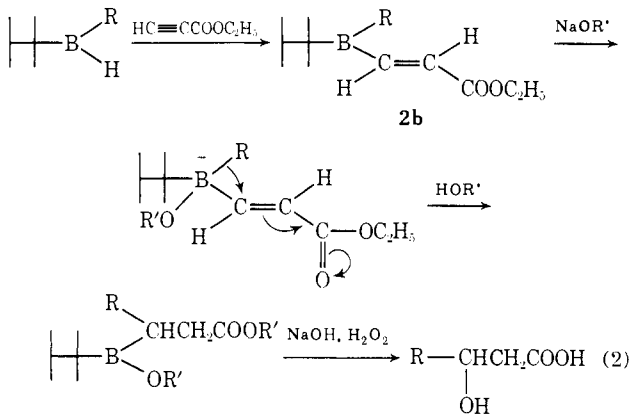
Table I. Preparation of Thexylalkyl(2-ethoxycarbonylethenyl)boranes and Their Conversion into β-Hydroxycarboxylic Acids

Alkyl group (R) of thexylmonoalkylborane	Hydroboration product: Yield (2b + 3b) by pmr,[a] %	Isomer distribution,[a] % 2b	3b	β-Hydroxycarboxylic acids[b]: Yield, % Glpc[c]	Isolated	Mp, °C
Cyclohexyl	94	>99	Trace	74	60	79.5–80.0
Norbornyl	93	90	10	57	51	80–82
3-Methyl-2-butyl	101	>99	Trace	72	68	50.5–51.5
trans-2-Methylcyclopentyl	89	>99	Trace	81	69	69.5–70.0
2-Methyl-1-pentyl	94	67	33	46[d]	*e*	

[a] Based on pmr examination of vinyl protons (benzene as an internal standard). The chemical-shift ranges: H_a (d, J = 19 Hz) 7.63–7.70; H_b (d, J = 19 Hz) 5.90–6.04; H_c (d, J = 3 Hz) 6.40–6.42, and H_d (d, J = 3 Hz) 5.31–5.40. [b] All new, isolated products yielded satisfactory analytical and spectral data. [c] By glpc examination of silylated products (SE-30). [d] By glpc examination after treatment of the product with an excess of diazomethane (SE-30). [e] Isolated by glpc as methyl 2-methoxy-4-methyloctanoate.

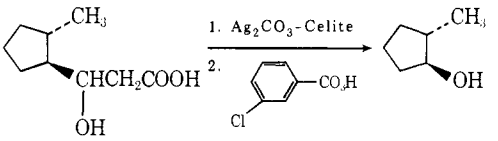
dicating that steric effect can be significant in determining the orientation in this reaction. Accordingly, we tested a series of thexylmonoalkylboranes[9] containing a highly bulky thexyl group as hydroborating agents. Fortunately, all but one of the thexylmonoalkylboranes of different steric requirements we tested placed at least 90% of the boron atoms in the desired β positions, producing only minor amounts of the isomeric products **3b**[6] (Table I). Moreover, the usual reluctance of the thexyl group to participate in the ionic reactions of organoboranes[10] was observed in the subsequent reaction of **2b** with base, thereby making the one-pot procedure shown by eq 2 a highly practical synthetic method which permits the maximum conversion of the starting olefins into β-hydroxycarboxylic acids.[11] The experimental results are summarized in Table I.



(2)

R = alkyl; R′ = H, methyl, or ethyl

That the transfer of an alkyl group from boron to carbon must involve an ionic mechanism is indicated by the following observations. First, use of a base is necessary to induce the facile transfer reaction. Second, addition of free-radical scavengers (5 mol %), such as galvinoxyl, does not have any noticeable effect on the rate of reaction. Finally, the stereochemistry of the group R is totally retained when R is *trans*-2-methylcyclopentyl as demonstrated by glpc analysis of 2-methyl-1-cyclopentanol obtained by oxidation of **1** with silver carbonate followed by the Baeyer–Villiger oxidation (eq 3). It should be noted that the procedure reported here provides a unique, new route to the Reformatsky products[12] with the possibility of incorporating, in a simple manner, stereochemically defined moieties in the β position.



(3)

1

The following procedure for the preparation of **1** is representative. To a dry 250-ml flask equipped with a septum inlet, a reflux condenser, and a magnetic stirring bar was placed 16.8 ml (30 mmol) of 1.78 *M* thexylborane in THF after flushing the system with nitrogen. To this were added in sequence 3.20 ml (30 mmol) of 1-methylcyclopentene (1 hr at −25 to −30°), 3.20 ml (30 mmol) of ethyl propiolate (1 hr at −25 to −30°), and 25 ml (75 mmol) of 3 *N* sodium hydroxide (5 min at −25°, then 1 hr at room temperature). The reaction mixture was oxidized with 10 ml of 30% hydrogen peroxide and heated for 2 hr at 40–50° to complete oxidation and hydrolysis. After the usual work-up, 4.10 g (79%) of crude product (*ca.* 90% pure) was obtained. After recrystallization (ether–pentane), the combined yield of pure **1** was 3.20 g (62%): mp 69.5–70°; ir (Nujol) 3150, 1690 cm^{-1}; pmr (CCl_4, TMS) δ 1.05 (d, J = 6 Hz, 3 H), 1.2–2.2 (m, 8 H), 2.45 (d, J = 6 Hz, 2 H), 3.6–4.2 (m, 1 H), 7.62 (s, 2 H) ppm.

We continue to explore the scope and synthetic applicability of this new carbon–carbon bond forming reaction.

Acknowledgment. We thank Syracuse University for financial support.

(9) (a) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **85**, 2066 (1963); (b) E. Negishi, J. J. Katz, and H. C. Brown, *Synthesis*, 555 (1972).

(10) H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5285, 5477 (1967).

(11) Only a trace quantity (<2%), if any, of the by-product corresponding to the transfer of the thexyl group was observed in each case.

(12) R. L. Shriner, *Org. React.*, 1, 1 (1942).

Ei-ichi Negishi,* Takao Yoshida
Department of Chemistry, Syracuse University
Syracuse, New York 13210
Received June 19, 1973

Dynamic Nuclear Magnetic Resonance Investigations of Intramolecular Catalysis in Amide Proton Exchange

Sir:

We have used dynamic nmr methods to explore neighboring group participation in the amide proton exchange of ortho-substituted *N*-methylbenzamides. Although the mechanism of amide proton exchange

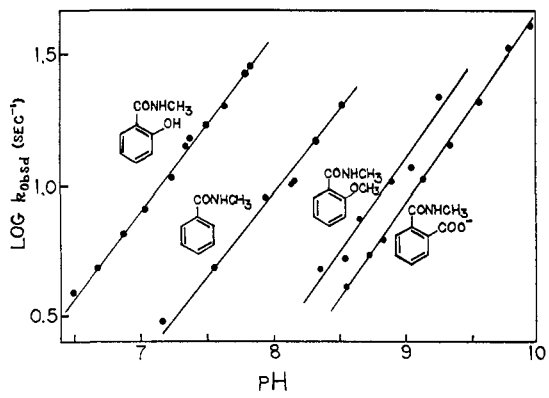
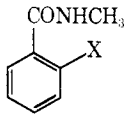


Figure 1. Log k_{obsd} *vs.* pH profiles for amide proton exchange of four *N*-methylbenzamides in 15% acetonitrile–water at 25°.



A, X = H
B, X = OH
C, X = OCH_3
D, X = CO_2^-

has been of interest to biochemists for a long time,[1-3] the details remain unknown. Indeed, the effect of electron-withdrawing substituents on the rate of the reaction was fully elaborated only last year.[4] In the present communication, we describe the first observation of intramolecular catalysis in an amide proton exchange.

N-Methylbenzamide exchanges its labile proton in water at a rate measurable by nmr when the pH lies between 7 and 8.5 (Figure 1). In weakly acidic solutions, proton transfer is slow relative to the nmr time scale, and the methyl group is split into a doublet (J = 4.9 Hz). As the pH is raised above neutrality, the rate of hydroxide-catalyzed exchange increases, causing the peaks to broaden and approach one another and finally to coalesce at pH 8.0. Further increases in pH narrow the peak into a sharp singlet. Rate constants in Figure 1 were calculated with the aid of an RCA Spectra 70/55 computer which adjusts τ (the reciprocal of k_{obsd}) so as to minimize deviations between experimental and theoretical spectral parameters.[5] Line-shape analysis is so fraught with pitfalls[6] that we must delineate at least a few of the experimental details and precautions. All runs were performed in 15% acetonitrile–water (v/v) and 0.1 M substrate. Spectra were secured using a Jeol JNM-MH-100 spectrometer equipped with a thermostated probe. The temperature, maintained at 25 ± 0.8° as determined by the equation of Van Geet,[7] was measured before and after each run. An optimun

Figure 2. General base and specific base–general acid mechanisms for amide proton exchange in *N*-methylsalicylamide.

constant homogeneity was achieved by adjusting the resolution controls prior to each run while observing the CH_3CN signal. We used slow sweep rates (0.1–0.2 Hz/sec), avoided excessive filtering of noise (10 Hz), and kept the rf field sufficiently low (0.1 mG) to preclude saturation. The 54-Hz sweep width used throughout this work was calibrated by the side band modulation technique.[8] Six to eight tracings were made at each pH, and the resulting rate constants were averaged. Effective relaxation times (T_2's) were calculated from the line widths (0.7 Hz for *N*-methylbenzamide) at slow and fast exchange rates. The accuracy of our data is limited by the usual assumption of Lorentzian line shape and by the uncertainty in T_2. On the other hand, our kinetic effects are sufficiently large that the error in k_{obsd} (estimated to be ±15%) is of little consequence.[9]

Log k_{obsd} *vs.* pH plots for the base-catalyzed amide proton exchange of several *N*-methylbenzamides are shown in Figure 1.[10,11] *N*-Methyl-*o*-anisamide exchanges slowly relative to *N*-methylbenzamide, and we attribute this to direct resonance interaction between the methoxy and amide groups. Electron release to the amide carbonyl would be expected to impede the base-catalyzed exchange.[4] But a far more noteworthy rate difference exists between the *o*-hydroxyamide and its analogs. Despite the electron-donating effect of its ortho hydroxyl, *N*-methylsalicylamide exchanges *faster* than *N*-methylbenzamide. Moreover, the coalescence pH of the salicylamide is lowered by 1.7 pH units relative to that of *N*-methyl-*o*-anisamide. Two kinetically indistinguishable mechanisms can explain this catalysis (Figure 2). In the first, phenolate anion (pK_a = 8.54 in 15% acetonitrile) removes the amide proton; the amide then retrieves another proton from the solvent or from the neighboring hydroxy group which in the meantime has exchanged its proton. In the second mechanism, proton exchange is subject to specific base–general acid catalysis. If this latter mechanism is correct, then the neighboring group enhancement is nearly two orders of magnitude.

A carboxylate anion has little electron donating or attracting ability (σ_p = 0.0).[12] Consequently, the slow rate of amide proton exchange of *N*-methyl-

(1) E. R. Blout, C. de Loze, and A. Asadourian, *J. Amer. Chem. Soc.*, **83**, 1895 (1961).
(2) B. H. Leichtling and I. M. Klotz, *Biochemistry*, **5**, 4026 (1966).
(3) S. O. Nielsen, W. P. Bryan, and K. Mikkelsen, *Biochim. Biophys. Acta*, **42**, 550 (1960).
(4) R. S. Molday and R. G. Kallen, *J. Amer. Chem. Soc.*, **94**, 6739 (1972).
(5) The computer program, kindly given to us by Dr. Donald E. Leyden, utilizes peak widths and peak-to-valley ratios for comparison purposes. We demonstrated the reliability of our methods by duplicating to within 15% rates from total line-shape analysis of *N*-methylacetamide exchange.[4]
(6) L. W. Reeves, *Advan. Phys. Org. Chem.*, **3**, 187 (1965).
(7) A. L. Van Geet, *Anal. Chem.*, **42**, 679 (1970).
(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 74.
(9) This is *not* true in much dnmr work where rate constants over a small temperature range are used to calculate activation parameters.
(10) The slopes of the plots are somewhat less than unity. This seems to be related to the 15% acetonitrile in the solution (necessary to solubilize the amides) which allowed us to measure only apparent pH values. The slope of the log k_{obsd} *vs.* pH plot for *N*-methylacetamide in pure water was found to be equal to one; addition of acetonitrile decreased the slope.
(11) Buffer catalysis was not observed, in agreement with previous work with other amides.[4] Rate constants were independent of the substrate concentration (0.1–0.2 M).
(12) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 173.

phthalamic acid, evident in Figure 1, must be attributed to electrostatic inhibition by the carboxylate. An alternative explanation, namely hydrogen bonding of the carboxylate to the labile N proton, is unlikely in view of the unfavorable seven-membered ring geometry of such an interaction. Our results suggest that a peptide linkage lying in proximity to anionic side chains might exchange only slowly despite being neither "buried" nor internally hydrogen bonded within the protein.[13]

Acid-catalyzed proton exchange is *not* accelerated by the ortho hydroxy group of *N*-methylsalicylamide. Thus, the coalescence pH is approximately 1.4 for both *N*-methylbenzamide and *N*-methylsalicylamide. Apparently, the phenol is too weak an acid to assist in the formation of a protonated amide intermediate assumed to be involved in the exchange.[14,15]

Intramolecular catalysis is even more effective in aprotic solvents than in water. For example, 0.02 *M* *n*-butylamine causes doublet-to-singlet coalescence of 0.1 *M* *N*-methylsalicylamide in dry acetonitrile at 25°. In contrast, a distinct doublet was still observed with 1.6 *M* *n*-butylamine and 0.1 *M* *N*-methylbenzamide in acetonitrile. We surmise that the ortho hydroxyl group stabilizes the anionic portion of an ion pair intermediate *via* chelation to the amide carbonyl. Full details will be reported later.

Acknowledgment. This work was supported in part by the National Science Foundation.

(13) H. A. Scheraga, "Protein Structure," Academic Press, New York, N. Y., 1961, p 192.
(14) A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem. Soc.*, **81**, 62 (1959).
(15) R. B. Martin and W. C. Hutton, *ibid.*, **95**, 4752 (1973).
(16) Recipient of a Camille and Henry Dreyfus Foundation Teacher Scholar Grant and a National Institutes of Health Research Career Development Award.

F. M. Menger,*[16] G. Saito
Department of Chemistry, Emory University
Atlanta, Georgia 30322
Received May 31, 1973

New Synthetic Reactions. Sulfenylation–Dehydrosulfenylation as a Method for Introduction of Unsaturation

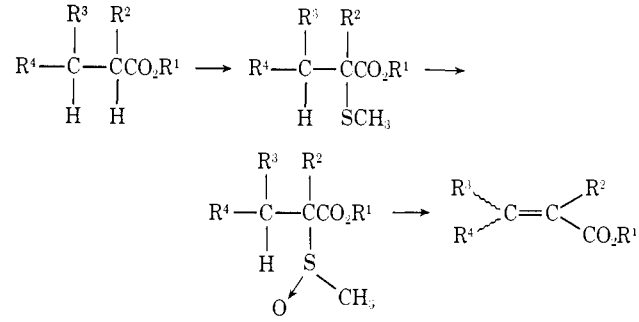
Sir:

Introduction of unsaturation α,β to a carbonyl group serves as a major method for elaboration of organic structures. Invariably, the basic approach involves bromination followed by dehydrobromination. The wide diversity of brominating agents and "bases" attests to the capriciousness of the method. Application of this method to esters and lactones[1] becomes even more difficult because of the lack of general methods to effect direct α halogenation.[2] Because of our needs to carry out such a transformation under very mild conditions, we developed a new method based upon the facile direct sulfenylating of enolates.[3,3g]

(1) (a) A. E. Greene, J. C. Miller, and G. Ourisson, *Tetrahedron Lett.*, 2489, 3375 (1972); (b) T. R. Kastur, G. R. Pettit, and K. A. Jaeggi, *Chem. Commun.*, 644 (1967); (c) for a new approach see G. Cainelli, G. Cardillo, and A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.*, 94 (1973).
(2) For some recent developments see P. L. Stotter and K. A. Hill, *Tetrahedron Lett.*, 4067 (1972); M. W. Rathke and A. Lindert, *ibid.*, 3995 (1972).

Addition of an ester to a tetrahydrofuran solution containing 1 equiv of lithium *N*-cyclohexyl-*N*-isopropylamide[4] at −78° followed by inverse quenching into a tetrahydrofuran solution containing a 15% excess of freshly distilled dimethyl disulfide[5a] led to 79–100% isolated yields of pure 2-methylthio esters. Oxidation with sodium metaperiodate[6] in aqueous methanol at room temperature followed by heating neat at 120° or in refluxing toluene led to exceptionally high isolated yields of α,β-unsaturated ester.[7] Scheme I and Table

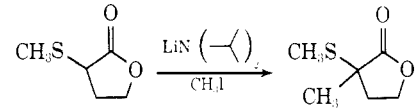
Scheme I. General Scheme for Introduction of Unsaturation into Esters



I exemplify the process.[8] No attempt has been made to optimize the yields listed.

The thermolysis of the α-methylsulfinyl derivative of ethyl decanoate was studied in some detail. At temperatures below 120°, elimination was sluggish. At 120° 5 hr was required. In refluxing toluene, completion occurred in about 14 hr. No difference in yield was noted for the two methods. Following the reaction by nmr revealed the exclusive formation of the *E* isomer during the entire course of the elimination.

Entry 5 illustrates the utility of a lactone as substrate. The same α-methylthiolactone (**1**) is also available by the methylation of α-methylthio-γ-butyrolactone.[9] This



1

facile alkylation illustrates the utility of the intermediate

(3) For alternative sulfenylation methods and reagents see (a) M. Ohno, N. Naruse, S. Torimitsu, and I. Terasawa, *J. Amer. Chem. Soc.*, **88**, 3168 (1966); (b) M. Ohno and I. Terasawa, *ibid.*, **88**, 5683 (1966); (c) M. Ohno, N. Naruse, S. Torimitsu, and M. O. Kamoto, *Bull. Chem. Soc. Jap.*, **39**, 1119 (1966); (d) R. L. Autry and P. W. Scullard, *J. Amer. Chem. Soc.*, **87**, 3284 (1965); (e) R. L. Autry and P. W. Scullard, *ibid.*, **90**, 4917, 4924 (1968); (f) S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972); T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Lett.*, 5115 (1970).
(3g) NOTE ADDED IN PROOF. Professor D. Seebach has informed us of his independent efforts in sulfenylating ketone enolates with diphenyl disulfide.
(4) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).
(5) (a) Available from Aldrich Chemical Co.; (b) available from Eastman Kodak Co.
(6) C. R. Johnson and J. E. Keiser, *Org. Syn.*, **46**, 18 (1966).
(7) (a) C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960); (b) C. Walling and L. Bollyky, *J. Org. Chem.*, **29**, 2699 (1964); (c) D. N. Jones and M. A. Saeed, *Proc. Chem. Soc., London*, 81 (1964); (d) S. I. Goldberg and M. S. Sahli, *J. Org. Chem.*, **32**, 2059 (1967); (e) D. W. Emerson and T. J. Korniski, *ibid.*, **34**, 4115 (1969); (f) D. N. Jones, E. Helmy, and A. C. F. Edmonds, *J. Chem. Soc. C*, 833 (1970), and references therein, (g) N. Grabowsky, *Justus Liebigs Ann. Chem.*, **175**, 348 (1875).
(8) A similar sequence involving the synthesis and elimination of α-phenylselenoxy esters has been independently developed. See H. J. Reich, I. Reich, and J. Renga, *J. Amer. Chem. Soc.*, **95**, 5813 (1973).
(9) B. M. Trost and H. Arndt, *J. Org. Chem.*, **38**, 3140 (1973).