J|A|C|S
ARTICLES

Mechanism of Electrophilic Chlorination: Experimental Determination of a Geometrical Requirement for Chlorine Transfer by the Endocyclic Restriction Test

Suk Joong Lee, Michael S. Terrazas, Daniel J. Pippel, and Peter Beak*

Contribution from the Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Received January 23, 2003; Revised Manuscript Received April 2, 2003; E-mail: beak@scs.uiuc.edu

Abstract: An endocyclic restriction test for acid-catalyzed transfer of chlorine from a protonated chloroamine to an aromatic ring provides data that are consistent with a transition structure with a large bond angle between the entering and leaving groups around chlorine. These results rule out a dissociative mechanism or a mechanism that has an oblique angle between the entering and leaving groups.

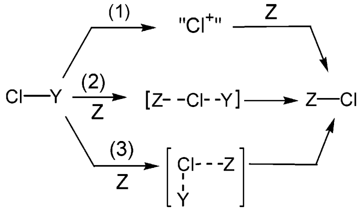
Reactions in which an electrophilic chlorine atom is transferred from a chlorinating agent to a nucleophilic substrate are among the most widely used chemical processes. Applications range from multitonnage scale for industrial applications to the microscale in organic synthesis.

The limiting mechanisms for electrophilic chlorinations are (1) a dissociative reaction, (2) a reaction through a trigonal bipyramidal transition structure with the entering and leaving groups at apical positions, or (3) a reaction through an intermediate or transition structure that has an oblique angle between the entering and leaving groups. These pathways, shown in Scheme 1 for the transfer of chlorine from a chlorine carrier Cl−Y to a nucleophile Z, may be distinguished by determining if there is a geometrical requirement for electrophilic chlorine transfer.

The information available about the stereochemistry of chlorine transfers is inferential. Paul and Haberfield interpreted the acid-catalyzed rearrangement of *N*-chloroanilines to a changing ratio of 2- and 4-substituted anilines and 2,4-disubstituted anilines as evidence of an intermolecular process.[1] Studies of the solid state by Parthasarathy, by Desiraju, and by Pascal favor a large angle for chlorine electron donor interactions.[2] Pascal noted nitrogen−chlorine−carbon bond angles that ranged from 166° to 180°.[2c] Boche and Cioslowski reported calculations that reveal a large bond angle to be preferred between methyl groups in the -ate complex transition structure for the reaction of methyllithium with methyl chloride.[3]

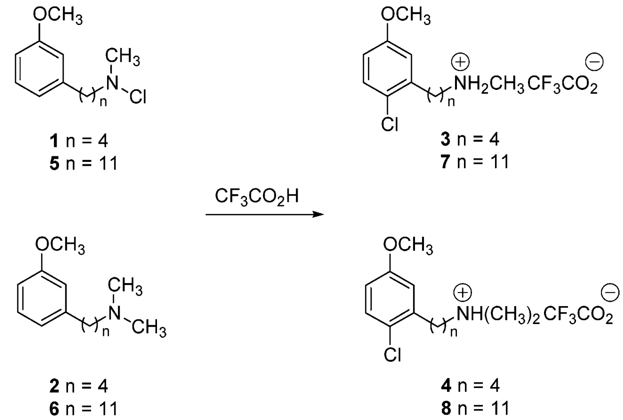
The acid-catalyzed transfer of an electrophilic chlorine to anisole by an *N*-chloroamine to give *p*-chloroaniline is a representative chlorination. Kinetic and regiochemical studies by Smith and co-workers provide a preference for an ionic process over a radical pathway for this reaction.[4]

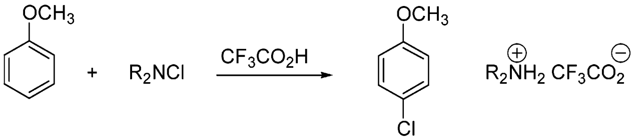
Scheme 1



Y = leaving group Z = nucleophile

Scheme 2





We have applied the endocyclic restriction test to a variant of the chlorination of anisole by connecting the electrophile and the nucleophile as shown in Scheme 2 and using a reporter molecule to evaluate molecularity.[5,6] To compare the effect of

---

(1) Paul, D. F.; Haberfield, P. *J. Org. Chem.* **1976**, *41*, 3170−3175.

(2) (a) Ramasubbu, N.; Parthasarathy, R.; Murray-Rust, P. *J. Am. Chem. Soc.* **1986**, *108*, 4308−4314. (b) Pedireddi, V. R.; Reddy, D. S.; Goud, B. S.; Craig, D. C.; Rae, A. D.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2353−2360. (c) Xu, K.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 105−110.

(3) Boche, G.; Schimeczek, M.; Cioslowski, J.; Piskorz, P. *Eur. J. Org. Chem.* **1998**, 1851−1860.

10.1021/ja0300463 CCC: $25.00 © 2003 American Chemical Society

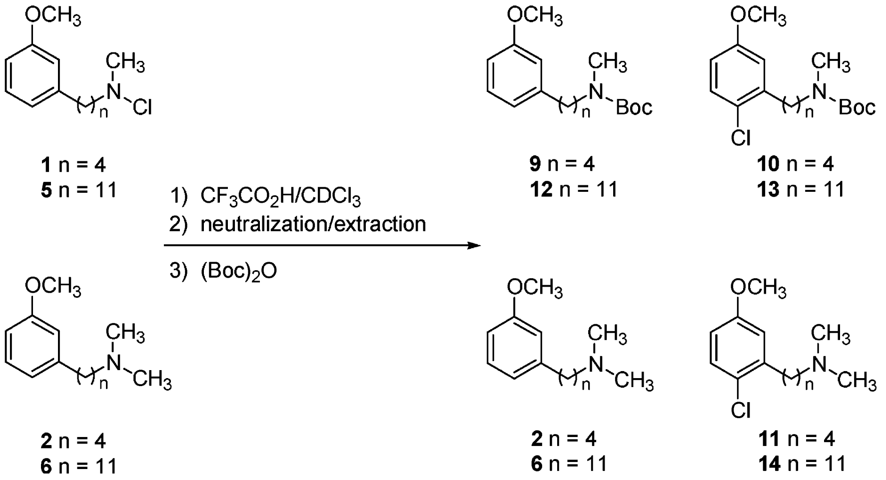


Table 1. Ratios of Chlorinated/Unchlorinated Compounds from the Endocyclic Restriction Test with **1** and **2** Bearing the Short Tether

concn[a] (M)	10/9	11/2
5.0×10^{-2}	1.0	1.1
5.0×10^{-4}	0.9	1.1
1.0×10^{-4}	1.4	0.8
2.0×10^{-5}	1.4	0.7

[a] Concentration is with respect to **1**; an equimolar quantity of **2** is present.

Table 2. Ratios of Chlorinated/Unchlorinated Compounds from the Endocyclic Restriction Test with **5** and **6** Bearing the Long Tether

concn[a] (M)	13/12	14/6
5.0×10^{-2}	1.1	0.8
5.0×10^{-4}	2.0	0.6
1.0×10^{-4}	4.3	0.3
2.0×10^{-5}	16	0.2

[a] Concentration is with respect to **5**; an equimolar quantity of **6** is present.

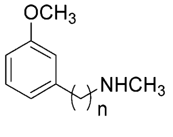
short and long tether connections between the reactive groups on the intra- and/or intermolecularity of chlorine transfer, compounds **1** and **5**, which give **3** and **7**, respectively, were investigated. The tertiary amines **2** and **6**, which have structures very similar to those of **1** and **5**, were used as reporter molecules to track intermolecular chlorine transfer by the formations of **4** and **8**, respectively. We are able to report experimental evidence that is consistent with a transition structure for chlorine transfer from a protonated chloroamine to an aromatic ring, which requires a large bond angle between the entering and leaving groups.

Results

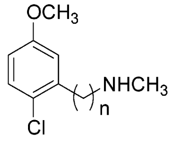
The syntheses of the substrate and reporter molecules were carried out as shown in Scheme 3.

The chlorinations were carried out with equimolar mixtures of **1** with **2** and of **5** with **6** in trifluoroacetic acid/chloroform-*d* at concentrations of the active chlorinating species of 5.0×10^{-2}, 5.0×10^{-4}, 1.0×10^{-4}, and 2.0×10^{-5} M. After reaction, the mixtures were neutralized and treated with $(Boc)_2O$ to convert the secondary amines present to carbamates. Chromatography of the resulting four-component mixtures provided separation of the carbamates from the tertiary amines, leaving two-component mixtures. These two-component mixtures were quantified by ^1H NMR spectroscopy on the basis of comparisons with authentic compounds. Directly determined compound ratios for the reactions of the short tethered substrates, **1** and **2**, and the long tethered substrates, **5** and **6**, are shown in Tables 1 and 2, respectively.

These reactions consistently provided incomplete mass balances. The problem was compounded at the highest dilutions, where reactions were executed with very small amounts of reactants. To determine the extent to which materials were lost during the postreaction sequence, we carried out a control experiment in which known amounts of the initial reaction products were taken through the aqueous workup and derivatization procedure. Mixtures of **15** and **16** corresponding to **9** and **10** along with the tertiary amines **2** and **11**, respectively, and mixtures of **17** and **18** corresponding to **12** and **13** along with the tertiary amines **6** and **14** were dissolved in trifluoroacetic acid to concentrations of 1.0×10^{-4} M and subjected to the standard workup procedure to allow evaluation of the losses.[7] The first experiment provided recoveries of 45 ± 2% of **9** and **10** and 86 ± 6% of **2** and **11**, representative of the reaction of **1** and **2**. The second experiment provided 44 ± 2% of **12** and **13** and 79 ± 2% of **6** and **14**, representative of the reaction **5** and **6**. These control experiments clearly indicate that the secondary amines are grossly underrepresented in the final isolated product mixtures. However, they also show that the workup procedure does not systematically differentiate between chlorinated and unchlorinated products within the carbamate or tertiary amine series. The results of the control experiments



15 n = 4
17 n = 11



16 n = 4
18 n = 11

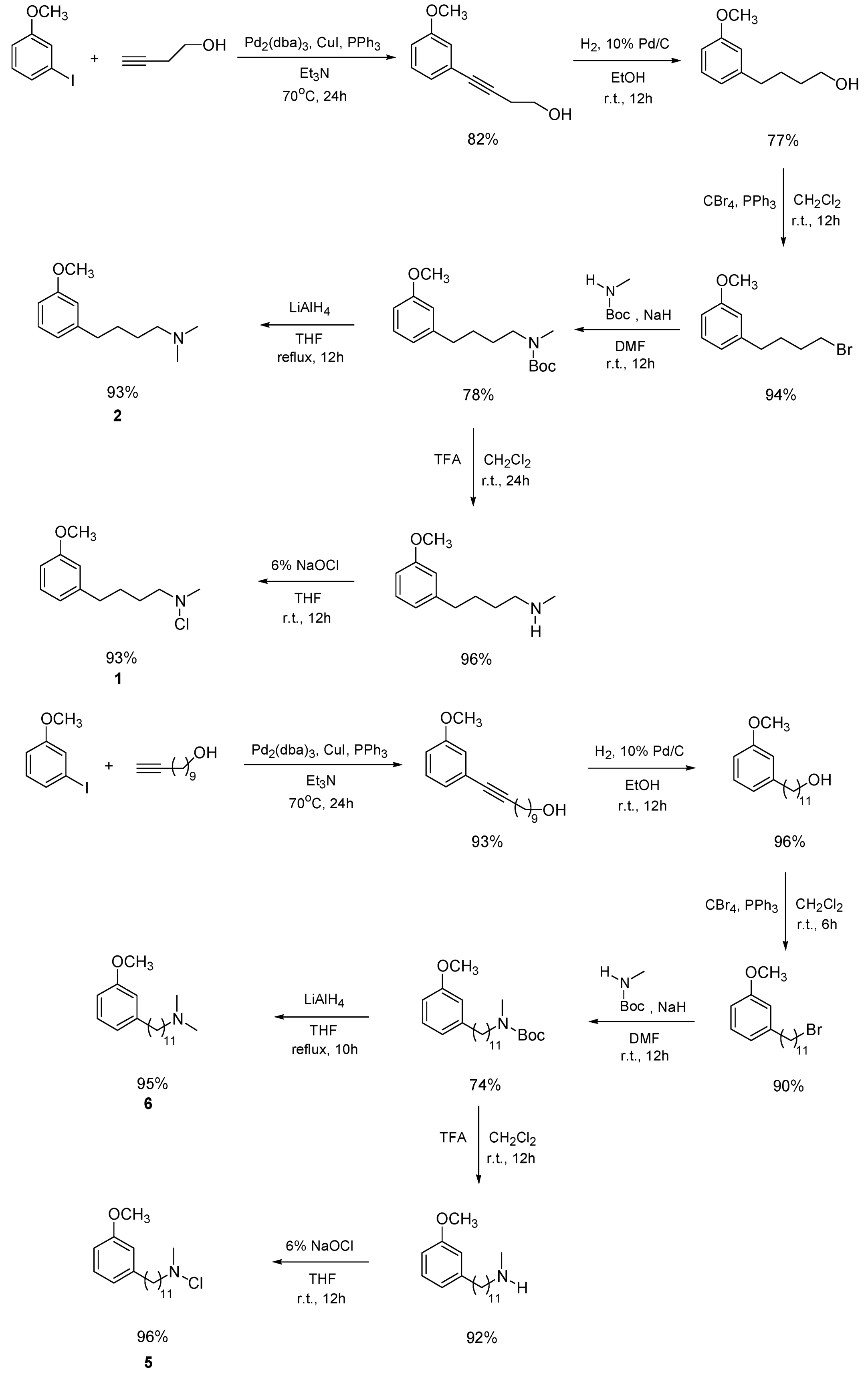
---

(4) (a) Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1533−1537. (b) Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 385−391. (c) Smith, J. R. L.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1529−1536.

(5) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215−222 and references therein.

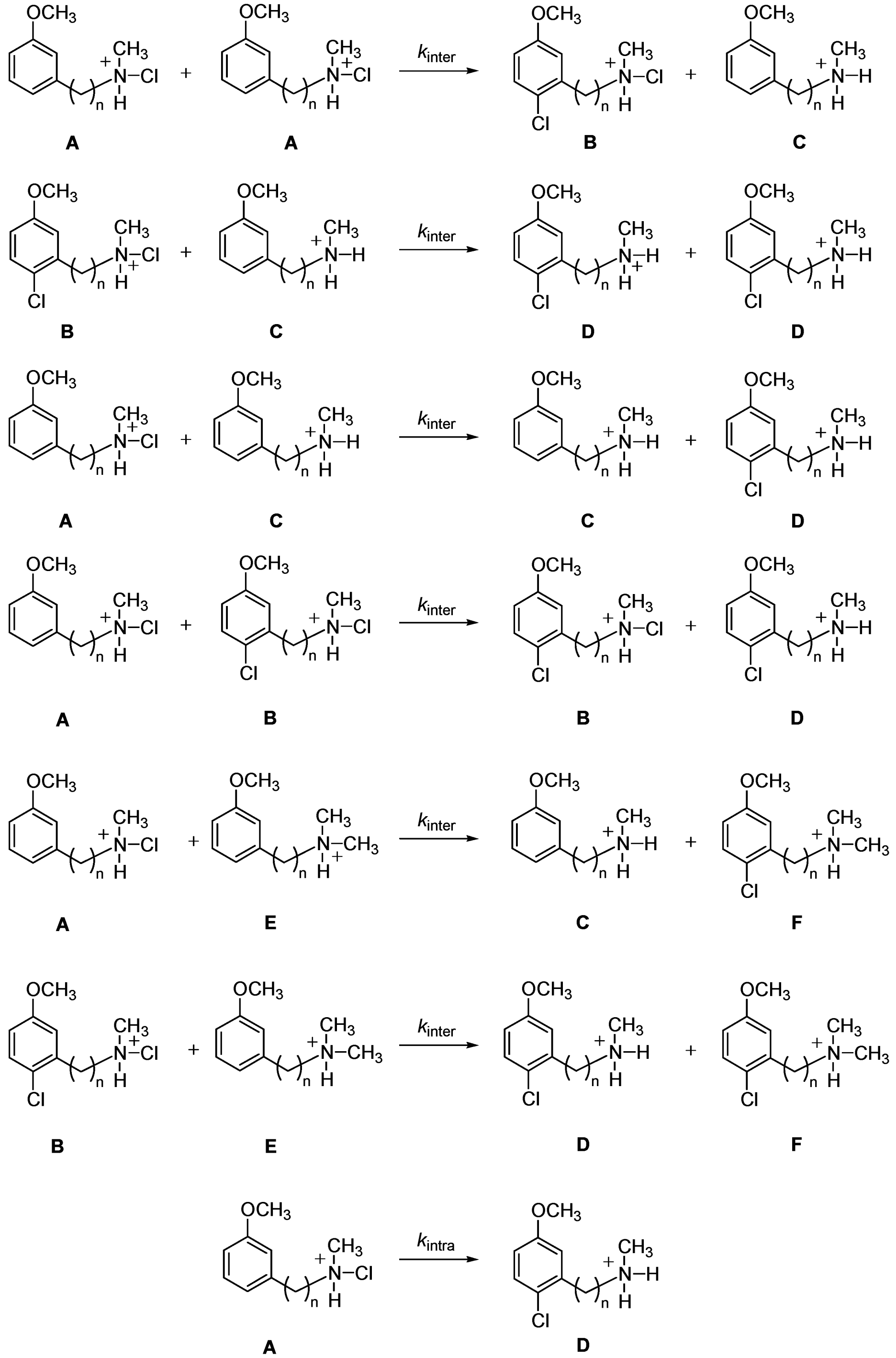
(6) Preliminary studies on related reactions ruled out the use of a double-labeling approach because of isotopic scrambling of the chlorinating reactants. For an earlier study demonstrating the use of a reporter molecule see: Anderson, D. R.; Woods, K. W.; Beak, P. *Org. Lett.* **1999**, *1*, 1415−1417.

Scheme 3



were used to justify normalization of the raw product data as shown in Tables 3 and 4. This normalization to quantitative yields provides values that are useful for comparison to simulated data (vide infra).

Scheme 4



Discussion

Under the endocyclic restriction test, comparison of molecularities of atom transfer reactions for substrates that have different length tethers between the groups donating and accepting the transferred atoms can allow evaluation of a geometrical requirement for the transfer.[5] For example, if a trigonal bipyramidal transition structure with a 180° bond angle between apical entering and leaving groups is required for atom transfer, that arrangement would not be readily achievable in a ring of less than ∼12 members but could be achieved in a ring of greater than ∼15 members.[5] In such a case, only an intermolecular reaction would be observed for a substrate with a short tether, whereas an intramolecular reaction could be observed, at sufficient dilution to overcome the intermolecular reaction, in a substrate with a long tether. If the transition structure for atom transfer did not have a geometrical dependence or was allowed with a small bond angle or if pseudorotations could occur in an intermediate that allows entering and leaving groups to be at an oblique angle, an intramolecular reaction could be observed independent of tether length.[5,8]

---

(7) The workup would convert residual **1** or **5** to the secondary amine, **15** or **17**, which would lead to **9** or **12**, respectively.

(8) Tollefson, M. B.; Li, J. J.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 9052–9061.

Table 3. Actual and Normalized Millimoles of Compounds from the Endocyclic Restriction Test with **1** and **2**

concn[a] (M)	**9**[b]	**10**[b]	**2**[b]	**11**[b]
5.0×10^{-2}	2.52×10^{-2} (3.7×10^{-2})	2.57×10^{-2} (3.8×10^{-2})	3.50×10^{-2} (3.6×10^{-2})	3.74×10^{-2} (3.9×10^{-2})
5.0×10^{-4}	1.77×10^{-2} (3.8×10^{-2})	1.68×10^{-2} (3.7×10^{-2})	3.43×10^{-2} (3.7×10^{-2})	3.60×10^{-2} (3.8×10^{-2})
1.0×10^{-4}	1.03×10^{-2} (2.9×10^{-2})	1.42×10^{-2} (4.1×10^{-2})	3.70×10^{-2} (3.8×10^{-2})	3.07×10^{-2} (3.2×10^{-2})
2.0×10^{-5}	0.34×10^{-2} (0.6×10^{-2})	0.46×10^{-2} (0.8×10^{-2})	0.74×10^{-2} (0.8×10^{-2})	0.52×10^{-2} (0.6×10^{-2})

[a] Concentration is with respect to **1**; an equimolar quantity of **2** is present. [b] Normalized values to quantitative yields are shown in parentheses.

Table 4. Actual and Normalized Millimoles of Compounds from the Endocyclic Restriction Test with **5** and **6**

concn[a] (M)	**12**[b]	**13**[b]	**6**[b]	**14**[b]
5.0×10^{-2}	2.56×10^{-2} (3.5×10^{-2})	2.93×10^{-2} (4.0×10^{-2})	4.05×10^{-2} (4.2×10^{-2})	3.24×10^{-2} (3.3×10^{-2})
5.0×10^{-4}	1.50×10^{-2} (2.5×10^{-2})	2.96×10^{-2} (5.0×10^{-2})	4.54×10^{-2} (4.9×10^{-2})	2.45×10^{-2} (2.6×10^{-2})
1.0×10^{-4}	0.55×10^{-2} (1.3×10^{-2})	2.35×10^{-2} (5.7×10^{-2})	5.31×10^{-2} (5.6×10^{-2})	1.38×10^{-2} (1.4×10^{-2})
2.0×10^{-5}	0.02×10^{-2} (0.1×10^{-2})	0.33×10^{-2} (1.3×10^{-2})	1.00×10^{-2} (1.2×10^{-2})	0.16×10^{-2} (0.2×10^{-2})

[a] Concentration is with respect to **5**; an equimolar quantity of **6** is present. [b] Normalized values to quantitative yields are shown in parentheses.

The reactions of **1** or **5** in the presence of equal amounts of appropriate reporters, **2** or **6**, respectively, allow analysis of the molecularity of the chlorine transfer. If, hypothetically, only intramolecular reactions occurred, **11** and **14** would not be observed after the reaction. In the other limiting case, if only intermolecular chlorine transfer occurred for equal amounts of the substrate and reporter, four compounds, **9**, **10**, **2**, and **11** or **12**, **13**, **6**, and **14**, respectively, would be present in equal amounts after reaction. We report ratios of chlorinated/unchlorinated for the analysis because they are independent of differential losses of secondary and tertiary amines during workup.

For the transfer of chlorine from **1**, the ratios for **10/9** and **11/2** in Table 1 show the substrate and reporter to have essentially the same values at each concentration. Such a result is consistent with the substrate and reporter having the same reactivities. This is the expected result if all chlorine transfers from **1** are intermolecular.[9]

The compound ratios for the chlorine transfers from **5**, shown in Table 2 for **13**/**12** and **14**/**6**, reveal that although the substrate and the reporter exhibit similar reactivity at higher concentrations, the compound ratios become significantly different at lower concentrations. Qualitatively, the increasing ratio for **13/12** versus the decreasing ratio for **14/6** is consistent with an increasing intramolecular chlorine transfer for **5** at a decreasing concentration of **5**.[10]

The possible intermolecular and intramolecular reactions for the chlorination reactions of the substrates and reporters in Scheme 2 are shown in Scheme 4. If the assumption is made that all of the intermolecular reactions would have the same rate constant, reaction progress curves can be constructed utilizing the simulation program KINSIM.[11,12] For the short tether case of **1** in the presence of **2**, k_{intra} was set equal to zero and 1:1 ratios were predicted for **10**:**9** and **11**:**2** at all concentrations as expected. This is in reasonable accord with the experimental results. For the reaction of the long tether of **5** in the presence of **6**, an optimized relative rate constant of $k_{\text{inter}}/k_{\text{intra}} = 2000{:}1$ was found to give a good fit to the data.[10] A specific reaction progress curve for the long-chain reaction at 1.0×10^{-4} is shown in Figure 1. In Table 5 the good agreement between simulated compound ratios and those determined experimentally is shown. This modeling shows that the different profiles which are observed for these reactions are consistent with an increasing intramolecular chlorine transfer for **5**, the substrate with long-chain tether on dilution.[13]

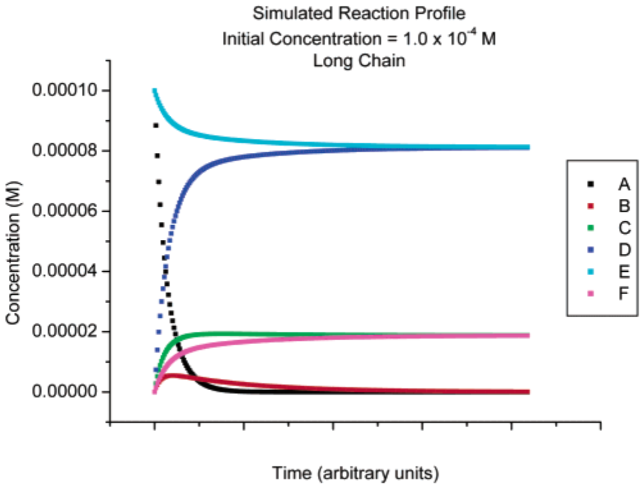


Figure 1. Simulated reaction progress curve for the reaction of **5** with **6** at 1.0×10^{-4} M.

Table 5. Comparison of Normalized Data and Simulated Results in Model for the Endocyclic Restriction Test with **5** and **6**

concn[a] (M)	**12**[b]	**13**[b]	**13/12**
5.0×10^{-2}	3.5×10^{-2} (3.7×10^{-2})	4.0×10^{-2} (3.8×10^{-2})	1.1 (1.0)
5.0×10^{-4}	2.5×10^{-2} (2.8×10^{-2})	5.0×10^{-2} (4.7×10^{-2})	2.0 (1.7)
1.0×10^{-4}	1.3×10^{-2} (1.3×10^{-2})	5.7×10^{-2} (5.7×10^{-2})	4.4 (4.4)
2.0×10^{-5}	0.1×10^{-2} (0.1×10^{-2})	1.3×10^{-2} (1.3×10^{-2})	13 (13)

concn[a] (M)	**6**[b]	**14**[b]	**14/6**
5.0×10^{-2}	4.2×10^{-2} (3.8×10^{-2})	3.3×10^{-2} (3.7×10^{-2})	1.3 (1.0)
5.0×10^{-4}	4.9×10^{-2} (4.7×10^{-2})	2.6×10^{-2} (2.8×10^{-2})	1.9 (1.7)
1.0×10^{-4}	5.6×10^{-2} (5.7×10^{-2})	1.4×10^{-2} (1.3×10^{-2})	4.0 (4.4)
2.0×10^{-5}	1.2×10^{-2} (1.3×10^{-2})	0.2×10^{-2} (0.1×10^{-2})	6.0 (13)

[a] Simulated values in parentheses. [b] Concentration is with respect to **5**; an equimolar quantity of **6** is present.

The present results are consistent with a geometrical requirement for chlorine transfer in the chlorination of an anisole ring

---

[9] The increasing ratios for both substrate and reporter with decreasing concentration may reflect an indirect intermolecular component due to the solvent acting as a chlorine carrier in a reaction that becomes more significant as the rate of the direct intermolecular reaction is reduced by the dilution.

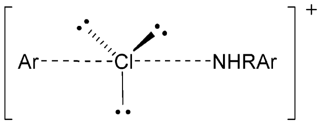
[10] The values for the lowest concentration, although most indicative of the different molecularities for the reactions of **5** and **6**, were determined with very small amounts of material and therefore subject to the greatest quantitative error.

[11] Barshop, B. A.; Wrenn, R. F.; Frieden, C. *Anal. Biochem.* **1983**, *130*, 134−145.

[12] http://www.biochem.wustl.edu/cflab/message.html.

by a protonated chloroamine. These results rule out a dissociative mechanism whether envisioned as the actual formation of "Cl^+" or the more likely pathway of transfer of a chlorine to a solvent or adventious nucleophilic carrier prior to product formation.[9] Also ruled out is an -ate complex that can undergo chlorine transfer at an oblique angle or in pseudorotation in a subsequent slow step.

This demonstration that a large angle is required between the entering and leaving groups in an electrophilic chlorination is consistent with reaction through a trigonal bipyramidal transition structure as a transition state or intermediate as shown for **19**. This geometry is consistent with precedent for reaction at bromine,[14] with calculations,[3] with the VSEPR model,[5] and with previous information.[1,2,15]



19

Acknowledgment. We are grateful to the National Science Foundation (CHE 98-19422) and to the National Institutes of Health (6M-18874) for support of this work.

Supporting Information Available: Experimental data for the synthesis and characterization of **1**, **2**, **5**, **6**, and **9**−**14** and for the results in Tables 1 and 2 are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0300463

---

(13) Simulated values do not provide a perfect match to the experimental data. We note both uncertainties in the exact amounts of products at the highest dilutions and the possibility that an adventitous nucleophile or even trifluoroacetic acid could act as a chlorine carrier.

(14) Allen, D. J.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 3420−3425.

(15) Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, *82*, 615−624.