Electrostatic Catalysis of Proton-Transfer Reactions: Hydrogen Exchange in Chloroform and Ionization of 2-Nitropropane

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Abstract: Rates of detritiation of chloroform-*t* catalyzed by a series of ω-trimethylammonioalkylamines, $(CH_3)_3N^+(CH_2)_nNH_2$ with n = 3–5, were measured in aqueous solution at 25 °C, and rates of ionization of 2-nitropropane catalyzed by the same amines with n = 2–5, four additional uncharged primary amines, two aminocarboxylate ions, and ethylenediamine and its monoprotonated conjugate acid were also measured. The uncharged primary amines give a good Brønsted correlation for the nitroalkane ionization, with $\beta = 0.61 \pm 0.03$; the positively charged catalysts show positive deviations from this correlation and the negatively charged catalysts show negative deviations. The ω-trimethylammonioalkylamines also give positive deviations from a previously constructed Brønsted correlation for the chloroform detritiation reaction; the latter deviations are much larger than the corresponding ones for 2-nitropropane ionization, which is consistent with the greater development and concentration of charge in the transition state of the chloroform reaction. The pattern of electrostatic effects provided by these results indicates a field rather than an inductive mechanism for transmission of the polar interaction.

The electrostatic effect of polar substituents on heterolytic reactions is a well-documented phenomenon. A classic example comes from the ionization of dicarboxylic acids: the negative charge produced by the first ionization impedes the second, and the magnitude of this effect, as measured by the difference between the first and second ionization constants, can be correlated quantitatively with the distance separating the two functional groups.[1]

Electrostatic effects on rate constants are also well known. Some recent examples are the effect of ammonio groups on the kinetics of enolization of ketones[2] and the effect of carboxylate groups on the rates of ionization of α-aryl bromides[3] and benzal chlorides[4] as well as on the rate of hydrolysis of acetals.[5] The latter system is of special interest as a model for the mechanism of lysozyme action; lysozyme is a hydrolytic enzyme with a carboxylate group at its active site whose electrostatic effect is believed to be an important component of this enzyme's catalytic effectiveness.[6]

We ourselves have found electrostatic effects on the rate of hydrolysis of vinyl ethers[7] as well as on the rate of hydrogen exchange of chloroform[8] and phenylacetylene.[9] We have also used this phenomenon to help detect general base catalysis in systems where this form of catalysis is particularly weak.[8] This application of electrostatic effects is based upon the fact that the rate law for a general base catalyzed reaction in aqueous solution consists of a term proportional to hydroxide ion concentration, $k_{HO^-}[HO^-]$, in addition to the general base component, $k_B[B]$ (eq 1). In reactions with large Brønsted exponents, such as hydrogen

$$k_{obsd} = k_{HO^-}[HO^-] + k_B[B] \quad (1)$$

exchange in chloroform,[9] k_{HO^-} is much greater than k_B, and the hydroxide ion term consequently overwhelms the general base catalyzed component, making the latter difficult to detect. Introduction of a positive charge at an appropriate position in the general base increases the value of k_B for a carbanion-forming reaction such as chloroform exchange, and that makes $k_B[B]$ a larger part of k_{obsd} and therefore more easily observed.

This work on electrostatic effects in chloroform exchange was published in preliminary form.[8] We describe it here in full and also present a companion study on the ionization of 2-nitropropane.

Experimental Section

Materials. ω-Trimethylammonioalkylamines, $(CH_3)_3N^+(CH_2)_nNH_2$, were prepared as the hydrobromide salts by published procedures, the ethyl derivative (n = 2) by treating 2-bromoethylamine with trimethylamine[10] and the others (n = 3–5) by a Gabriel synthesis.[11] Titration of the finished products in ethylenediamine–water solution with sodium methoxide dissolved in methanol and benzene[12] showed them to be at least 99% pure. Other primary amines were obtained commercially, converted to their hydrochloride salts, and purified and used as such. Tritiated chloroform was made by exchange as described previously,[9] and 2-nitropropane was a commercial product purified by gas chromatography. All other materials were best available commercial grades. Solutions were prepared with deionized water purified further by distillation in glass apparatus.

Acid Dissociation Constants. The pK_a's of the conjugate acids of the ω-trimethylammonioalkylamines, $(CH_3)_3N^+(CH_2)_nNH_2$ with n = 3, 4, 5, were determined by measuring the pH of buffer solutions of these amines and their hydrobromide salts. Concentrations were varied systematically by starting with a given solution and diluting it serially a number of times (usually 11) until a solution approximately one-third of the original concentration was reached; a typical series might cover the range 0.02–0.006 M in amine hydrobromide concentration and 0.10–0.03 M in ionic strength. Two to four series of measurements of this kind were made for each amine; the solutions were thermostated at 25.0 ± 0.05 °C, and the measurements were made with a Model 1019 Beckman Research pH meter. All operations were carried out under a nitrogen atmosphere; concentrations were determined by weighing out solution components.

Kinetics. Rates of detritiation of chloroform-*t* were measured by liquid scintillation counting as described previously.[9] Rates of ionization of 2-nitropropane were determined spectrophotometrically, using for the most part the absorption maximum of the nitronate ion at λ 224 nm; in a few instances the amine buffers absorbed strongly at this wavelength

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Table I. General Base Catalytic Coefficients for the Detritiation of Chloroform-*t* by ω-Trimethylammonioalkylamines in Aqueous Solution at 25 °C[a]

catalyst	pK(BH^{+n})	$10^4 k_B$, M^{-1} s^{-1}
$(CH_3)_3N^+(CH_2)_3NH_2$	8.34	0.177
$(CH_3)_3N^+(CH_2)_4NH_2$	9.35	1.47
$(CH_3)_3N^+(CH_2)_5NH_2$	9.83	4.97

[a] Ionic strength 0.10 M, maintained with NaBr.

and then the shoulder of this band at λ 236 nm was used instead. Measurements were made with a Beckman DBGT spectrometer which had a thermostated (25.0 ± 0.05 °C) cell block. For the most part, reactions were followed either to completion or for 3–4 half-lives, and first-order rate constants were obtained either as slopes of plots of ln ($A_\infty - A_t$) vs. time or by the method of Swinbourne.[13] A few reactions, however, were very slow, and here an initial rate method was used: the zero-order rate of increase of absorbance at λ 236 nm was measured for about 1.0% reaction at a concentration of 2-nitropropane (7×10^{-3} M) which gave a sizable absorbance change (0–0.5), and this was then converted into a first-order rate constant using the known concentration of substrate and the molar extinction coefficient of the nitronate anion, $\lambda_{236} = 7.69 \times 10^3$ M^{-1} cm^{-1}.

Results

Acid Dissociation Constants. Thermodynamic acid dissociation constants, K_a, for the hydrobromide salts of the ω-trimethylammonioalkylamines, $(CH_3)_3N^+(CH_2)_nNH_3^+Br_2^-$ with n = 3–5, were obtained by extrapolating pH and concentration measurements to zero ionic strength. The function given as eq 2 was used

$$\text{pH} - \log([BH^{2+}]/[B^+]) - (3)(0.5115\sqrt{\mu})/(1 + \sqrt{\mu}) = \text{p}K_a - (b_{2+} - b_+)\mu \quad (2)$$

for this purpose; here b_{2+} and b_+ are the ionic interaction coefficients in the expressions for the activity coefficients of the amine conjugate acid, BH^{2+}, and the amine, B^+, respectively, and μ is the ionic strength.

This treatment gave the following results: pK_a = 8.34 for $(CH_3)_3N^+(CH_2)_3NH_3^+$, 9.35 for $(CH_3)_3N^+(CH_2)_4NH_3^+$, and 9.83 for $(CH_3)_3N^+(CH_2)_5NH_3^+$. None of these acidity constants appear to have been determined before, but the values obtained here are appropriate for ammonium ions of this structure, and they also form a consistent set with the known acidity constant for the next lower member of the series, $(CH_3)_3N^+(CH_2)_2NH_3^+$, p$K_a$ = 6.59.[10]

Kinetics. First-order rate constants for the detritiation of chloroform-*t* were measured in buffer solutions of the three ω-trimethylammonioalkylamines, $(CH_3)_3N^+(CH_2)_nNH_2$ with n = 3–5. For each amine, four to five solutions of constant stoichiometric buffer ratio but different buffer concentration were used; buffer base concentrations generally covered the range [B$_+$] = 0.04–0.008 M. The data are summarized in Table S1.[14]

Series of buffer solutions of this kind usually have constant hydroxide ion concentrations, but significant variations in the latter can occur if the base is fairly strong or the base concentration is low. This was the case here, and that had to be taken into account before the data could be treated by a simple linear fitting to eq 1. This was accomplished by adjusting observed rate constants to values they would have had under conditions of constant hydroxide ion concentration as described before,[9] using the acidity constants and activity coefficients for B^+ and BH^{2+} determined here plus activity coefficients for H^+ and HO^- recommended by Bates.[15] This treatment gave hydroxide ion catalytic coefficients of k_{HO^-} = 0.157, 0.154, and 0.160 M^{-1} s^{-1}, which are in good agreement with the directly measured value for chloroform-*t* detritiation k_{HO^-} = 0.163 M^{-1} s^{-1}.[9] The general base catalytic coefficients which were obtained are listed in Table I.

Rates of ionization of 2-nitropropane were also measured in ω-trimethylammonioalkylamine buffer solutions, and in addition in buffer solutions of five uncharged monobasic primary amines, two amino acids, and ethylenediamine. Series of solutions of constant stoichiometric buffer ratio were used; buffer concentrations were usually varied by a factor of 5, and four to five solutions were used to make up a series. The data are summarized in Tables S2 and S3.[14]

Adjustments for nonconstancy of hydroxide ion concentrations along a series of buffer solutions were made wherever necessary as described above for the detritiation of chloroform. The hydroxide ion catalytic coefficient k_{HO^-} = 0.355 M^{-1} s^{-1} [16] was used for this purpose. Concentrations of solution species were calculated using literature pK_a's for the monofunctional primary amines and activity coefficients for the amine conjugate acids calculated by the Debye–Hückel equation with an ion-size parameter of 6 Å.[17] For the amino acids, glycine, and β-alanine, an activity coefficient function determined in the measurement of the pK_a of glycine[18] was used for both. In the case of ethylenediamine, concentration dissociation constants for the first and second ionizations of the diprotonated base, pQ_1 = 7.106 and pQ_2 = 9.958 at μ = 0.10 M, were obtained by interpolating published values.[19] Catalysis by both the free amine, B, and its monoprotonated conjugate acid, BH^+, was taken into account for solutions of this amine by fitting the data to the rate law of eq 3 in the form of eq 4, in which $\gamma = [B]/[BH^+]$.

$$k_{obsd} = k_{HO^-}[HO^-] + k_B[B] + k_{BH^+}[BH^+] \quad (3)$$

$$k_{obsd} = k_{HO^-}[HO^-] + (k_B\gamma + k_{BH^+})[BH^+] \quad (4)$$

Experiments were performed in two series of buffer solutions with different values of γ (1.0 and 0.0067), and the coefficient of $[BH^+]$ obtained by fitting the data to eq 4 was then separated into k_B and k_{BH^+} by its dependence upon γ. In the more basic of these buffer solution series, hydrolysis of B produced a slight variation in γ as the buffer concentration was changed. This was compensated for by adjusting k_{obsd} to values it would have had at constant γ. A knowledge of k_B was required for this purpose, and an iterative calculation was therefore performed, using as the first guess a value obtained by ignoring the variation in γ; because the adjustments were small, one iteration proved to be sufficient to give self-consistent results.

In some of the less basic solutions investigated, the ionization of 2-nitropropane did not go to completion but rather reached an equilibrium state in which significant amounts of un-ionized nitroalkane were present. This was taken into account by using a rate law in these cases which expresses observed first-order specific rates of appearance of the nitronate ion as sums of forward and reverse rate constants, e.g., by using eq 5 in place of eq 1.

$$k_{obsd} = k^f_{HO^-}[HO^-] + k^r_0 + k^f_B[B] + k^r_{BH}[BH^+] \quad (5)$$

In this expression the superscript "f" denotes forward rates constants and the superscript "r" denotes reverse rate constants; k^r_0 is the rate constant for the "uncatalyzed" portion of the reverse process, i.e., for reprotonation of the nitramide ion by solvent water (eq 6). These reverse rate constants can be related to forward

$$(CH_3)_2CHNO_2 + HO^- \underset{k^r_0}{\overset{k^f_{HO^-}}{\rightleftharpoons}} (CH_3)_2CNO_2^- + H_2O \quad (6)$$

rate constants through known equilibrium constants for the overall reaction, and the concentrations of the acidic species participating in the reverse reactions can be related to concentrations of the basic species involved in the forward reaction through the buffer ratio R (=[BH$^+$]/[B]). These manipulations produce the expression given as eq 7, which is eq 1 modified by a correction term

$$k_{obsd} = (k^f_{HO}[HO^-] + k^f_B[B])\{1 + RQ(BH^+)/Q(SH)\} \quad (7)$$

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Table II. General Base Catalytic Coefficients for the Ionization of 2-Nitropropane in Aqueous Solution at 25 °C[a]

catalyst	pK(BH$^+$)	$10^4 k_B$, M^{-1} s^{-1}
$(CH_2OH)_3CNH_2$	8.07[b]	3.45[c]
$(CH_2OH)_2C(CH_3)NH_2$	8.80[d]	11.5
$CH_2OHCH_2NH_2$	9.50[e]	23.4
$CH_3(CH_2)_3NH_2$	10.64[f]	119
$(CH_3)_3CNH_2$	10.69[g]	158
$^-CO_2CH_2NH_2$	9.78[h]	16.9
$^-CO_2(CH_2)_2NH_2$	10.24[i]	34.9
$NH_2(CH_2)_2NH_2$	9.93[j]	55.8
$^+NH_3(CH_2)_2NH_2$	6.85[j]	2.29
$(CH_3)_3N^+(CH_2)_2NH_2$	6.59[k]	1.47
$(CH_3)_3N^+(CH_2)_3NH_2$	8.35[l]	23.2
$(CH_3)_3N^+(CH_2)_4NH_2$	9.35[l]	47.2
$(CH_3)_3N^+(CH_2)_5NH_2$	9.83[l]	79.2

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$\{1 + RQ(BH^+)/Q(SH)\}$. Corrections were made using concentration dissociation constants for the buffer conjugate acids at μ = 0.10 M, Q(BH$^+$), obtained as described above; the concentration dissociation constant of the substrate at μ = 0.10 M, Q(SH), was taken as pQ(SH) = 7.475.[16] These corrections were significant for only 4 of the 13 buffer solution series studied, and even for these 4 they were quite small, the largest being only 4.5%.

The catalytic coefficients for the ionization of 2-nitropropane produced in this way are summarized in Table II. These analyses also provided quantities from which hydroxide ion catalytic coefficients could be calculated; the fact that the average of these 13 values, k_{HO^-} = 0.387 M^{-1} s^{-1}, is in good agreement with the result obtained by direct measurement in sodium hydroxide solutions, k_{HO^-} = 0.355 M^{-1} s^{-1},[16] attests to the general validity of the data reduction methods employed.

Brønsted Relation. The catalytic coefficients for the ionization of 2-nitropropane by the four primary amines determined here plus the literature value for another, tris(hydroxymethyl)-methylamine,[16] gave a good Brønsted correlation: log (k_B/q) = $-8.656 \pm 0.279 + (0.608 \pm 0.028)$ log (qK_a/p); this is shown in Figure 1. Statistical factors p = 3 and q = 1 were used in the construction of this correlation. A positive deviation from this line of 160% is shown by ethylenediamine, and larger deviations in the same direction are given by the positively charged catalysts monoprotonated ethylenediamine and the four ω-trimethylammonioalkylamines; these are listed in Table III. The negatively charged aminocarboxylate anions, on the other hand, give negative deviations, a factor of 2.6 for glycinate and a factor of 2.3 for β-alaninate.

The catalytic coefficients determined here for the detritiation of chloroform by ω-trimethylammonioalkylamines also gave positive deviations from a previously constructed Brønsted correlation based upon primary amines;[9] these are listed in Table III.

Discussion

Both of the reactions investigated here are proton-transfer processes which give carbanion products, and in both cases introduction of charged substituents into the proton acceptor produced effects consistent both in direction and in relative magnitude with electrostatic interaction between these substituents and the negative charge generated on the substrate. Positively charged substituents, for example, would be expected to give an energy-lowering interaction which would stabilize the transition states of these reactions, and that should lead to rate acceleration, as

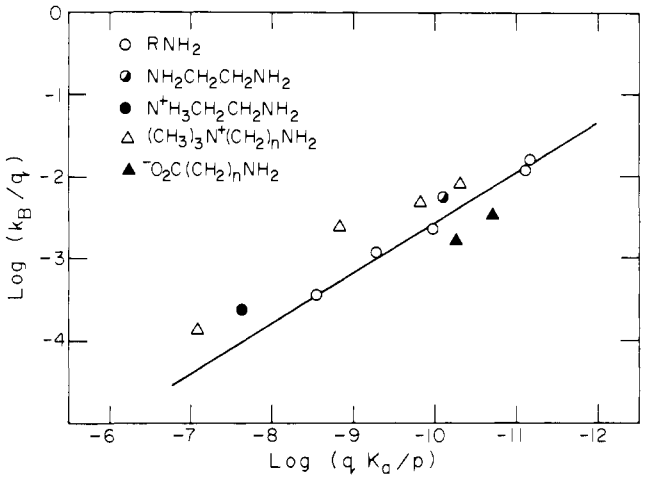


Figure 1. Brønsted plot for the ionization of 2-nitropropane.

Table III. Deviations of Catalytic Coefficients for Positively Charged Amines from Brønsted Correlations

	deviation	
catalyst	chloroform exchange[a]	nitropropane ionization[b]
$(CH_3)_3N^+(CH_2)_2NH_2$		3.4x
$(CH_3)_3N^+(CH_2)_3NH_2$	73x	4.4x
$(CH_3)_3N^+(CH_2)_4NH_2$	46x	2.2x
$(CH_3)_3N^+(CH_2)_5NH_2$	45x	1.9x
$^+NH_3(CH_2)_2NH_2$		2.4x

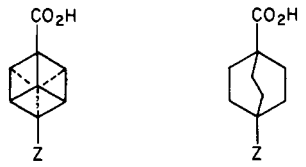
[a] Deviation from the Brønsted relation log $(k_B/q) = -16.468 + 1.117$ log (qK_a/p). [b] Deviation from the Brønsted relation log $(k_B/q) = -8.656 + 0.608$ log (qK_a/p).

observed. Negatively charged substituents, on the other hand, would give an energy-raising interaction leading to rate retardations, also as observed. These effects, moreover, should be greater for chloroform detritiation than for 2-nitropropane ionization, inasmuch as the carbanionic charge is already fully formed in the rate-determining transition state of the chloroform reaction but is still being generated in the rate-determining transition state of the 2-nitropropane process: in the latter reaction proton transfer is the slow step, but in chloroform detritiation proton transfer is rapid and reversible and separation of the proton transfer products is slow.[9] That, plus the fact that the charge is concentrated on a single (carbon) atom in the trichloromethyl carbanion but is delocalized over a number of atoms in the 2-nitropropanate ion would lead to a much stronger interaction in the chloroform than in the nitropropane system; comparison of the two groups of effects detailed in Table III shows that such a difference is, in fact, observed.

The data for 2-nitropropane (Table III) show that the accelerative effect of the positive charge for the ω-trimethylammonioalkylamine series peaks with the amine having three carbon atoms between the positive charge and the basic center; the effect is smaller when two or four carbon atoms separate these groups. This dependence on chain length is incompatible with an inductive mechanism for transmission of the present polar effects, but it is consistent with a direct or through-space field interaction. Inductive effects are transmitted through bonds and should fall off in a regular manner as the number of bonds between the interacting groups is increased. Field effects, on the other hand, obey Coulomb's law and are inversely proportional to the actual distance separating the groups involved. Inspection of models shows that the positive end of an ω-trimethylammonioalkylamine cannot approach a substrate from which the amine end is abstracting a proton quite as closely when the alkyl chain is two carbon atoms long as when it is three or more carbons long; the energy of interaction should therefore reach a maximum at three carbons and remain more or less constant after that, but unfavorable entropy changes will reduce the overall effect (on free

energy) in the case of longer chains.

This choice of a field mechanism for the electrostatic interaction in the present situation is consistent with current opinion on the nature of polar effects.[20] An important part of the evidence bearing on this matter comes from a comparison of substituent effects on the ionization of cubane- and bicyclo[2.2.2]octanecarboxylic acids.[21] When the substituents are situated in the 4 positions of these acids, as in **1** and **2**, the distance between them



1 2

and the carboxylic acid function is exactly the same (to within 0.1 Å) in the two series. In **1**, however, there are six (overlapping) three-bond pathways between Z and CO_2H, whereas in **2** there are only three such pathways. Field effects in the two series should therefore be the same, but inductive effects in **1** should be twice as strong as in **2**. It is found experimentally that substituent effects are actually the same in the two series, and this is taken as indication that the interaction occurs by a field rather than by an inductive mechanism.

This argument, however, loses some of its force if, instead of counting the number of equivalent bond pathways between the substituents in **1** and **2**, one regards the bonds as small capacitors of equal size, C. Application of the laws of electrical conduction then gives an equivalent capacitance of 6C/17 to an array with the shape of **1**, and an equivalent capacitance of 6C/18 to an array with the shape of **2**. The ratio of these results differs from unity by only 1 part in 18 or 6%, which is within experimental uncertainty the same as the unit ratio of substituent effects found in the two series of carboxylic acids **1** and **2**. With this interpretation of these effects, therefore, these data are just as consistent with the inductive as with the field interpretation of the polar effect.

The largest electrostatic effect found in the present study is the factor of 73 obtained in the detritiation of chloroform catalyzed by 3-trimethylammoniopropylamine. This amounts to a reduction in free energy of activation of 2.5 kcal mol^{-1}. If 5.0 Å is taken as the distance separating the positively charged nitrogen and negatively charged carbon atoms in the transition state of this reaction, application of Coulomb's law gives $\epsilon = 26$ as the effective dielectric constant of the medium surrounding these charges which is required to produce this energy reduction; this is not an unreasonable value.

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Registry No. $(CH_3)_3N^+(CH_2)_3NH_2 \cdot Br^-$, 28841-49-8; $(CH_3)_3N^+(CH_2)_4NH_2 \cdot Br^-$, 30834-99-2; $(CH_3)_3N^+(CH_2)_5NH_2 \cdot Br^-$, 30835-02-0; $(CH_2OH)_3CNH_2$, 77-86-1; $(CH_2OH)_2C(CH_3)NH_2$, 115-69-5; CH_2OH-CH_2NH_2, 141-43-5; $CH_3(CH_2)_3NH_2$, 109-73-9; $(CH_3)_3CNH_2$, 75-64-9; $O_2CCH_2NH_2$, 23297-34-9; $O_2C(CH_2)_2NH_2$, 23297-31-6; $NH_2(CH_2)_2N$-H_2, 107-15-3; $NH_2(CH_2)_2NH_2 \cdot HCl$, 18299-54-2; $(CH_3)_3N^+(CH_2)_2NH_2 \cdot Br^-$, 53759-29-8; $(CH_3)_3N^+(CH_2)_3NH_2 \cdot Br^- \cdot HBr$, 33968-64-8; $(CH_3)_3N^+(CH_2)_4NH_2 \cdot Br^- \cdot HBr$, 33968-65-9; $(CH_3)_3N^+(CH_2)_5NH_2 \cdot Br^- \cdot HBr$, 33968-66-0; chloroform, 67-66-3; hydrogen, 1333-74-0; 2-nitropropane, 79-46-9.

Supplementary Material Available: Tables S1-S3 of rate constants (6 pages). Ordering information is given on current masthead page.

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Alkylation of Amino Acids without Loss of the Optical Activity: Preparation of α-Substituted Proline Derivatives. A Case of Self-Reproduction of Chirality[1,2]

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Abstract: Proline is condensed with pivalaldehyde to give a single stereoisomer of 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**2**). This is deprotonated with LDA to give a chiral, nonracemic enolate (**3**), which combines with electrophiles such as D^+ (to **4**), the more reactive alkylating reagents (to **5**, **8-12**), and carbonyl derivatives (to **7**, **15-26**, **28-30**). It can also be phenylated with (benzene)(tricarbonyl)chromium (to **13**) and thiolated with diphenyl disulfide (**14**). The products arise from Re attack of the electrophiles on the enolate carbon, i.e., with relative topicity *lk*, as shown by chemical correlation in two cases (**4**, **6**) and by an X-ray crystal structure analysis of the benzaldehyde adduct (**7**). With the addition of the enolate **3** to aldehydes and to unsymmetrical ketones some Michael-additions (**24**, **26**, **27**) occur with high enantioface differentiation. Cleavage of the products from enolate **3** furnishes α-alkylated proline derivatives (**4**, **6**, **31**, **33-39**). The overall process is an electrophilic substitution of the α-proton of proline with retention of configuration at the asymmetric carbon atom. Since no external chiral auxiliary is necessary to achieve this transformation without loss of enantiomeric purity, it is called a self-reproduction of chirality (Scheme I).

Most amino acids are inexpensive and available in both enantiomeric forms. They can be valuable starting materials[5,6] for the synthesis of other enantiomerically pure products.[7,8] Thus, any new type of transformation of amino acids occurring without

(1) For a preliminary account, see: Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704.

(2) Following a different concept, an aspartate derivative was α-alkylated to give products of ca. 65% ee: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.

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