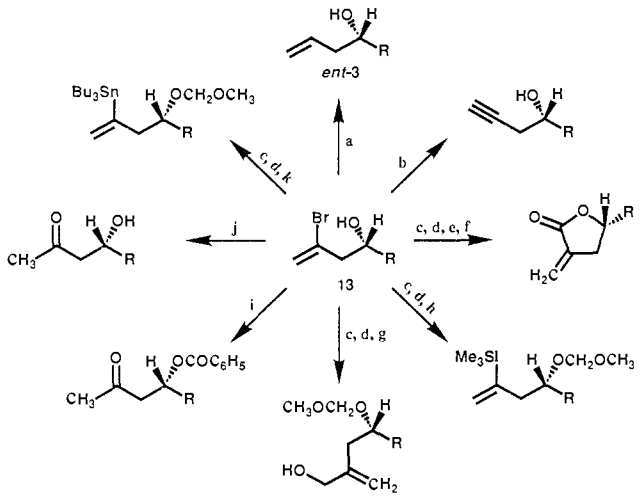
Table II. Reaction of Aldehydes with Chiral 2-Haloallyl Boranes **11** and **12** (*S,S*)-Forms, at −78 °C in CH_2Cl_2 To Give Alcohols **13** and **14**, Respectively

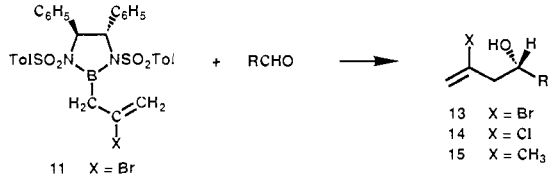
R of RCHO	reagent	% yield of **13** or **14**	% ee of **13** or **14**	abs config
C_6H_5	**11**	73	79	*S*
C_6H_5	**12**	79	84	*S*
(*E*)-C_6H_5CH=CH	**11**	79	87	*S*
(*E*)-C_6H_5CH=CH	**12**	84	92	*S*
c-C_6H_{11}	**11**	75	94	*S*
c-C_6H_{11}	**12**	81	99	*S*
n-C_5H_{11}	**11**	71	94	*R*
n-C_5H_{11}	**12**	77	99	*R*

Scheme I[a]



[a] Transformations of **13**, R = cyclohexyl, reagents and conditions: (a) 3.3 equiv of *t*-BuLi, Et_2O, −78 °C, 2 h; H_2O, 75%; (b) 2.5 equiv of *t*-BuOK, THF, 0 °C, 1 h, 91%; (c) CH_3OCH_2Cl, *i*-Pr_2NEt, CH_2Cl_2, 23 °C, 10 h, 95%; (d) 2.1 equiv of *t*-BuLi, THF, −78 °C, 2 h; (e) CO_2, THF, 0 °C, 1 h, 73%; (f) 4 N HCl, 15:1 H_2O-THF, 60 °C, 2 h, 94%; (g) CH_2O, THF, −10 °C, 1 h, 95%; (h) 2 equiv of Me_3SiCl, THF, 0 °C, 1 h, 87%; (i) C_6H_5COCl, pyridine, 23 °C, 1 h, 95%; 2 equiv of $Hg(OCOCF_3)_2$, CH_3NO_2, 23 °C, 1 h; pH = 1, H_2O-THF, 1 h, 89%; (j) 2 equiv of $Hg(OCOCF_3)_2$, CH_3NO_2, 23 °C, 1 h; 10 equiv of K_2CO_3, H_2O-THF, 23 °C, 2.5 h, 91%; (k) (*n*-Bu)$_3$SnOTf, THF, −78 °C, 1 h, 82%.

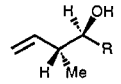
The enantioselective addition of substituted allyl groups to aldehydes at −78 °C has been demonstrated in a number of cases. The 2-haloallyl reagents **11** and **12** were made by reaction of the (*S,S*)-enantiomer of **1** with the corresponding 2-haloallyltri-*n*-butyltin[8] at 0 °C initially and then 23 °C for 20 h. Table II summarizes the results. The absolute configuration of each product was established by dehalogenation to the corresponding allyl carbinols (*ent*-**3**) (reaction with 3.3 equiv of *tert*-butyllithium in ether at −78 °C for 2 h followed by quenching with aqueous acid) and measurement of optical rotation; ee values were determined by 500 MHz ^{1}H NMR analysis of the MTPA esters. In each case the favored transition state for the reaction of aldehydes with **11** or **12** is analogous to **4a**/**4b** although it is apparent that the degree of enantioselectivity diminishes somewhat for the series of chiral borane reagents in the order allyl (**2**) > 2-chloroallyl (**12**) > 2-bromoallyl (**11**).



(7) Determined by 500 MHz ^{1}H NMR analysis of the reaction products.

The synthetic utility of the 2-haloallyl carbinols **13** and **14** is clear from a number of transformations which have been demonstrated for both. Scheme I summarizes several of these conversions for the specific case of bromide **13**, R = cyclohexyl; they proceed as well with the corresponding chloride **14**, R = cyclohexyl. The combination of outstanding and predictable enantioselectivity and the versatility of the adducts **13** and **14** suggests that this methodology will be widely useful.

Although the scope of the new enantioselective chemistry described herein is still under investigation, the general pattern of results obtained thus far encourages optimism. The methallyl analogue of **11** or **12**, which is not expected to be as favorable with regard to enantioselectivity, still affords with hexanal adduct **15**, X = CH_3, R = *n*-C_5H_{11} in 88% ee (79% isolated yield). The



16 R = C_6H_5, *E*-C_6H_5CH=CH, cyclo-C_6H_{11}, *n*-C_5H_{11}

trans-crotyl analogue of **2** reacts in THF solution at −78 °C with the four aldehydes listed in Tables I and II to form mainly the anti adducts **16** in 74–82% yield with ee's in the range 91–95%. We believe that the enantioselective allylation of aldehydes, a process of clear synthetic potential, has advanced to a new level of practicality and predictability as a result of the present investigation because of the efficacy and simplicity of the reaction and the ready availability and efficient recovery of the chiral controller.[9]

Supplementary Material Available: An experimental procedure is given for the preparation of **1**, **2**, and **3**, R = C_6H_5 (2 pages). Ordering information is given on any current masthead page.

(8) The preparation of 2-bromoallyltri-*n*-butyltin was accomplished by the following sequence: (1) mesylation of 2-bromo-2-propen-1-ol with 1.1 equiv of methanesulfonyl chloride and 1.5 equiv of triethylamine in methylene chloride at 0 °C for 1 h (91% after distillation); and (2) reaction of this mesylate at −78 °C to 0 °C for 2.5 h with a reagent made from tri-*n*-butyltinlithium (Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481) and 1.0 equiv of cuprous bromide–dimethyl sulfide complex in THF at −78 °C for 2 h to form 2-bromoallyltri-*n*-butyltin in 89% yield. The corresponding 2-chloroallyltin reagent was prepared in the same way.

(9) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Reactive Dissolution of NO_2 in Aqueous $^{15}NO_2^-$: The First Experimental Determination of a Main-Group Electron-Exchange Rate in Solution

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Received March 13, 1989

The rates of electron self-exchange for redox couples of coordination complexes and organic compounds have often been determined directly by using isotope tracer methods and spectroscopic line-broadening methods and indirectly by measuring rates of electron transfer between related complexes and applying the cross relationship of Marcus theory.[1,2] For main-group compounds, however, only indirect measurements have been used. In this way we now have estimates of the self-exchange rate constants for the following systems in aqueous solution: NO_2/NO_2^-,[3] ClO_2/ClO_2^-,[4]

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Table I. Rate Data for $^{15}NO_2^-$ Solutions Bubbled with NO_2[a]

bubbling time	$[^{15}NO_2^-]$, mM	$d[NO_3^-]/dt$	$d[^{15}NO_3^-]/dt$	$k_1^{1/2}/k_2$
40	1.2	1.3×10^{-7}	1.2×10^{-8}	16
40	1.1	1.3×10^{-7}	1.1×10^{-8}	16
60	1.3	1.3×10^{-7}	1.2×10^{-8}	17
80	1.1	1.7×10^{-7}	1.3×10^{-8}	16
80	1.1	1.8×10^{-7}	1.4×10^{-8}	15
22[b]	1.1	3.2×10^{-7}	2.5×10^{-8}	11
80[c]	1.1	1.4×10^{-7}	1.6×10^{-8}	11
310[d]	1.0	2.2×10^{-8}	4.9×10^{-9}	11
315[d]	1.1	2.3×10^{-8}	5.9×10^{-9}	10
70	0.22	2.0×10^{-7}	6.0×10^{-9}	8
90	3.1	2.2×10^{-7}	3.3×10^{-8}	18
80	3.4	1.3×10^{-7}	2.2×10^{-8}	22

[a] Bubbling time in minutes, rates in M s^{-1}. All reactions performed at 25 °C, in 4 mM NaOH, with 100 ppm NO_2, and a gas flow rate of ≈0.8 L min^{-1}. $k_1^{1/2}/k_2 = [^{15}NO_2^-](R_1 - 2R_2)^{1/2}/(2R_2)$. [b] Gas flow rate ≈ 2.2 L min^{-1}. [c] Unrecrystallized $Na^{15}NO_2$ used. [d] 17 ppm NO_2.

SO_2/SO_2^-,[5] N_3/N_3^-,[6] O_2/O_2^-,[7] SO_3^-/SO_3^{2-},[8] I_2/I_2^-,[9] Br_2/Br_2^-,[10] Cl_2/Cl_2^-,[10] I/I^-,[11] $ON(SO_3)_2^{2-}/ON(SO_3)_2^{3-}$,[12] HO_2/HO_2^-,[13] and CO_2/CO_2^-.[14] The present work describes the first experimental measurement of electron self-exchange for a main-group system in aqueous solution, namely the NO_2/NO_2^- system.

Our method uses competition kinetics between the following reactions

$$2NO_{2(aq)} + H_2O \rightarrow NO_2^- + NO_3^- + 2H^+ \qquad k_1 \quad (1)$$

$$NO_{2(aq)} + {}^{15}NO_2^- \rightarrow NO_2^- + {}^{15}NO_2 \qquad k_2 \quad (2)$$

It owes much to a prior study of NO_2 hydrolysis,[15] in which ^{18}O tracer experiments provided qualitative evidence that electron exchange occurs.

$Na^{15}NO_2$ (99% ^{15}N, CIL) as supplied contained about 7% NO_3^-. This level of contamination was reduced to 1.7% by recrystallization from 71% v/v ethanol/water. Reactant solutions were prepared with this $Na^{15}NO_2$ and sufficient $NaOH \cdot H_2O$ ("Ultrapure", Alfa) to ensure that the solutions remained alkaline at all times. Each 70-mL sample was divided into halves. One half was added to the reactor, a 25 °C water-jacketed 2 × 50 cm vertical tube having a sintered-glass frit at the bottom. A dilute mixture of NO_2 in N_2 was allowed to flow vigorously through the frit into the solution, and the solution was then analyzed for NO_3^- by ion chromatography (Wescan Ion Analyzer, conductivity detection). An aliquot of natural abundance $NaNO_3$ (as internal standard) was added to the second half. Both halves were analyzed according to the method of Ligon and Dorn,[16] by using negative-ion FAB mass spectrometry on a VG-70EHF instrument. Ratios of $^{15}NO_3^-/^{14}NO_3^-$ were obtained by alternately focusing on the two ion signals. The isotope ratio for the second half showed the amount of $^{15}NO_3^-$ introduced with the $^{15}NO_2^-$. The amount of NO_3^- generated by bubbling was calculated as the amount determined by ion-chromatography minus the amount introduced with the $^{15}NO_2^-$. The amount of $^{15}NO_3^-$ generated by bubbling was determined from the isotope ratio, the total NO_3^- generated, and the amount introduced with the $^{15}NO_2^-$ (^{15}N deriving from natural abundance in the NO_2 was neglected). The rates, R_1 as $d[NO_3^-]/dt$ and R_2 as $d[^{15}NO_3^-]/dt$, were calculated by dividing the amounts generated by the bubbling times.

From reactions 1 and 2 above, we have $R_1 = k_1[^{14}NO_{2(aq)}]_{ss}^2 + k_1[^{14}NO_{2(aq)}]_{ss}[^{15}NO_{2(aq)}]_{ss}$, and $2R_2 = k_1[^{14}NO_{2(aq)}]_{ss} \cdot [^{15}NO_{2(aq)}]_{ss}$ (neglecting the self reaction of $^{15}NO_{2(aq)}$ and kinetic isotope effects), where the subscript ss designates the steady-state concentration. Thus $R_1 - 2R_2 = k_1[^{14}NO_{2(aq)}]_{ss}^2$, or $[^{14}NO_{2(aq)}]_{ss} = \{(R_1 - 2R_2)/k_1\}^{1/2}$. Moreover the mechanism implies that $2R_2 = k_2[^{14}NO_{2(aq)}]_{ss}[^{15}NO_2^-]$ (as long as $[^{14}NO_2^-]$ is low), so we obtain the final expression $k_1^{1/2}/k_2 = [^{15}NO_2^-](R_1 - 2R_2)^{1/2}/(2R_2)$. The compounded random errors lead to an estimated uncertainty in this final ratio of a factor of 2, which is close to the observed fluctuations seen in Table I.

There are various possible sources of systematic error. (1) As $^{14}NO_2^-$ accumulates, exchange will diminish $[^{15}NO_{2(aq)}]_{ss}$; correction for this effect is difficult, but it is not expected to be significant except possibly in the experiments at low NO_2 partial pressures. (2) A central assumption is that the distribution of NO_2 is homogeneous in solution, i.e., that its hydrolysis does not occur immediately in the regions close to the bubbles. This problem has been examined for NO_2/N_2 mixtures.[17] Our reactor has been designed to generate conditions of homogeneous distribution, and experiments with variable flow rates and variable NO_2 partial pressures show that the assumption is good. However, the mild dependence of $k_1^{1/2}/k_2$ on $[^{15}NO_2^-]$ may reflect some degree of breakdown in the assumption of homogeneous distribution. (3) Another assumption is that $[NO_{2(aq)}]_{ss}$ is constant during the experiment. NO_2 is very reactive, for example, oxidizing uric acid (pH 7.5, phosphate buffer) with great efficiency in our reactor, so impurities may scavenge NO_2 during the initial period of bubbling. The experiments with variable periods of bubbling show that this is not a major problem. (4) Carbonate in the sample may perturb the isotopic ratio; however, blank runs have shown that this too is not a problem. (5) Direct exchange between NO_2^- and NO_3^- has been shown to occur only in acidic media;[18] we have found that our samples are isotopically stable for periods of two months.

Another potential complication is that the reaction

$$^{14}NO_{2(aq)} + {}^{15}NO_2^- \rightleftharpoons {}^{15}NO_3^- + {}^{14}NO_{(aq)} \qquad k_3, k_{-3}, K_3 \quad (3)$$

is our source of $^{15}NO_3^-$. If this were to occur, its reverse would lead to the reaction

$$2NO_{(aq)} + NO_3^- + 2OH^- \rightarrow 3NO_2^- + H_2O \qquad K_4 \quad (4)$$

with the rate-limiting step being k_{-3}. Solutions containing 0.5 M $NaNO_3$ and 4 mM NaOH, when prepared anaerobically and then saturated with NO, after 5.7 days yield <0.5 mM NO_2^- (Wescan, amperometry). From standard thermochemical data[19] the value of K_4 is 1.1×10^{20} M^{-2}, and thus reaction 4 should proceed to completion. Since $[NO_{(aq)}]$ is 1.9 mM,[20] the upper limit for k_{-3} is 3.6×10^{-7} M^{-1} s^{-1}, which is consistent with prior studies.[21] Established thermochemical data[19,22,23] give a value of 4.7×10^5 for K_3, which then yields an upper limit of 0.17 M^{-1} s^{-1} for k_3. Since the electron-exchange rate constant derived below exceeds this value considerably, it can be concluded that the isotopic incorporation occurs by electron transfer rather than atom transfer.

From the results in Table I the ratio $k_1^{1/2}/k_2$ has the value 14 ± 4 $M^{1/2}$ $s^{1/2}$. The literature value of k_1 is 6.5×10^7 M^{-1} s^{-1}, but it has an uncertainty of a factor of 2.[20] Thus a value of $k_2 = 580$ M^{-1} s^{-1} (within a factor of 3) is obtained for the self-exchange rate constant for the $NO_{2(aq)}/NO_2^-$ couple. The value of k_2 may

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be contrasted with the value of 2×10^{-2} M^{-1} s^{-1} obtained from studies using the Marcus cross-relationship.[3] Apparently the direct self-exchange reaction occurs by a pathway that is more efficient than the outer-sphere mechanism implicit in Marcus theory. Presumably the transition state has substantial bonding between $NO_{2(aq)}$ and NO_2^-. As noted in our study of the reaction between ClO_2 and NO_2^-, strong overlap in the transition state may be a general property of main-group electron-transfer reactions.[24]

Acknowledgment. This research was supported by the NSF, Grant CHE-8716929. Dr R. Smith is thanked for his contributions with the uric acid experiments.

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Nonstereospecific Proton Removal in the Enzymatic Formation of Orsellinic Acid from Chiral Malonate

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Received March 13, 1989

The biosynthesis of orsellinic acid (**1**, Scheme I) involves the assembly of one molecule of acetyl-CoA and three molecules of malonyl-CoA into a tetraketide which then cyclizes, connecting carbons 2 and 7, and enolizes to the final structure. The enzyme catalyzing this process has been isolated from *Penicillium madriti* and some of its properties have been reported.[1]

Following the elucidation of the steric course of fatty acid formation by Cornforth and his colleagues,[2] various aspects of the stereochemistry of polyketide biosynthesis have been studied in different systems.[3] However, except in a few cases, e.g., 6-methylsalicylic acid and rubrofusarin formation,[4] no information has been obtained on the stereospecificity of hydrogen removal from the polyketide precursor, by enolization or dehydration, during the transformation into aromatic products. The recent synthesis of the two enantiomers of chirally labeled malonate[5] and the availability of orsellinic acid synthase[6] enabled us to examine this question.

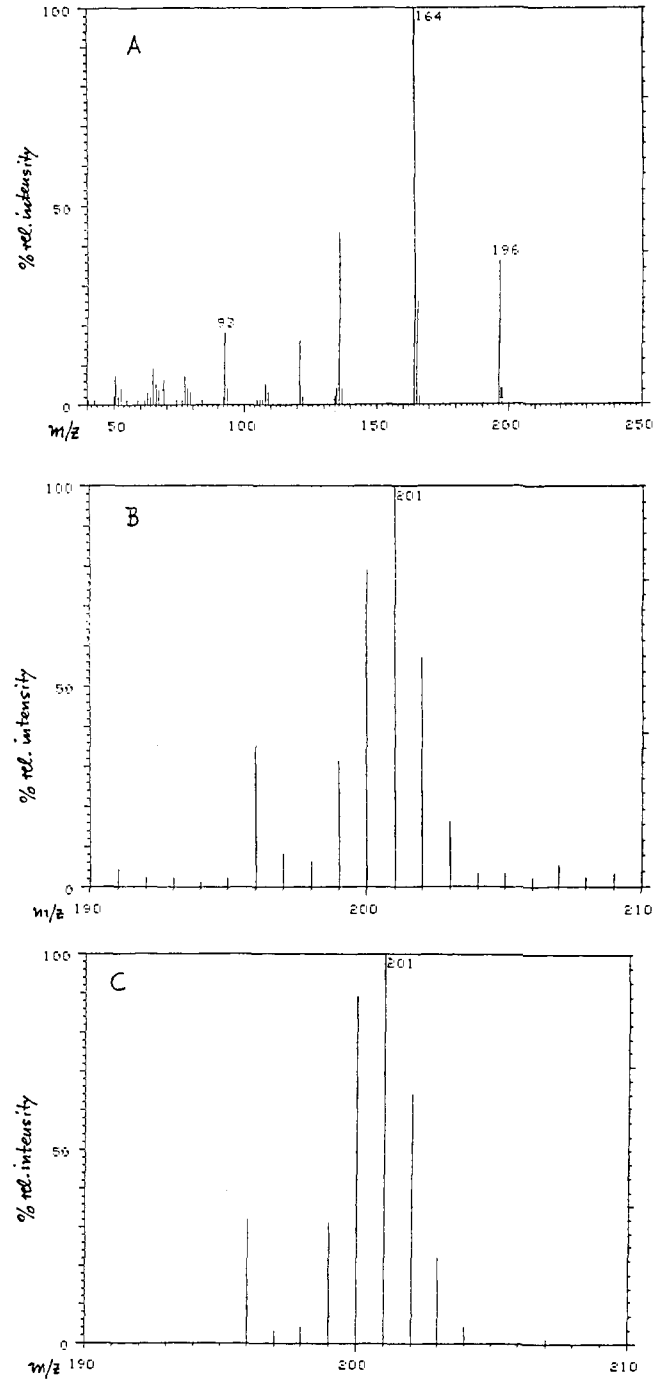

Figure 1. A: GC-mass spectrum of unlabeled dimethyl orsellinate; B, C: molecular ion region of the mass spectra of dimethyl orsellinate from (A) *R*-[1,2-$^{13}C_2$,$^2H_1$]malonate and (B) *S*-[1,2-$^{13}C_2$,$^2H_1$]malonate.

S- and *R*-[1,2-$^{13}C_2$,2-$^2H_1$]malonate were prepared from (2*S*,3*R*)-[2,3-$^{13}C_2$,3-$^2H_1$]malate and (2*S*,3*S*)-[2,3-$^{13}C_2$,2,3-$^2H_2$]malate, respectively, by oxidation with an equimolar amount of $KMnO_4$ at pH 9.5 for 15 or 40 min,[5a] respectively, at room temperature. Without isolation, these samples were used directly in enzyme incubations containing 6 milliunits of orsellinic acid synthase from *Penicillium cyclopium*[6] and 3.75 units[7] of succi-

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