chunks (0.28 × 0.38 × 0.45 mm) which become opaque rapidly in an open container, presumably due to loss of water of hydration, monoclinic space group $P2_1/c$ [C_{2h}^5-No. 14];[38] a = 10.651 (2) Å, b = 6.521 (2) Å, c = 16.277 (4) Å, β = 95.41 (2)°; Z = 4, $\mu_{MoK\alpha}$ = 0.9340 mm^{-1}; 1973 independent reflections ($+h,+k,\pm l$) measured. The 14 independent non-hydrogen atoms were refined anisotropically, and the 18 hydrogen atoms were treated as described for **3**. The final agreement factors[35] were R = 0.048 and R_w = 0.090 for the 1652 reflections having $I \geq 2\sigma_I$.

(38) Reference 34, p 99.

Acknowledgment. The support of this research by the National Science Foundation is gratefully acknowledged.

Supplementary Material Available: Thermal parameters, additional bond lengths and angles, hydrogen atom parameters, atomic coordinates, and refined hydrogen atom parameters for **1-4** (Tables S1-S14) (15 pages). Ordering information is given on any current masthead page.

Chelates as Intermediates in Nucleophilic Additions to Alkoxy Ketones According to Cram's Rule (Cyclic Model)†

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Abstract: Chelates have been considered intermediates in the often highly stereoselective reactions of α-alkoxy and similarly substituted ketones for over 30 years,[10] but without mechanistic evidence. It is now shown, by stop-flow ("rapid injection") NMR kinetics,[15] that the specific rates of reaction of ketones $C_6H_5COCH(OR)CH_3$ with Me_2Mg, where R = $(i\text{-Pr})_3Si$ ("TIPS"), t-$BuPh_2Si$, t-$BuMe_2Si$, Et_3Si, Me_3Si, and Me, parallel the diastereoselectivity of the reaction; i.e., the fastest reacting compound (R = Me) is the one which gives the highest proportion of the product predicted by Cram's chelate rule. The major product of the slowest reacting compound (R = TIPS) is not in accord with Cram's chelate rule, and this compound reacts at the same specific rate as the parent, $C_6H_5COCH_2CH_3$. This is in accord with earlier work indicating that TIPSO does not chelate. Compounds intermediate in the series react at intermediate rates and give the two diastereomeric products in proportions which can be calculated by assuming two competing reactions (cf. Figure 2): one proceeding via the chelated transition states giving the product predicted by the chelate rule and one not involving chelation which gives the same product composition as the R = TIPS compound. Direct steric effects on carbonyl reactivity due to the remote bulky silyloxy substituents have been excluded by the study of carbon analogues bearing similar bulky groups. Thus, the kinetic effect in the above series appears to be due to steric hindrance to chelation; hence, the parallel of specific rate and stereoselectivity demonstrates that high stereoselectivity is associated with strong chelation, as postulated by Cram and Kopecky in 1959.[10]

Introduction

The amazing progress over the last 15 years in the development of enantioselective syntheses has revolutionized the organic chemist's ability to prepare compounds in enantiopure form. However the progress in understanding the mechanistic basis for many of these stereoselective reactions has been much slower. In general, the stereochemical outcome of a particular reaction has led to the proposal of a transition-state model, and thereafter the observation of similar stereochemical results has been taken as evidence for the reaction proceeding via the proposed transition state. Exceptions to the postulated transition-state model simply lead to the proposal of as many competing transition states as necessary to explain the experimental results. While such reasoning is useful, in so far as it allows the extrapolation of results to different substrates or conditions, it is clearly circular and does not necessarily address the mechanism of the reaction in question.

Chelation is often invoked to account for the stereochemical outcome of the reaction between organometallic reagents and substrates containing more than one functional group capable of coordination.[1-10] In acyclic systems, this bidentate interaction between reagent and substrate is proposed to lead to the very high levels of stereoselection often observed. The classical explanation of this phenomenon was presented in 1959 by Cram and Kopecky,[10] who postulated that the steric outcome of additions of organometallic reagents to chiral α-alkoxy ketones rested on the

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‡ University of North Carolina.
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‖ Glaxo Fellow.

(1) For a review of chelation-controlled reactions of α- and β-alkoxy carbonyl compounds, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1035.
(2) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2 p 125. Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: New York, 1971; Chapter 3.
(3) For some recent examples of stereoselective additions to α-alkoxy aldehydes and ketones rationalized by chelation, see: Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129. Amouroux, R.; Ejjiyar, S.; Chastrette, M. *Tetrahedron Lett.* **1986**, *27*, 1035. Asami, M.; Kimura, R. *Chem. Lett.* **1985**, 1221. Uenishi, I.-i.; Tomozane, H.; Yamato, M. *J. Chem. Soc., Chem. Commun.* **1985**, 717.
(4) For some recent examples of stereoselective additions to β-alkoxy aldehydes and ketones rationalized by chelation, see: Baldwin, S. W.; McIver, J. M. *Tetrahedron Lett.* **1991**, *32*, 1937. Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1990**, *55*, 6246. Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1989**, *30*, 1563. Gennari, C.; Cozzi, P. G. *J. Org. Chem.* **1988**, *53*, 4015. Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.
(5) For some recent examples of stereoselective additions to carbonyl compounds proposed to involve chelation by metal alkoxides, see: Kallmerten, J.; Coutts, S. J. *Tetrahedron Lett.* **1990**, *30*, 4305. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(6) Chelation by nitrogen has also been invoked recently: Decamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. Polt, R.; Peterson, M. A. *Tetrahedron Lett.* **1990**, *31*, 4985. Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909. Prasad, V.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. For a structural investigation of nitrogen chelation, see also: Arnett, E. M.; Nichols, M. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 7059. See also ref 9b.

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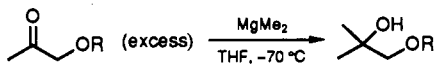
Table I. Pseudo-First-Order Reaction Rates between α-Alkoxy Ketones and $MgMe_2$



ketone	R	rate constant k_2[a]
1	Me	100 ± 7 (n = 2)[b]
2	CH_2Ph	82 ± 13 (n = 3)
3	CMe_3	4 ± 1 (n = 2)
4	$SiMe_3$	3.1 ± 0.1 (n = 2)
5	$Si(iPr)_3$	0.5 ± 0.1 (n = 3)
16	2-hexanone	0.47 ± 0.01 (n = 4)

[a] $\times 10^2$ M^{-1} s^{-1}. [b] n is the number of kinetic experiments averaged to give the result reported along with its standard deviation.

ability of the reagent to coordinate with the alkoxy substituent as well as the carbonyl oxygen. Evidence other than the observed stereochemistry for the role of chelation has been scarce until recently. Stable chelates formed between alkoxy aldehydes and ketones and Lewis acids in CD_2Cl_2 have been observed by NMR under equilibrium conditions.[8b,d,e,9f] In addition, there is a claim of direct evidence for a chelate intermediate on the basis of ^{13}C NMR spectra recorded during the reaction of $MeTiCl_3$ with an α-alkoxy ketone.[9c] Nevertheless, in the absence of appropriate kinetic studies, it is not certain whether such chelates are intermediates (eq 1) of just products of a nonproductive equilibrium (eq 2).[11]

ketone + organometallic reagent ⇌ chelate → product (1)

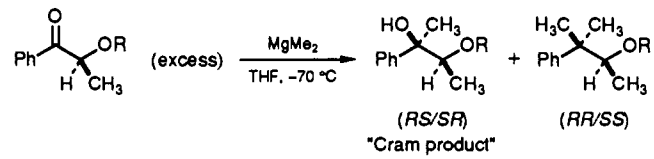
(chelate an intermediate)

chelate ⇌ ketone + organometallic reagent → product (2)

(chelate not an intermediate)

We have previously presented kinetic evidence for a chelated transition state in the reaction of α-alkoxy ketones with dimethylmagnesium,[12] where the large difference in relative rate between (benzyloxy)acetone and [(triisopropylsilyl)oxy]acetone was interpreted as being due to chelation. Reetz[9d] and Kauffmann[13] have also presented kinetic evidence for chelation based on competition experiments between α-alkoxy and deoxy ketones reacting with titanium and chromium organometallics, assuming that rate acceleration in the alkoxy ketones is not due to an inductive effect. Coates[7c] has also looked for rate acceleration due to chelation in Grignard additions to β-alkoxynitrones but failed to observe any. We now report the full results of our studies with alkoxy ketones **1–13** including static complexation, as well as concordant kinetics and stereochemical results which provide conclusive evidence for chelation in the transition state of the reaction between α-alkoxy ketones and dimethylmagnesium.[14]

Table II. Second-Order Rate Constants and Product Composition for Reaction of α-Alkoxy- and α-(Silyloxy)propiophenones and $MgMe_2$



ketone	R	k_2[a]	found[c] (*RS/SR*)/(*RR/SS*)	calcd % (*RS/SR*)[d]
8	Me	~1000	>99/1	(100)
9	$SiMe_3$	100 ± 30 (n = 2)[b]	99/1	99.7 ± 0.1
10	$SiEt_3$	8 ± 1 (n = 5)	96/4	96.7 ± 0.7
11	$Si(tBu)Me_2$	2.5 ± 0.3 (n = 3)	88/12	89 ± 2
12	$Si(tBu)Ph_2$	0.82 ± 0.06 (n = 3)	63/37	68 ± 5
13	$Si(iPr)_3$	0.45 ± 0.04 (n = 3)	42/58	(42)
15	propiophenone	0.51 ± 0.02 (n = 5)		
16	2-hexanone	0.47 ± 0.01 (n = 4)		
17	3,3-dimethylbutyl phenyl ketone	0.47 ± 0.03 (n = 2)		

[a] $\times 10^2$ M^{-1} s^{-1}. [b] n is the number of kinetic experiments averaged to give the result reported along with its standard deviation. [c] Measured at −78 °C in THF. [d] See eq 3 in text.

Results and Discussion

Chelation as a Kinetic Phenomenon. The rate of reaction of ketones **1–13** and **15–17** with dimethylmagnesium in THF-d_8 at −70 °C was examined under pseudo-first-order conditions (excess ketone) by rapid injection NMR (RINMR);[14,15] the results of these experiments appear in Tables I and II. The reaction was easily monitored by observing the disappearance of the magnesium-bound methyl groups resonating from −1.5 to −2 ppm.[16] Integration of the signal for $MgMe_2$ versus internal pentamethylbenzene allowed the calculation of concentration as a function of time. Second-order rate constants (k_2, Table I) were calculated by division of the pseudo-first-order rate constant by the concentration of ketone employed. Ketone **8** was too reactive for its rate to be determined directly, and therefore its rate was estimated from a competition experiment versus **9**. Competition experiments were also carried out for **2/5**, **6/7**, **9/10**, **13/15**, and **15/17**, and the results were consistent with the rates determined directly.

Dimethylmagnesium was chosen as the organometallic reactant because it has been well-characterized as a single, monomeric species in solution in THF (thereby simplifying interpretation of kinetic results), and the mechanism of its addition to benzophenone has been thoroughly investigated.[11,17,18] The initial reaction with

(7) The effect of varying protecting groups on the stereoselectivity of reactions proposed to involve chelation has been previously reported: (a) Cirillo, P. F.; Panek, J. S. *J. Org. Chem.* **1990**, *55*, 6071. (b) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 5058. (c) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464 and 3475. (d) Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021. (e) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484. (f) McCarthy, P. A.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681. (g) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, *27*, 3223. (h) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. See also refs 8 and 9e.

(8) (a) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (b) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (c) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (d) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480. (e) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (f) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (g) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. (h) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265.

(9) (a) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881. (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (c) Reetz, M. T.; Hullmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477. (d) Reetz, M. T.; Maus, S. *Tetrahedron* **1987**, *43*, 101. (e) Reetz, M. T.; Hullmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600. (f) Reetz, M. T.; Kesseler, K.; Schmidtberger, S. *Angew. Chem. Suppl.* **1983**, 1511.

(10) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.

(11) Laemmle, J.; Ashby, E. C.; Neumann, H. M. *J. Am. Chem. Soc.* **1971**, *93*, 5120.

(12) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862.

(13) Kauffmann, T.; Moller, T.; Rennefeld, H.; Welke, S.; Wieschollek, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 348.

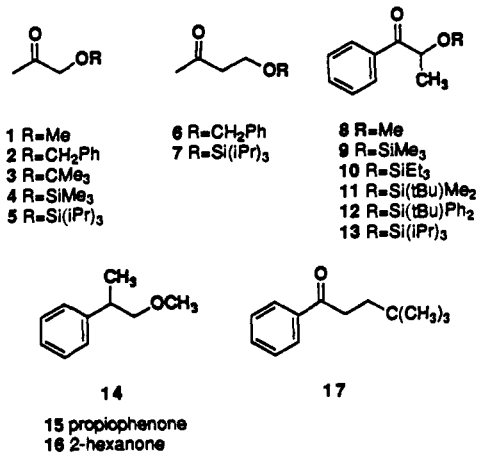
(14) A preliminary account of the kinetic portion of this work has appeared: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130.

(15) McGarrity, J. F.; Olgle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. McGarrity, J. F.; Prodolliet, J. *J. Org. Chem.* **1984**, *49*, 4465. McGarrity, J. F.; Prodolliet, J.; Smyth, T. *Org. Magn. Reson.* **1981**, *17*, 59.

(16) The signals due to ketones and alkoxide products downfield from TMS are consistent with our observations based on Mg–Me resonances. Thus the disappearance of dimethylmagnesium coincides with the dimunition of the resonances due to ketones and the appearance of signals due to the corresponding alkoxides.

(17) (a) Parris, G. E.; Ashby, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 1206. (b) House, H. O.; Oliver, J. E. *J. Org. Chem.* **1968**, *33*, 929. (c) House, H. O.; Latham, R. A.; Whitesides, G. M. *J. Org. Chem.* **1967**, *32*, 2481.

(18) See ref 7 for synthetic evidence for the chelating ability of $MgMe_2$.



benzophenone is first order in both $MgMe_2$ and ketone, and the first-formed product is the methylmagnesium alkoxide. Ashby assumed rapid dimerization of the alkoxide on the basis of the structural work of Coates.[11,19,20] We restricted our study to the reaction of the first methyl group of $MgMe_2$, disregarding the subsequent, much slower, reactions of the methylmagnesium alkoxide. Ketones **2** and **10** were chosen to examine the order of the reaction in $MgMe_2$ in its addition to chelatable ketones; the plots of $-\ln [MgMe_2]$ versus time in Figure 1 confirm that this reaction is also first order in dimethylmagnesium.[21] These plots also serve to illustrate the quality of the data available using the RINMR technique.

Ketones **1–7** were examined to explore the effect of chelation on reactivity in the absence of a stereochemical concern, while ketones **8–13** allow the stereochemical outcome to be compared to the reactivity. The alkoxy protecting groups were chosen in order to vary the chelating ability of the alkoxy oxygen in a systematic fashion.[7e,g] The major assumption of this approach is that the protecting groups have no direct effect, steric or electronic, upon the reactivity of the carbonyl—they only vary the chelating ability of the alkoxy oxygen. Justification for this assumption is found in the identical rate of reaction of the five ketones where there is either no α-oxygen (**15–17**) or where there is a (triisopropylsilyl)oxy group (**5**, **13**). Though the equivalent rates could be due to a coincidental cancelation of steric deceleration and electronic acceleration for **5** and **13**,[22] the finding that ketone **17** reacts at the same rate as **15** and **16** argues against any substantial steric effect of γ-substitution on the reactivity of the carbonyl. If the results in Table I are interpreted on the basis of this assumption, the diminution in rate from compound **1** to **5** is seen to parallel the increasing bulk of the protecting group and its resulting ability to prevent chelation.[23] Rate enhancement of a ketone that can chelate versus one that cannot is a requirement of Cram's chelate rule:[10] In order for chelation to control the stereochemistry, it must also lower the activation energy or the normal nonchelated, less stereoselective addition pathway will be followed. (See also Figure 2 and discussion below.) Obviously the rate enhancement is independent of any stereochemical issue, and this fact has been exploited in manipulating regioselectivity

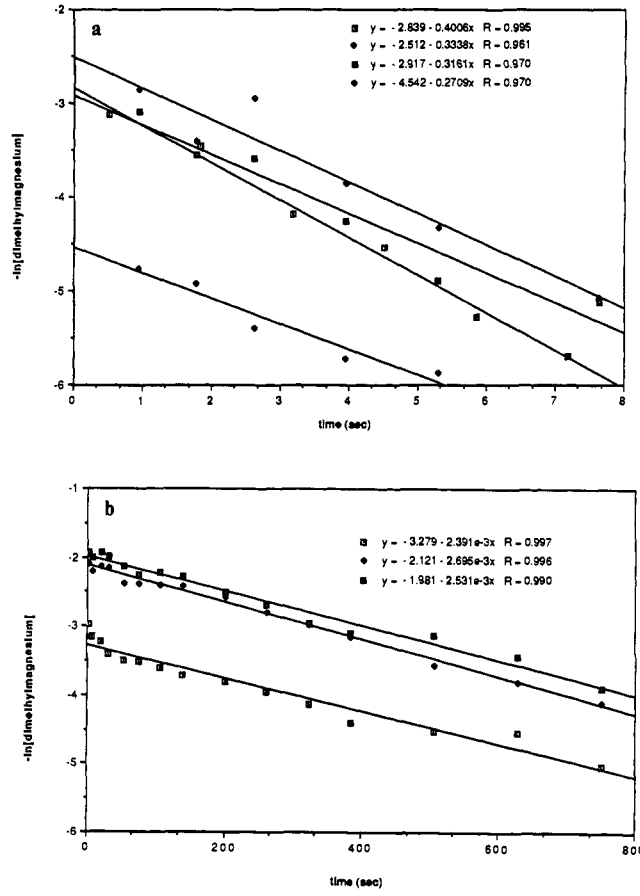


Figure 1. Pseudo-first-order reaction of ketones **2** (a) and **10** (b) with dimethylmagnesium (four and three experiments were performed, respectively).

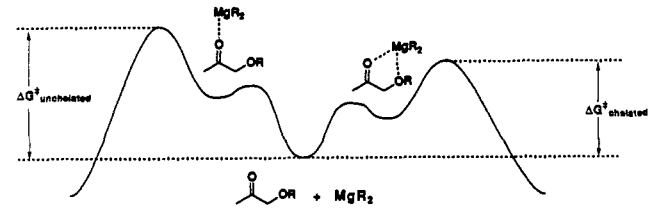


Figure 2. Competing chelated and nonchelated transition states.

via chelation[24,25] and reactivity via prevention of chelation.[26]

β-Alkoxy ketones **6** and **7** did not differ markedly in their reactivity toward $MgMe_2$ (only by a factor of 2.5 at 203 K),[12] although complexation studies demonstrated the ability of **6** to chelate with $MgBr_2$ (Scheme I). This result is consistent with stereochemical studies which have generally pointed to less stereochemical control in the reactions of chiral β-alkoxy ketones as compared to α-alkoxy ketones.[1,27] Perhaps, though the six-membered chelate is quite stable, its rate of formation is slower than addition via the nonchelated reaction path, and thus chelation does not have an opportunity to affect the stereoselectivity. An alternative, or additional, explanation is that six-membered-chelate formation does not lead to a more reactive assembly of $MgMe_2$ and ketone, and therefore the reaction proceeds primarily through the less stereoselective, nonchelated addition pathway. These issues are under investigation.

Correlation of Reactivity and Stereoselectivity. The stereoselectivity of addition of $MgMe_2$ to ketones **8–13** (Table II) was

(19) Coates, G. E.; Heslop, J. A.; Redwood, M. E.; Ridley, D. *J. Chem. Soc. A* **1968**, 1118.

(20) We have also presented evidence for the conversion of initially monomeric methylmagnesium alkoxides into dimers (ref 12).

(21) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1981; Chapter 2.

(22) Large inductive effects apparently play a role in the rate accelerations of aldol reactions involving α-alkoxy ketones: Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 5360. However, Swenton (Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 2953) has recently shown that the σ value of a t-Bu(Me)$_2$SiO substituent is essentially identical to that of a methoxy substituent, supporting our assumption that the difference in rate in going from **1** to **5** (Table I) is due to chelation—not a change in the inductive effect of the α-substituent.

(23) V_{eff}: Me, 0.52; CH_2Ph, 0.70; t-Bu, 1.24; Me_3Si, 1.40. A plot of V_{eff} vs ln $[k_2]$ for these ketones has a correlation coefficient of 0.972. V_{eff} is defined in the following: Charton M. *Top. Curr. Chem.* **1983**, *114*, 68–74.

(24) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417.

(25) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1990**, *55*, 4265.

(26) Wender, P. A.; Cooper, C. B. *Tetrahedron Lett.* **1987**, *28*, 6125.

(27) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019.

determined at −78 °C in THF by adding excess $MgMe_2$ to the ketone, quenching after 1–10 min, and measuring the product ratio by ^1H NMR. The configuration of the products was established by correlation with the known (*RR/SS* and *RS/SR*)-2-phenyl-2,3-butanediols.[28] It is immediately obvious that the addition of $MgMe_2$ to the most reactive α-methoxy ketone **8** is much more stereoselective than addition to the least reactive (triisopropylsilyl)oxy ketone **13** and that the stereoselectivity of the intermediate members of the series decreases with decreasing reactivity. These results are readily interpretable on the basis of competition between two transition states as outlined in Figure 2. Ketones partition between chelated (highly stereoselective) and unchelated (poorly stereoselective) transition states, depending on the nature of the protecting group on the α-oxygen. Initial formation of chelates and complexes higher in energy than the reactants is assumed on the basis of prior experimental studies[29] and theoretical calculations which support the accepted role of the metal in polarizing the carbonyl and stabilizing the negative charge forming on oxygen in the transition state.[30] The analysis of proton spectra acquired during reactions where the ketone and $MgMe_2$ are at similar concentrations is consistent with this assumption, as no appreciable concentrations of chelates or complexes in THF (corresponding to a preequilibrium) are detected (this is also consistent with the complexation studies discussed below). In composing Figure 2, we have also assumed that the transfer of the methyl group is the rate-determining step in each case,[31] although our conclusions do not depend upon this assumption.

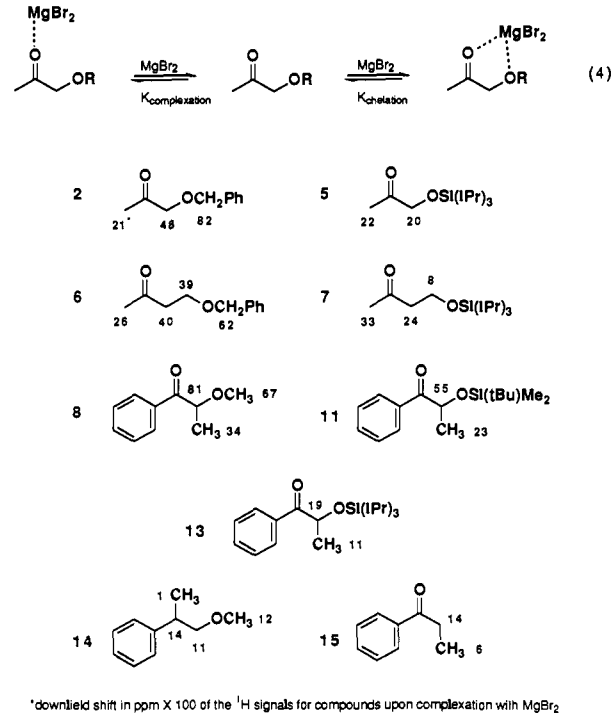
A quantitative relationship between reactivity and stereoselectivity may be derived on the basis of the following hypothesis: Let us assume that the specific rate for traversing the unchelated transition state (Figure 2) is that for compound **13** (very similar to simple alkyl ketones **15**–**17**), $k_{unchelated} = 0.45 \times 10^{-2}\ M^{-1}\ s^{-1}$, and is constant for all members of the series. Further, let us assume that the rate for traversing the chelated transition state is the difference between the observed rate, k_2, and $k_{unchelated}$; $k_{chelated} = k_2 - k_{unchelated}$. Moreover, let us assume that the stereoselectivity of the unchelated pathway gives a 42/58 ratio of (*RS/SR*) (chelate product) to (*RR/SS*), the actual ratio for ketone **13**, and that reaction via the chelated pathway gives 100% (*RS/SR*), the limiting ratio for ketone **8**. Since there is no palpable preequilibrium, the relative amounts of each product depend only upon the activation energy of each competing transition state,[32] and the stereoselectivty of the reactions may be calculated as

$$\%(RS/SR) = 100(k_{chelated} + 0.42k_{unchelated})/k_2 \qquad (3)$$

The product composition calculated from eq 3 is shown in the last column of Table II, and it is apparent that the calculated compositions agree with the experimental within the error limits of the rate determinations. These results correlating reactivity and stereoselectivity in conjunction with the results of complexation studies with these same ketones provide overwhelming mechanistic evidence for the role of chelation in additions to α-alkoxy ketones.

Static Complexation Studies. At the beginning of our mechanistic studies on α-alkoxy ketones, complexation experiments between ketones **2**, **5**, **6**, and **7** and $MgBr_2$ in THF-d_8 were carried out. In the presence of excess $MgBr_2$ there is no change in the proton NMR spectra of these ketones, suggesting that the equilibrium constants in eq 4 (Scheme I) are much less than 1 in this solvent. With this not unexpected result[33] in hand, kinetic

Scheme I. Complexation Studies with $MgBr_2$ in CD_2Cl_2



[a]downfield shift in ppm X 100 of the ^1H signals for compounds upon complexation with $MgBr_2$

experiments more pertinent (see eqs 1 and 2) to the mechanistic issues were undertaken. Meanwhile, several reports of complexation studies[8b,d,e,9c,f,34] appeared, and it seemed of interest to reexamine representative ketones from the kinetic studies in CD_2Cl_2 for the sake of comparison and to determine the extent of complexation/chelation observable in a poorly coordinating solvent. The outcomes of complexation experiments with magnesium bromide etherate are presented in Scheme I. All ketones studied as well as ether **14** experience a change in their proton NMR chemical shifts upon complexation in CD_2Cl_2.[35] Ketones **2**, **6**, and **8** experience substantial downfield shifts of protons adjacent to both the carbonyl and ether oxygen, consistent with bidentate complexation (chelation), while for ketones **5**, **7**, and **13** the effect on α- and β-protons on the side of the oxygen substituent is considerably smaller, consistent with monodentate complexation of the carbonyl oxygen. The magnitude of these shifts due to chelation and complexation is consistent with the observations of Keck.[8d,e] Ketone **11** experiences shifts intermediate between **8** and **13** suggestive of an equilibrium between chelated and complexed forms; this is consistent with its reactivity toward $MgMe_2$ in THF (vide supra). Ether **14** and ketone **15** are included for the sake of comparison, and it is noteworthy that ketone **13** undergoes only slightly greater changes in chemical shifts upon complexation than **15**. It is clear from these experiments that the protecting group on the ether oxygen can control the extent of chelation[8] with methyl and benzyl substituents allowing chelation, while TIPS prevents it.[7e,g] Intermediate degrees of chelation are also possible (cf. compound **11**, which evidently chelates appreciably more than **13**; see also Table II).

Effect of Silicon Protecting Groups. The effect of silicon protecting groups upon the coordinating ability of an oxygen has been observed in many studies[7-9,26] and has been interpreted as primarily of steric origin by many investigators.[7,9e] However, it has also been suggested[8] that the lower basicity of silicon-protected oxygens makes a major contribution to their diminished chelating

(28) Katzenellenbogen, J. A.; Bowlus, S. B. *J. Org. Chem.* **1973**, *38*, 627.
(29) Smith, S. G. *Tetrahedron Lett.* **1963**, *4*, 409. For a detailed discussion of the mechanism of Grignard additions to ketones, see: Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545.
(30) Bachrach, S. M.; Steitwieser, A. *J. Am. Chem. Soc.* **1986**, *108*, 3946.
(31) Experiments are underway to elucidate the rate-determining step for a series of α-alkoxy ketones: Chen, X. Unpublished observations.
(32) See ref 21, chapter 3, p 55.
(33) THF is very effective at solvating magnesium compounds, and as it is present as solvent, the alkoxy ketones do not effectively compete for coordination to magnesium. For example, see the discussion of aggregation properties of magnesium species in THF versus diethyl ether by Ashby, ref 29.
(34) For a recent complexation study employing lanthanide shift reagents and α-alkoxy aldehydes, see: Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 4647.
(35) It is worthwhile noting that in the absence of these compounds $MgBr_2 \cdot Et_2O$ is essentially insoluble in CD_2Cl_2. In some cases ^{13}C NMR spectra were also recorded, but as noted previously[8d,e] these spectra proved less useful than the proton spectra, apparently due to the confounding steric and electronic effects of chelation on the ^{13}C chemical shifts.

ability, and synthetic results involving prevention of chelation with silicon protecting groups have been cited as supportive of theoretical and structural investigations concerned with the lower basicity of silyl ethers.[36] The major flaw in this interpretation of the synthetic and complexation studies with silyl ethers is that the silyl ethers chosen are always more highly substituted than the alkyl ethers with which they are compared. In fact, when the physical measurements of relative basicity cited as supporting an electronic interpretation of the effect of silicon protecting groups are consulted, one finds that Me_3SiOR(R = primary alkyl) is a *stronger* base than ROR in terms of both gas-phase proton affinity[37] and hydrogen bonding to phenol in solution.[38] Therefore, if extrapolation from these protic acids to a metal is appropriate, the experimental determinations of relative basicities actually predict that, in the absence of steric effects, the silicon protecting groups most often studied (all trialkyl) would chelate *more* effectively than the primary alkyl ethers to which they are compared! Our experimental results, both complexation and kinetic, showing a steady decrease in chelating ability upon an increase in size of the protecting group on oxygen, regardless of whether an alkyl or silyl ether is involved [perhaps best illustrated by the ability of $OSiMe_3$ to chelate[9e] as effectively as O*t*Bu (Table I)], are consistent with a simple steric interpretation.

Conclusions

Formation of a chelated intermediate in additions of organometallic reagents to chiral α-alkoxy ketones on the one hand lowers the transition-state energy and thus increases the reaction rate[39] and, on the other hand, restricts bond rotation and increases stereoselectivity. The most reactive substrates are therefore the most stereoselective. A provocative analogy may be drawn between this simultaneous effect of chelation on reactivity and stereoselectivity and the relationship between an enzyme and its substrate where these two features also often go hand in hand.[41] This correlation between reactivity and stereoselectivity demonstrates conclusively the mechanistic importance of chelation long inferred from stereochemical results alone.

Experimental Section

General Methods. Proton and carbon-13 NMR spectra were recorded on a Bruker AC200 spectrometer at 200 and 50.2 MHz, respectively; chemical shifts are referenced to Me_4Si. Chromatographic separations were carried out on a Harrison Research Model 7924 Chromatotron using plates coated with EM Science 7749 silica gel $60PF_{254}$.

Compounds **1**, **15**, and **16**, monoperoxyphthalic acid magnesium salt hexahydrate (MMPP·$6H_2O$), 3,3-dimethyl-1-butanol, acetol, iodobenzene diacetate, and 2-phenyl-1-propanol were purchased from Aldrich. THF-d_8 was obtained from Cambridge Isotope Laboratories and purified by distillation from Na/K alloy before use. Standard dimethylmagnesium solution in THF was prepared from dimethylmercury and magnesium according to a literature procedure.[42] Ketones **2**,[43] **3**,[44] **4**,[45] **6**,[46] and **9**[47] were synthesized using literature procedures.

2-Hydroxy-1-phenyl-1-propanone.[48] To a solution of 15.8 mL (124 mmol) of TMSCl and 31.4 g of Et_3N in 100 mL of dry DMF was added 13.9 g (104 mmol) of propiophenone. The mixture was stirred and refluxed under N_2 for 48 h, cooled to room temperature, and diluted with 80 mL of hexane. This solution was washed with saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated. The product, 1-phenyl-1-[(trimethylsilyl)oxy]-1-propene,[49] (16.8 g, 78% yield) was purified by distillation (69 °C/4 mmHg): ^1H NMR ($CDCl_3$) δ 0.14 (s, 9 H), 1.74 (d, J = 7 Hz, 3 H), 5.33 (q, J = 7 Hz, 1 H), 7.2–7.5 (m, 5 H), in agreement with reported values.[49] This compound (2.01 g, 9.7 mmol) was then oxidized by MMPP·$6H_2O$ (5.78 g, 9.7 mmol) in 60 mL of $CHCl_3/H_2O$ (1/1) with 0.2 g of $(n\text{Bu})_4NCl$ at 50 °C for 13 h. The organic and aqueous phases were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to yield 1.21 g (83% yield) of product after purification by chromatography: ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 7 Hz, 3 H), 3.9 (br, 1 H), 5.17 (q, J = 7 Hz, 1 H), 7.55 (m, 3 H), 7.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.2 (CH_3), 69.4 (CH), 128.7 (CH), 129.8 (CH), 130.1 (CH), 134.0 (C), 202.4 (C), in agreement with previous reports (^1H,[48a] ^{13}C[48b]).

2-Hydroxy-1-phenyl-1-propanone was also prepared by the method described by Gupta.[50] A solution of 1.3 g (10 mmol) of propiophenone, 3.5 g (11 mmol) of $C_6H_5I(OAc)_2$, and 3.8 g of NaOH in 15 mL of MeOH was stirred for 4 h at 0–25 °C. After neutralization by hydrochloric acid, the solution was extracted with ether, washed with brine, and dried over $MgSO_4$. Purification by chromatography gave 0.83 g (57% yield) of pure product.

Ketones 5, 7, and 13 were prepared by silylation of the corresponding alcohols with $(i\text{-Pr})_3SiCl$ under standard conditions.[51] Chromatography (5% EtOAc/hexane) gave pure samples. Ketone **5**: ^1H NMR ($CDCl_3$) δ 1.09 (m, 21 H), 2.23 (s, 3 H), 4.21 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.8, 17.8, 26.0, 69.9, 209.7. Ketone **7** (30% yield): ^1H NMR ($CDCl_3$) δ 1.05 (m, 21 H), 2.20 (s, 3 H), 2.64 (t, J = 6.3 Hz, 2 H), 3.98 (t, J = 6.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 17.7, 30.8, 46.7, 59.3, 208.1. Ketone **13** (86% yield): ^1H NMR ($CDCl_3$) δ 1.05 (m, 21 H), 1.55 (d, J = 7 Hz, 3 H), 4.98 (q, J = 7 Hz, 1 H), 7.50 (m, 3 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.9 (CH), 17.8 (CH_3), 22.6 (CH_3), 74.2 (CH), 125.7 (CH), 128.8 (CH), 129.3 (CH), 133.0 (C), 200.6 (C).

Ketone 8[52] was prepared following a literature procedure.[53] A solution of 1.0 g (6.7 mmol) of 2-hydroxy-1-phenyl-1-propanone, 2.8 g (10 mmol) of MeI, and 3.1 g (13.1 mmol) of Ag_2O in 30 mL of dry DMF was stirred for 1 h at 0 °C and 16 h at room temperature under N_2. The resulting solution was diluted with 50 mL of ether, and the solid was removed by vacuum filtration. The solution was washed with brine, dried over $MgSO_4$, and concentrated to give 0.64 g (59% yield) of **8** after purification by chromatography: ^1H NMR ($CDCl_3$) δ 1.49 (d, J = 7 Hz, 3 H), 3.39 (s, 3 H), 4.65 (q, J = 7 Hz, 1 H), 7.50 (m, 3 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.4, 57.2, 80.2, 128.6, 130.1, 133.3, 134.8, 200.5, in agreement with reported values.[52]

Ketones 10, 11, and 12. Ketones **10**, **11**, and **12** were prepared by appropriate silylation of 2-hydroxy-1-phenyl-1-propanone by the methods described by Oppolzer et al.,[54] Corey et al.,[55] and Hanessian et al.,[56]

(36) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. See, however, the more detailed calculations of Blake, J. F.; Jorgensen, W. L. *J. Org. Chem.* **1991**, *56*, 6052, which suggest little difference in proton affinity between dialkyl ethers and sterically analogous alkyl silyl ethers.

(37) Pitt, C. G.; Bursey, M. M.; Chatfield, D. A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 434.

(38) West, R.; Wilson, L. S.; Powell, D. L. *J. Organomet. Chem.* **1979**, *178*, 5.

(39) The origin of the high reactivity of chelated ketones is currently under investigation. However, simple considerations of the relative geometries in complexed versus chelated ketones may lend a clue as to the source of this reactivity. Complexes of magnesium and simple ketones are expected to have a linear geometry between the carbonyl and magnesium on the basis of ab initio calculations,[40] while chelation necessarily requires a nonlinear geometry (cf. Figure 2). Since the kinetics are first order in $MgMe_2$ for chelating and nonchelating ketones, a four-membered-ring transition state[30] involving transfer of an alkyl substituent from magnesium to the ketone seems the most reasonable. A chelate between $MgMe_2$ and a ketone is therefore further along the reaction coordinate toward product than the corresponding complex, since the alkyl group in the chelate is required to be above the plane of the carbonyl, assuming tetrahedral geometry for magnesium, and closer to the carbonyl carbon than a linearly complexed $MgMe_2$. Therefore, chelation may accelerate the reaction by simply providing, in the form of the complexation energy of the alkoxy ligand, some compensation for the increased organization and steric interactions present in the transition state.

(40) Raber, D. J.; Raber, N. K.; Chandrasekhar, J.; Schleyer, P. v. R. *Inorg. Chem.* **1984**, *23*, 4076. For a more general discussion of the geometries of carbonyl–Lewis acid (but not including magnesium) complexes, see: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256.

(41) We thank Professor R. Breslow (Columbia University) for pointing this analogy out to one of us (E.L.E.).

(42) Ashby, E. C.; Arnott, R. C. *J. Organomet. Chem.* **1968**, *14*, 1.

(43) Ito, M.; Abe, K. *Kitami Kogyo Tanki Daigaku, Kenkyu, Hokoku* **1967**, *2*, 97.

(44) Schmitz, E.; Brede, O. *J. Prakt. Chem.* **1979**, *43*, 312.

(45) Reetz, M. T.; Heimbach, H. *Chem. Ber.* **1983**, *116*, 3702.

(46) Lawson, J. A.; Colwell, W. T.; DeGraw, J. I.; Peters, R. H.; Dehn, R. L.; Tanabe, M. *Synthesis* **1975**, *11*, 729.

(47) Davis, F. A.; Sheppard, A. C. *J. Org. Chem.* **1987**, *28*, 954.

(48) (a) Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1040. (b) Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062.

(49) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

(50) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.

(51) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

(52) Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Musallam, H. A. *J. Org. Chem.* **1987**, *52*, 150.

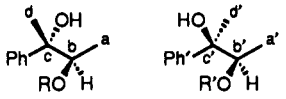
(53) Walker, H. G.; Gee, M.; McCready, R. M. *J. Org. Chem.* **1962**, *27*, 2100.

(54) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002.

(55) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(56) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

Table III. Proton NMR Data[a] for the Alkylation Products of Ketones **8–13**



proton	R =	OCH_3	TMS[c]	TES[d]	TBDMS[e]	TBDPS[f]	TIPS[g]	H
a[b]		0.89 (6)	0.88 (6)	0.85 (6)	0.85 (6)	0.78 (6)	0.89 (6)	0.95 (6)
a′				1.13 (6)	1.14 (6)	0.98 (6)	1.14 (6)	1.08 (6)
b		3.44 (6)	3.91 (6)	3.96 (6)	4.03 (6)	4.15 (6)	3.89 (6)	3.89 (6)
b′				3.91 (6)	3.95 (6)	4.04 (6)	4.12 (6)	3.96 (6)
d		1.59	1.58	1.54	1.53	1.58	1.59	1.60
d′				1.43	1.44	1.45	1.47	1.49
R		3.41	0.13	0.61	0.08	0.88	1.0	
				0.92	0.93	7.4		
R′				0.61	−0.32, −0.04	0.88	1.0	
				0.92	0.78	7.4		
Ph		7.4	7.4	7.4	7.4	7.4	7.4	7.4
Ph′		7.4	7.4	7.4	7.4	7.4	7.4	7.4

[a] In $CDCl_3$ referenced to internal TMS. [b] Chemical shift in ppm followed by coupling constants in parentheses in hertz. [c] Trimethylsilyl. [d] Triethylsilyl. [e] *tert*-Butyldimethylsily. [f] *tert*-Butyldiphenylsilyl. [g] Triisopropylsilyl.

Table IV. ^{13}C NMR Data[a]

^{13}C[b]	R =	OCH_3	TMS	TES	TBDMS	TBDPS	TIPS
a		12.9	18.1	18.1	18.0	17.7	18.2
a′					17.9	17.6	18.1
b		83.4	75.1	75.1	75.1	75.6	75.7
b′					75.6	76.6	76.2
c		76.1	76.4	76.3	76.3	76.7	76.5
c′					76.5	76.9	76.9
d		27.2	27.8	27.9	27.9	28.1	28.1
d′					23.9	24.1	23.3
R		57.4	0.05	5.2, 6.8	−0.5, −4.2, 18.2, 25.9	19.2, 26.8, 127.1, 129.6, 134.3, 135.9	12.9, 18.1
R′				−5.5, −4.5, 18.2, 25.7	19.2, 26.8, 127.4, 129.6	12.8, 18.1, 134.5, 135.7	
Ph		125.3, 126.6, 127.9, 144.5	125.2, 126.7, 127.7, 145.1	125.2, 126.4, 127.9, 145.0	125.1, 126.4, 127.9, 145.1	125.5, 126.7, 127.8, 146.3	125.2, 126.4, 127.8, 145.0
Ph′					125.3, 126.5, 127.8, 146.9	125.6, 126.6, 127.6, 146.6	125.8, 126.7, 127.9, 146.2

[a] Chemical shift in $CDCl_3$, in ppm referenced to internal TMS. [b] See Table III, footnotes c–g.

respectively. Ketone **10** (91% yield): ^1H NMR ($CDCl_3$) δ 0.60 (q, J = 8 Hz, 6 H), 0.92 (t, J = 8 Hz, 9 H), 1.50 (d, J = 7 Hz, 3 H), 4.97 (q, J = 7 Hz, 1 H), 7.50 (m, 3 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 4.8 (CH_2), 6.6 (CH_3), 22.1 (CH_3), 73.1 (CH), 128.3 (CH), 129.2 (CH), 132.9 (CH), 134.8 (C), 201.5 (C). Ketone **11** (74% yield): ^1H NMR ($CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.50 (d, J = 7 Hz, 3 H), 4.96 (q, J = 7 Hz, 1 H), 7.50 (m, 3 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.9 (CH_3), −4.8 (CH_3), 18.2 (C), 22.0 (CH_3), 25.7 (CH_3), 73.6 (CH), 128.3 (CH), 129.2 (CH), 132.9 (CH), 134.6 (C), 201.3. Ketone **12** (78% yield): ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H), 1.44 (d, J = 7 Hz, 3 H), 4.94 (q, J = 7 Hz, 1 H), 7.2–8.1 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 19.2(C), 21.8 (CH_3), 26.8 (CH_3), 73.2 (CH), 127.6 (CH), 128.2 (CH), 128.8 (CH), 129.8 (CH), 132.8 (CH), 133.7 (CH), 134.9 (C), 135.8 (C), 200.9 (C).

Ether 14.[57] 2-Phenyl-1-propanol (0.50 g, 3.7 mmol) was treated with NaH (4 mmol) and MeI (0.58 g, 4.1 mmol) in THF (15 mL) at 25 °C for 24 h. The solution was diluted with 30 mL of ether, washed with 5% HCl and brine, and dried over $MgSO_4$. Purification by chromatography gave 0.33 g (59% yield) of pure product: ^1H NMR ($CDCl_3$) δ 1.31 (d, J = 7 Hz, 3 H), 3.07 (m, J = 7 Hz, 1 H), 3.35 (s, 3 H), 3.46 (dd, J = 7, 13 Hz, 1 H), 3.52 (dd, J = 7, 13 Hz, 1 H), 7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_3), 39.9 (CH), 58.8 (CH_3), 78.2 (CH_2), 126.3 (CH), 127.2 (CH), 128.3 (CH), 144.4 (C).

Ketone 17.[58] In a 50-mL round-bottomed flask were placed 5.0 g (49 mmol) of 3,3-dimethyl-1-butanol, 8.4 g of (48%) hydrobromic acid, and 2.2 g of concentrated sulfuric acid. The mixture was refluxed for 6 h and diluted with water. The bromide layer was separated and washed with water and then diluted sodium carbonate solution. The bromide was dried over $CaCl_2$ and purified by Kugelrohr distillation (7.2 g, 89% yield): ^1H NMR ($CDCl_3$) δ 0.91 (s, 9 H), 1.82 (m, 2 H), 3.37 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.1 (CH_3), 29.6 (CH_2), 31.8 (C), 47.5 (CH_2). A solution of this bromide (1.65 g, 10 mmol), magnesium turnings (0.24 g, 10 mmol), and a catalytic amount of I_2 in THF was stirred and refluxed for 2 h; then 1.03 g (10 mmol) of benzonitrile was added dropwise at 0 °C, and the entire mixture was stirred for 3 h at 25 °C. After the addition of 10 mL of 5% HCl, the aqueous layer was separated and extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. Purification by chromatography gave 1.01 g (53% yield) of pure ketone **17**: ^1H NMR ($CDCl_3$) δ 0.95 (s, 9 H), 1.63 (m, 2 H), 2.92 (m, 2 H), 7.45 (m, 3 H), 7.97 (m, 2 H), in agreement with reported values;[58] ^{13}C NMR ($CDCl_3$) δ 29.2 (CH_3), 30.1 (C), 34.2 (CH_2), 38.1 (CH_2), 128.0 (CH), 128.5 (CH), 132.8 (CH), 137.0 (C), 200.9 (C).

Alkylation Products. Ketones **2**, **5–13**, and **17** were alkylated cleanly with $MgMe_2$ in THF at −78 °C to give the corresponding alcohols essentially pure according to NMR analysis. The proton NMR spectra of the products from alkylation of the benzyloxy ketones **2** and **6** are described below; the spectra of the corresponding TIPS products were similar. 1-(Benzyloxy)-2-methyl-2-propanol: ^1H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 3.31 (s, 2 H), 4.58 (s, 2 H), 7.34 (m, 5 H). 4-(Benzyloxy)-2-methyl-2-butanol: ^1H NMR ($CDCl_3$) δ 1.23 (s, 6 H), 1.80 (t, J = 6.5 Hz, 2 H), 3.73 (t, J = 6.5 Hz, 2 H), 4.53 (s, 2 H), 7.33 (m, 5 H). The proton and ^{13}C NMR data for the alkylation products of ketones **8–13** are listed in Tables III and IV respectively. 4,4-Dimethyl-2-phenyl-2-hexanol (the product of **17**): ^1H NMR ($CDCl_3$) δ 0.83 (s, 9 H), 1.05 (m, 2 H), 1.56 (s, 3 H), 1.83 (m, 2 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.2 (CH_3), 29.8 (C), 30.2 (CH_3), 37.6 (CH_2), 38.7 (CH_2), 74.7 (C), 124.7 (CH), 126.4 (CH), 128.1 (CH), 134.8 (C). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.27; H, 10.83.

The configurations of the alkylation products of **8–13** were assigned by correlation with the known (*RR*/*SS* and *RS*/*SR*)-2-phenyl-2,3-butanediols.[28] The (*RS*/*SR*) diastereomer, obtained by the alkylation of 2-hydroxy-1-phenyl-1-propanone with CH_3MgCl in THF at 0 °C, was methylated with 1 equiv of NaH and MeI to provide (*RS*/*SR*)-3-methoxy-2-phenyl-2-butanol, identical with the alkylation product of ketone **8**. The two diasteromers of the products of ketones **12** and **13** were separated by TLC and hydrolyzed to the two corresponding diols with

(57) Cook, M. J.; Khan, T. A.; Nasri, K. *Tetrahedron Lett.* **1984**, *25*, 5129.
(58) McWilliam, D. C.; Balasubramanian, T. R.; Kuivila, H. G. *J. Am. Chem. Soc.* **1978**, *100*, 6407.

(nBu)$_4$NF in THF. The products of **9-11** were analyzed by ^{1}H and ^{13}C NMR and then hydrolyzed without separation under acidic conditions to form a mixture of the same two diols (in the same ratio as the silyloxy precursors).

Equilibrium Studies of Chelates. In a typical experiment, ca. 0.07 mmol of ketone was dissolved in 0.60 mL of CD_2Cl_2, and excess anhydrous magnesium bromide etherate was added. The resulting suspension was stirred for 30 min and then centrifuged until the supernatant liquid was clear. The clear solution was transferred to an NMR tube, and the proton NMR spectrum was recorded. Substantial changes in the chemical shift of many protons in the ketones were observed (see Scheme I). The concentration of $MgBr_2{\cdot}Et_2O$ was equal to the concentration of the ketone according to the integration of the Et_2O peaks relative to those of the ketone.

RINMR Methods. RINMR spectra were recorded in a Bruker WM-250 spectrometer at −70 °C. The rapid injection insert was functionally equilvalent to the one described by McGarrity,[15] which is capable of injecting 10–50 μL of solution into a spinning sample in the probe of a high-resolution NMR apparatus.

Solutions for injection were prepared by removing ca. 0.3 mmol of standard $MgMe_2$ solution, evaporating THF under vacuum, redissolving in 100 μL of THF-d_8, evaporating the solvent again, and redissolving in 600 μL of THF-d_8, which was then drawn into the dried injector syringe under argon. In a typical experiment, a 5-mm NMR tube truncated to a length of 11 cm was dried on a vacuum line and filled with argon. The proper amount of pentamethylbenzene (PMB) as internal standard, 320 μL of THF-d_8, and ca. 0.15 mmol of ketone were added. The tube was placed in the NMR probe where it was under a bath of N_2 from the spinner air and the liquid N_2 used for cooling. The injector containing a solution of $MgMe_2$ was then lowered into the previously shimmed NMR and the injection carried out. The FEDs of single-pulse proton NMR were recorded rapidly following the injection at preset intervals, and the signals due to $MgMe_2$ (−1.78 ppm) were monitored. For fast reactions, fast spectra were obtained in less than 10 s. The rate of disappearance of $MgMe_2$ was determined by integration relative to PMB.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (grant 17171-AC1), and to the National Science Foundation (grant CHE-8703060) for partial support of this research.

Registry No. 1, 5878-19-3; **2**, 22539-93-1; **3**, 28047-99-6; **4**, 26205-43-6; **5**, 107299-93-4; **6**, 6278-91-7; **7**, 98264-29-0; **8**, 135271-21-5; **9**, 138513-35-6; **10**, 138513-36-7; **11**, 138513-37-8; **12**, 138513-38-9; **13**, 138513-39-0; **14**, 65738-46-7; **15**, 93-55-0; **16**, 591-78-6; **17**, 37608-93-8; dimethylmagnesium, 2999-74-8; magnesium bromide, 7789-48-2; (*R**,*S**)-3-methoxy-2-phenyl-2-butanol, 138432-83-4; (*R**,*S**)-2-phenyl-3-[(trimethylsilyl)oxy]-2-butanol, 138432-84-5; (*R**,*R**)-2-phenyl-3-[(triethylsilyl)oxy]-2-butanol, 138432-86-7; (*R**,*S**)-2-phenyl-3-[(triethylsilyl)oxy]-2-butanol, 138432-85-6; (*R**,*R**)-3-[(*tert*-butyldimethylsilyl)oxy]-2-phenyl-2-butanol, 138432-88-9; (*R**,*S**)-3-[(*tert*-butyldimethylsilyl)oxy]-2-phenyl-2-butanol, 138432-87-8; (*R**,*R**)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-phenyl-2-butanol, 138432-90-3; (*R**,*S**)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-phenyl-2-butanol, 138432-89-0; (*R**,*R**)-2-phenyl-3-[(triisopropylsilyl)oxy]-2-butanol, 138432-92-5; (*R**,*S**)-2-phenyl-3-[(triisopropylsilyl)oxy]-2-butanol, 138432-91-4; (*R**,*R**)-2-phenyl-2,3-butanediol, 138432-94-7; (*R**,*S**)-2-phenyl-2,3-butanediol, 138432-93-6; 2-hydroxy-1-phenyl-1-propanone, 5650-40-8; 1-(benzyloxy)-2-methyl-2-propanol, 91968-72-8; 4-(benzyloxy)-2-methyl-2-butanol, 138432-95-8; 4,4-dimethyl-2-methyl-2-hexanol, 138432-96-9.

An Investigation into the Minimum Requirements for Peptide Hydrolysis by Mutation of the Catalytic Triad of Trypsin

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Abstract: The catalytic triad of rat anionic trypsin has been systematically altered by site-directed mutagenesis to determine the activity of alternate combinations of amino acids toward the hydrolysis of peptide bonds. Genetically modified rat trypsins H57A, H57D, H57E, H57K, H57R, H57A/D102N, H57D/D102N, H57L/D102N, H57K/D102N, D102N, S195A, S195T, and H57A/D102N/S195A have been generated. Rigorous steps were taken to show that the resultant catalysis was due to the mutant enzymes and not contaminants. Each of the variants exhibit measurable activity toward the activated amide substrate Z-GPR-AMC. At pH 8.0 k_{cat} ranges from 0.011 to 1.3 min^{-1} (0.0004–0.04% of wild-type). At pH 10.5 k_{cat} ranges from 0.012 to 140 m^{-1} (0.0004–5% of wild-type). The mutant trypsins were subsequently assayed for their ability to hydrolyze the unactivated amide linkages of protein substrates. Trypsins D102N, H57K, and H57K/D102N exhibited the highest level of activity. The k_{cat} for the D102N enzyme was 4 h^{-1} (0.003% of wild-type). The H57A/D102N double mutant was not as active but was chosen for further study since it was the simplest trypsin to exhibit peptidase activity. Its k_{cat} was ~0.1–0.2 h^{-1} at pH 8.0 and 0.7 h^{-1} at pH 10.1. These experiments demonstrate that an intact catalytic triad is not a requirement for peptide bond cleavage and that designed serine peptidases need not include a catalytic histidine or aspartic acid.

The development of peptidases with designed specificities would facilitate the manipulation of peptides and proteins. The challenge in designing such catalysts is the inclusion of interdependent binding and catalytic motifs within a common structural framework to achieve the energetically demanding hydrolysis of peptide bonds.[1] Initial studies have involved the derivatization of small molecules with reactive moieties to partially or fully mimic the chemistry of the serine protease catalytic triad. These catalysts have helped elucidate some aspects of the interactions between members of the triad[2,3] but have not yet been shown to catalyze the cleavage of amide linkages. Recently, this approach has been extended with a de novo designed four helix bundle polypeptide bearing catalytic serine, histidine, and aspartic acid residues. This protein exhibited significant chymotrypsin-like esterase activity.[4] Another strategy has been to elicit monoclonal antibodies to molecules which mimic the transition state of amide hydrolysis.

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(1) Kahne, D.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 7529–7534.

(2) Esterase catalysis by a cyclodextrin derivatized with a moiety resembling the Asp-His-Ser triad (D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, 146–152) has been shown to be independent of the attached triad: Breslow, R.; Chung, S. *Tetrahedron Lett.* **1989**, *30*, 4353–4356. Zimmerman, S. C. *Tetrahedron Lett.* **1989**, *30*, 4357–4358.

(3) (a) Cramer, K. D.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 3680–3682. (b) Huff, J. B.; Askew, B.; Duff, R. J.; Rebek, J. *J. Am. Chem. Soc.* **1988**, *110*, 5908–5909.

(4) Hahn, K. W.; Klis, W. A.; Stewart, J. M. *Science* **1990**, *248*, 1544–1547.

0002-7863/92/1514-1784$03.00/0