M. R.; Rotger, C.; Vinter, J. G.; Zonta, C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4873−4876.
(5) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 915−918. McCurdy, A.; Jimenez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314−10321. Ngola, S. M.; Dougherty, D. A. *J. Org. Chem.* **1996**, *61*, 4355−4360.
(6) The reaction rates in $CDCl_3$ were measured by ^{1}H NMR spectroscopy, following the decrease in the intensity of the signals due to compound **1** under pseudo-first-order conditions. The first 15−20% of the reaction was fitted to a first-order model using the equation $\ln[A] = \ln[A_0] - k_{obs}t$.
(7) The difference between the stabilities of A and B ($\Delta G_A - \Delta G_B$), includes the interaction of interest and associated changes in H-bond strength and secondary interactions. These secondary effects are quantified by the difference $\Delta G_C - \Delta G_D$, and thus it is possible to dissect out the thermodynamic contribution of the interaction of the transition state with the aromatic ring from all of the other interactions involved in Complex A.
(8) Fabbrizzi, L.; Gatti, F.; Pallavicini, P.; Zambarbieri, E. *Chem. Eur. J.* **1999**, *5*, 682−690.
(9) Due to the poor solubility of the iodide salts, it was not possible to perform the NMR titrations with the iodide product. However, we have shown that changing the anion has a negligible effect on the interaction energy; therefore, the hexafluorophosphate results should be representative of the behavior of the reaction products. Hunter, C. A.; Low, C. M. R.; Rotger, C.; Vinter, J. G.; Zonta, C. *Chem. Commun.* **2003**, 834−835.
(10) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892−5902.
(11) Smith, P. J.; Soose, D. J.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 7412−7414.
(12) Fong, T. M.; Cascieri, M. A.; Yu, H.; Bansal, A.; Swain, C.; Strader, C. D. *Nature* **1993**, *362*, 350−353.

JA034767D