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# Rates and Mechanisms of Reaction of Nitrogen Dioxide with Alkenes in Solution

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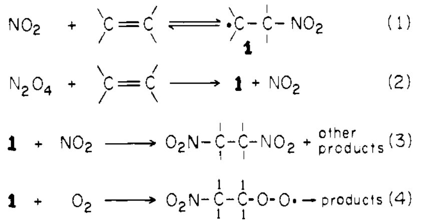
**Abstract:** Rates of reaction of alkenes with nitrogen dioxide have been determined in aprotic solvents. The reactions are first order in the alkene. At high concentrations of $NO_2/N_2O_4$, a kinetic dependence that is first order in $N_2O_4$ or second order in $NO_2$ is observed. As the concentration of $NO_2/N_2O_4$ approaches zero, the kinetic order in $NO_2$ approaches unity. These data indicate the presence of at least two distinct reaction pathways: one involving the diamagnetic dimer, $N_2O_4$, in an addition mechanism and the other(s) involving the paramagnetic monomer $NO_2$. The reaction of the monomer proceeds, at least in part, through abstraction of allylic hydrogen atoms.

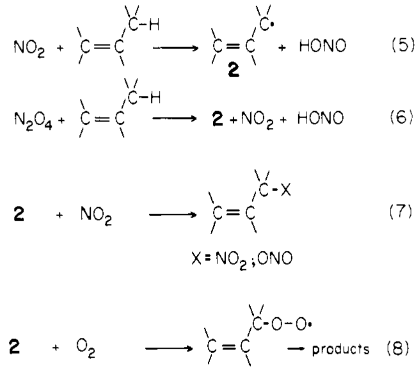
The reaction of nitrogen dioxide with alkenes is worthy of study, not only from a mechanistic viewpoint but also because $NO_2$ is a critical environmental pollutant. The reaction of $NO_2$ with olefins in the atmosphere produces a variety of hazardous materials, and this aspect of $NO_2$ chemistry has been studied in some depth by several authors.[1-5] In addition, gaseous $NO_2$ is inhaled when polluted air is breathed and may react with a variety of biological substrates in the lung, including alkenes such as polyunsaturated fatty acids (PUFA).[6-9] Unlike the atmospheric reactions of $NO_2$, reactions in the lung could take place either at the gas-liquid interface in the lung or in a condensed phase. Earlier work from these laboratories has modeled reactions at the gas-liquid interface.[6,7] Other authors have carried out mechanistic studies of alkenes with $NO_2$ in solution,[10-14] which may serve as a model for reactions in the lung.

A comparison of our earlier work to the gas-phase studies or to studies in solution reveals some interesting discrepancies. Most notably, while we have reported the formation of two different types of products, addition products and allylic substitution products,[6] other authors have observed only addition products. Furthermore, we find that varying the concentration of $NO_2$ changes the addition/substitution ratio; as the $NO_2$ concentration is decreased, the relative amounts of substitution products increase. These observations were first made with cyclohexene as the substrate,[6,7] and we have recently verified them using methyl oleate as the substrate.[15]

Scheme I



Scheme II



In principle, either $NO_2$ or its dimer, $N_2O_4$, may be involved in any of these reactions. These are kinetically and mechanistically distinct possibilities, but they are often difficult to distinguish experimentally. For convenience we will use the term N(IV) to represent the quantity $[NO_2 + 2N_2O_4]$, which is the total concentration or nitrogen oxide species formally in the +4 oxidation state. Note that this term does not indicate whether the monomer or the dimer, or both, is the reactive species.

To explain the product studies cited above,[6] it was proposed that the reaction of N(IV) with alkenes occurs by two mechanisms, each of which might involve $NO_2$, $N_2O_4$, or both. These pathways are summarized in Schemes I and II.[6] Scheme I represents the radical addition mechanism proposed by other authors.[10-14] In the gas phase, particularly at the low N(IV) concentrations used experimentally in the gas-phase studies,[1-5] the $NO_2/N_2O_4$ equilibrium favors the monomer. With the exception of some early work,[16,17] the gas-phase reactions of N(IV) with alkenes are first order in $NO_2$.[1-5] The anomalous reports are for the reaction of N(IV) with ethylene and propylene at elevated temperatures with little or no dioxygen present,[16,17] reactions that were reported to be 1.8 order in $NO_2$ and 1.2 order in alkene. All the other gas-phase work was done in the presence of dioxygen, and under these conditions (and especially at the low N(IV) concentrations used), eq 4 is more important than eq 3 and dioxygen rather than N(IV) traps the $\beta$-nitroalkyl intermediate **1**. Therefore, the stoichiometry is near 1:1 for $NO_2$ and the alkene, and the kinetics

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can be expected to approach first order in $NO_2$.[4,5]

In solution, particularly at high N(IV) concentrations, the $NO_2/N_2O_4$ equilibrium constant favors the dimer, so eq 2, involving $N_2O_4$, might be the major pathway for the reaction; this reaction would be second order in $NO_2$. If N(IV) is present in concentrations much higher than dioxygen is, then eq 3 will predominate over eq 4, and the intermediate **1** will be trapped by N(IV). The products will be dinitro compounds and nitro nitrites, and the stoichiometry would be expected to be 2:1 N(IV) to alkene, as is observed experimentally.[6,7,10-14]

The second pathway, presented in Scheme II, involves hydrogen atom abstraction, a process that ultimately leads to the formation of allylic substitution products. While in principle the first step in this sequence could involve either $NO_2$ or $N_2O_4$, allylic substitution products are observed only at low N(IV) concentrations and, therefore, probably involve $NO_2$. Furthermore, $NO_2$ is a free radical, whereas $N_2O_4$ is diamagnetic, so H atom abstraction appears inherently more likely to involve $NO_2$. The hydrogen-abstraction pathway is expected to be first order in $NO_2$, since the first step (eq 5) should be rate limiting. The stoichiometry should be 2:1 in the absence of oxygen or in the presence of much more N(IV) than dioxygen, since $NO_2$ would be the trapping species (eq 8).

In the present work we examine the reactivity of N(IV) toward alkenes as a function of the N(IV) concentration for a better comparison of N(IV) reactions in solution to the gas-phase work.

## Experimental Section

**Materials.** The substrates used in this study were purchased from Aldrich. The materials used in the absolute rate measurements were distilled prior to use, with the exception of 2,5-dimethyl-2,4-hexadiene and norbornene, which were used as received. HPLC-grade solvents were used without further purification. Nitrogen dioxide, 99.5%, was purchased from Matheson.

**Stopped-Flow Kinetics.** Absolute rate data were collected with a Hitech stopped-flow spectrophotometer (Model SF-3L) interfaced to an On-Line Instrument Systems Model 3820 data system.[18] Equal volumes of a solution of the substrate and a solution of $NO_2$ were mixed, and the disappearance of $NO_2$ from the resulting solution was followed by monitoring the decrease in absorbance at 410 nm. The rates were calculated as described earlier[19] over a time course in which less than 10% of the $NO_2$ was consumed. For some runs the reactions were followed to completion with excess alkene, and rates were calculated at each point on the curve. (Note that traces of dissolved dioxygen would be depleted in the first small part of the reaction and may therefore be assumed to be absent.) The initial concentration of $NO_2$ was determined from the absorbance at 410 nm by using an extinction coefficient of 160 $M^{-1}\,cm^{-1}$.[19,20] The equilibrium constant at 30 °C, $[NO_2]^2/[N_2O_4] = 2.644 \times 10^{-4}$ M, was calculated from the thermochemical data of Redmond and Wayland.[21] Details of the data analysis are given in the Results. All of these data were collected in $CCl_4$ at 30 ± 0.1 °C.

**Relative Rate Measurements: High N(IV).** All relative rate experiments were begun at ambient temperature in a water bath. However, since some of the reactions were very exothermic, heat transfer to the bath was inefficient and the final temperatures were not the same for all runs. Relative rates at high $NO_2$ concentration were determined in the following manner: A solution of two substrates and an internal standard (either *n*-nonane or *n*-decane) in the appropriate solvent was prepared, such that the total concentration of solutes was 5–10%. A small volume (ca. 0.1 mL) of a concentrated solution of N(IV) (>1 M in the same solvent) was added to a 1-mL portion of the solution. The resulting solutions became warm, and a transient green or blue color developed, persisting for a few seconds in hexane and several minutes in the chlorinated solvents. After 5–10 min, the solutions were degassed (to remove any remaining $NO_2$), but no further workup was performed. Each sample and each starting solution were analyzed in quadruplicate by GC on a Varian 3700 gas chromatograph with a flame-ionization detector, an electronic integrator, and a 30-m capillary column, either DB-1 or DB-17. The areas of substrate peaks were calculated relative to the internal standard, and $k_{rel}$ was calculated by eq 9 (see Scheme III), where $A_0$ and $B_0$ are the ratios of substrates relative to the standard before adding N(IV) and $A$ and $B$ are the ratios after N(IV) treatment. Each experiment was replicated three to six times. Allylbenzene was used as one of the two substrates in each pair, except with norbornene and β-pinene, which were measured versus α-pinene. Experiments using β-pinene with either 1-octene or cyclooctene yielded relative reactivities within ±15% of values determined versus allylbenzene and α-pinene.

**Scheme III**

$$k_{rel} = \frac{k_A}{k_B} = \frac{\log(A/A_0)}{\log(B/B_0)} \qquad (9)$$

$$\frac{dP}{dt} = k\,[\text{Alkene}]^m\,[NO_2]^n \qquad (10)$$

$$\frac{dP}{dt} = k_1[\text{Alkene}][NO_2] + k_2[\text{Alkene}][NO_2]^2 \qquad (11)$$

**Relative Rate Measurements: Low N(IV).** Measurements of relative rates at low $NO_2$ differed only in the method of exposure to N(IV). Small permeation tubes containing N(IV), similar to those described earlier,[6,7,22] were used; the N(IV) slowly diffuses through poly(tetrafluoroethylene) tubing to maintain a constant low level of the reactant. The rate of N(IV) release was determined by immersing permeation tubes in solutions of $CCl_4$ containing phenol and monitoring the amount of *o*-nitrophenol formed.[23] In this way, rate of release of N(IV) was determined to be 0.06 ± 0.02 mmol $h^{-1}$. In the relative rate experiments, a permeation tube was immersed in a 10-mL portion of a solution containing substrates and an internal standard and was sealed. Aliquots taken periodically over 2–5 days were analyzed by GC as described above. (Note that any endogenous dioxygen would be consumed in the first small fraction of the reaction so that it does not significantly affect the product distribution.) Each experiment was repeated three to four times; reported values are averages.

## Results

**Absolute Rates.** The kinetics of the reactions of N(IV) with simple alkenes were first investigated by stopped-flow spectroscopy. The course of the reactions was followed by monitoring the loss of $NO_2$ at 410 nm, where neither $N_2O_4$ nor the products absorb to a significant extent. Treatment of the data was carried out either as described earlier[19] or by a modification in which only a very small portion of the reaction was followed and the quantity $^1/_2 d[N(IV)]/dt$ was calculated. N(IV) is calculated from the absorbance at 410 nm and the $NO_2/N_2O_4$ equilibrium constant. Note that, for the stoichiometry of 2:1 $NO_2$ to alkene,[6] the rate of product formation, $dP/dt$, is equal to $^1/_2 d[N(IV)]/dt$.

Reaction orders were calculated with initial rate based on the empirical rate expression presented in eq 10, where $m$ and $n$ represent the order in alkene and $NO_2$, respectively. When the N(IV) was held constant, the calculated reaction orders in alkene for 2,3-dimethyl-2-butene, cyclohexene, and 1-hexene were 1.0 ± 0.17, 0.91 ± 0.2, and 0.96 ± 0.2, respectively. We believe all of these values represent reactions that are first order in alkene. At 30 °C in $CCl_4$, and at high N(IV) (greater than 50 mM), the order in N(IV) was found to be 2.0 ± 0.15 for 2,3-dimethyl-2-butene, 1-hexene, 3,3-dimethyl-1-butene, and cyclohexene. The rates of reactions of the last three substrates listed were measured over a wider range of $NO_2$ concentrations, from less than 0.1 to 760 mM N(IV). Representative data, collected for single runs in which $NO_2$ concentrations and rates were determined for successive small portions of the curves are illustrated in Figure 1. For all of these substrates, the order in $NO_2$ is near 2.0 at high $NO_2$ and decreases to near 1.0 as the concentration of $NO_2$ is decreased.

The simplest expression that fits these data is eq 11. The results of multiple-regression analyses of the data as a function of $[NO_2]$

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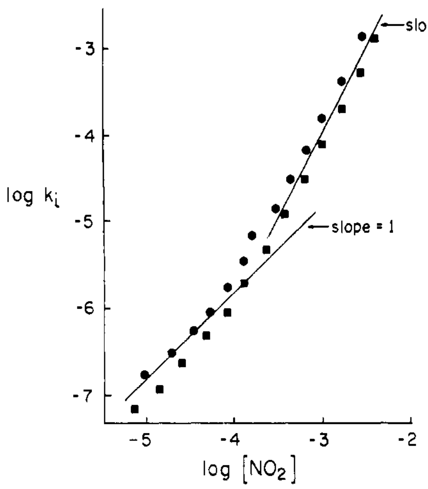

**Figure 1.** A plot of log $[NO_2]$ versus the log of the initial rate for 0.50 M cyclohexene (circles) and 0.77 M 3,3-dimethylbutene (squares), in $CCl_4$ at 30.0 °C. The solid lines represent hypothetical lines that would indicate that the reactions were first order (slope 1) and second order (slope 2) in $NO_2$.

**Table I.** Absolute Rates of Reaction of Alkenes toward N(IV)[a]

| substrate | $k_2$, $M^{-2}$ $s^{-1}$ | $k_1$, $M^{-1}$ $s^{-1}$ |
|---|---|---|
| allyl cyanide | 40 ± 10 | |
| allyl chloride | 60 ± 10 | |
| allylbenzene | 125 ± 10 | |
| 1-hexene | 230 ± 30 (190 ± 7) | (0.17 ± 0.07) |
| cyclohexene | 380 ± 50 (318 ± 13) | (0.63 ± 0.12) |
| 3,3-dimethyl-1-butene | 77 ± 10 (76 ± 1) | (0.02 ± 0.002) |
| cyclopentene | 530 ± 30 | |
| 1,4-hexadiene | 1230 ± 150[b] | |
| norbornene | 2100 ± 300 | |
| 2-methyl-2-pentene | 2550 ± 150 | |
| 2,3-dimethyl-2-butene | 4350 ± 500 | |
| 2,5-dimethyl-2,5-hexadiene | | 18500 ± 800[c] |

[a] These values were measured at 30 °C in $CCl_4$, in the presence of at least 50 mM N(IV). The given error limits are ±1 standard deviation; values in parentheses are calculated by a multiple-regression analysis from rates determined at several concentrations. See the text for details. [b] This value was measured in the presence of 3 mM total N(IV). [c] This reaction is first order in $NO_2$.

and $[NO_2]^2$ are collected in Table I, along with some other rate constants determined at high $NO_2$ concentration.

The order in N(IV) was also determined for a conjugated diene, 2,5-dimethyl-2,4-hexadiene, at high N(IV). Data collected at three N(IV) concentrations (20, 35, and 230 mM) indicate that the order of the reaction in $NO_2$ was 1.0 ± 0.1.

Data were also collected at 30 °C at high N(IV) concentrations in $CCl_4$ for some other alkenes. Generally, only a single set of concentrations was used, and the rate constant was calculated assuming that the reactions were first order in alkene and second order in N(IV). These rate constants also are given in Table I.

**Relative Rates.** Relative rates of reaction were determined at high $NO_2$ concentrations for a number of substrates in $CCl_4$, hexane, and $CH_2Cl_2$. Each value represents the average of at least three determinations; if three runs did not agree to within ±10%, one to three additional replicates were performed, and the average of all runs is reported. These rates are presented relative to allylbenzene in Table II.

A more limited number of relative rates were determined at low concentrations of N(IV) with $CCl_4$ as the solvent. (One experiment using dichloromethane as the solvent is also included.) The pairs of substrates were chosen to vary the possible contribution of the allylic H-atom abstraction reaction. The substrates used, as well as the relative rates measured at high and at low N(IV), are compiled in Table III.

## Discussion

**High N(IV) Concentrations.** Rates of reaction of alkenes with high concentrations of N(IV) were measured both as absolute rates (Table I) and as relative rates versus allylbenzene (Table II). Although experimental errors are often large and the relative rate determinations were not thermostated, there is fairly good agreement between Tables I and II.

**Table II.** Relative Rates of Reaction of Alkenes with High Concentrations of N(IV)[a]

| | solvent | | |
|---|---|---|---|
| substrate | $CCl_4$ | $CH_2Cl_2$ | hexane |
| allyl cyanide | 0.1 ± 0.03 | 0.06 ± 0.01 | 0.4 ± 0.05 |
| 3,3-dimethyl-3-phenylpropene | 0.3 ± 0.02 | | |
| allyl chloride | 0.3 ± 0.1 | | |
| 3,3-dimethyl-1-butene | 0.6 ± 0.2 | | |
| allyl bromide | 0.8 ± 0.1 | 0.6 ± 0.1 | 0.8 ± 0.1 |
| allylbenzene[b] | 1.0 | 1.0 | 1.0 |
| 1-octene | 1.8 ± 0.1 | 2.4 ± 0.1 | 1.7 ± 0.1 |
| 1-hexene | 2.3 ± 0.3 | | |
| methyl oleate | 2.6 ± 0.1 | 3.6 ± 0.3 | 2.4 ± 0.1 |
| cyclooctene | 4.5 ± 0.3 | 6.4 ± 0.4 | 5.3 ± 0.1 |
| α-pinene | 13.0 ± 3.0 | 39.0 ± 1.5 | 16.0 ± 2.0 |
| β-pinene | 15.0 ± 3.5 | 40.0 ± 4.0 | 21.0 ± 3.0 |
| norbornene | 21.0 ± 3.5 | 74.0 ± 9.0 | 33.0 ± 4.0 |
| 2-methyl-2-pentene | 16.0 ± 4.0 | | |

[a] All values were measured at ambient temperatures in the solvent indicated, in the presence of greater than 0.1 M total N(IV). Error limits are ±1 standard deviation. See the text for a discussion of experimental error. [b] All values are reported relative to allylbenzene.

**Table III.** Relative Rates of Reactions in $CCl_4$ at High and Low N(IV) Concentrations[a]

| substrates | high N(IV) | low N(IV) |
|---|---|---|
| diphenylmethane/1-octene | <0.01 | 0.05 |
| triphenylmethane/1-octene | <0.02 | 0.25 |
| allylbenzene/1-octene | 0.55 (0.4)[b] | 0.70 (0.5)[b] |
| allylbenzene/cyclooctene | 0.22 | 0.37 |
| allylbenzene/3,3-dimethyl-3-phenylpropene | 3.0 | 4.3 |

[a] See the text for a description of the $NO_2$ concentrations. All values are ±15%. [b] The values in parentheses were obtained with dichloromethane as the solvent.

The data collected at high N(IV) concentrations for simple alkenes are consistent with a radical addition mechanism involving $N_2O_4$. The radical addition of $N_2O_4$ would be expected to be first order in alkene and either first order in $N_2O_4$ or second order in $NO_2$, as we have found. Radical addition of $NO_2$, which is observed in the gas phase, can be excluded from consideration since it should be first order in $NO_2$. Evidence against other reactions of alkenes with $N_2O_4$, such as an electrophilic addition mechanism with a cationic intermediate, have been presented earlier.[10-14] For example, when cyclohexene is allowed to react with N(IV) in bromoform[12] or in the presence of bromotrichloromethane,[14] 2-nitro-1-bromocyclohexane is formed, suggesting the formation of a β-nitroalkyl radical intermediate. Also, product studies of the reaction of N(IV) with norbornene[10] demonstrated that the products are a mixture of *cis*- and *trans*-1,2-dinitronorbornenes, with no evidence for norbornyl cation rearrangements, which would be expected for a carbocation intermediate.

The present work provides further evidence against an ionic mechanism. The rate of reaction of norbornene relative to the rates of other alkenes does not support the presence of a cationic intermediate: No large rate acceleration is observed for the reaction of norbornene, although it would give a highly stabilized norbornyl cation. In addition, the differences in relative rates in the solvents we have studied are too small to support an ionic mechanism, although these rates are consistent with a mechanism involving the addition of an electrophilic radical.

**Low N(IV) Concentrations.** At lower concentrations of N(IV), an apparent increase in reactivity of the alkenes was observed. As shown in Figure 1, the log of the initial rate does not change linearly with the log of the $NO_2$ concentration. Rather, the slope is near 2.0 at high N(IV) concentrations and appraoches 1.0 as the concentration is lowered. A kinetic expression such as eq 11, with a first- and a second-order term in $NO_2$, represents the simplest scheme that fits our data. The reaction might be more complex, but for the purposes of this discussion, we will consider only reactions that should exhibit either first-order or second-order dependence on the $NO_2$ concentration.

**Possible First-Order Reactions.** A reasonable possibility for the kinetic order in N(IV) in dilute solutions moving from second order to first order is a radical addition mechanism involving $NO_2$ rather than $N_2O_4$ in the rate-determining step. This appears to be the course of the reaction in the gas phase[1-5] and might be observed in solution at very dilute N(IV) where the concentration of $NO_2$ exceeds that of $N_2O_4$.

Alternatively, a different mechanism could compete with the radical addition pathway. The hydrogen atom abstraction mechanism proposed earlier,[6] and presented in Scheme II, falls in this category. This could account for the reduction of the order in N(IV) observed for 1-hexene and cyclohexene, as well as for the allylic substitution products observed from the reaction of N(IV) with cyclohexene[6] and methyl oleate.[15]

To further test the likelihood of allylic hydrogen atom abstraction competing with radical addition, we undertook a limited relative-reactivity study using low levels of $NO_2$ with substrates of differing ease of allylic hydrogen atom abstraction. As illustrated in Table III, diphenylmethane and triphenylmethane are relatively nonreactive at high N(IV) concentrations but exhibit increased reactivity at lower N(IV) concentrations. These substrates have no olefinic double bonds, but they have readily abstractable hydrogen atoms. Therefore, they should not react via a radical addition mechanism but should undergo hydrogen atom abstraction at rates comparable to a 1,4-diene or allylbenzene. From these data a clear trend emerges: Substrates with more readily abstractable hydrogen atoms are relatively more reactive at low $NO_2$ than at high $NO_2$. This observation is our first independent evidence for a hydrogen atom abstraction mechanism accounting for a significant portion of the total reactivity of appropriate alkenes toward low levels of N(IV) in solution.

Another line of reasoning also suggests the reality of the H atom abstraction pathway. The first-order component observed for 3,3-dimethyl-1-butene (and illustrated in Figure 1) cannot be due to the allylic abstraction mechanism, since this substrate has no allylic hydrogen atoms. However, the calculated rate constant for the first-order portion of the reaction for this substrate ($0.02 \pm 0.002$ $M^{-1}$ $s^{-1}$) is much smaller than those calculated for 1-hexene and cyclohexene ($0.17 \pm 0.07$ and $0.63 \pm 0.12$ $M^{-1}$ $s^{-1}$, respectively). Thus, although a hydrogen atom abstraction pathway cannot account for all of the lowering of the order in N(IV), it appears to be the major reaction at low N(IV) for substrates with allylic hydrogen atoms.

The kinetics of reaction of $NO_2$ with 2,5-dimethyl-2,4-hexadiene, a conjugated diene, cannot be fully accounted for by either of the mechanisms discussed above. This reaction appears to be first order in N(IV). This observation implies that the substrate preferentially reacts with $NO_2$ rather than $N_2O_4$, either by a radical addition mechanism or by some other process, even where the equilibrium concentration of $N_2O_4$ is high. We have no explanation for this observation. However, since this substrate is the only conjugated diene we studied and its rate of reaction is much faster than the rates of simple alkenes, it is not unreasonable that the mechanism of this reaction should be different. In addition, rates of reaction of conjugated dienes with N(IV) in the gas phase appear to vary over 2 orders of magnitude with small changes in structure;[2] reactions of N(IV) with conjugated dienes clearly require further study.

**Comparison to Gas-Phase Reactions.** This study, as well as earlier work,[6] suggests that at low N(IV) concentrations allylic hydrogen atom abstraction can compete effectively with radical addition of $NO_2$ to simple alkenes in solution. However, the abstraction pathway has not been observed in the gas phase. This difference in products can be accounted for in terms of Schemes I and II. A major difference between our work and most of the reported gas-phase studies[1-5] is that, in the gas-phase work, dioxygen was present in large amounts relative to N(IV). Thus, the trapping of the $\beta$-nitroalkyl intermediate (eq 4) remains fast, and eq 1 is rate determining. In fact, in the gas-phase reaction of 2,3-dimethyl-2-butene with N(IV), it has been shown that decreasing the pressure of dioxygen lowers the observed rate.[5]

Also, two early reports on the kinetics of gas-phase N(IV) reactions have been studied under conditions in which dioxygen was rigorously excluded,[16,17] and nearly second-order dependence on $NO_2$ was observed. Unfortunately, these studies were carried out only with ethylene and propylene, neither of which has readily abstractable allylic hydrogens. They also were studied at high temperatures, and the gaseous products from ethylene included the fragmentation or overoxidation products $CO_2$, CO, and NO. While no comparison of products can be made and the H atom abstraction mechanism cannot be evaluated, these data do support the mechanism presented in Scheme I.

In the present solution-phase work, dissolved dioxygen is not rigorously excluded, but its concentration is lower than that of N(IV). Dioxygen may be assumed to be completely absent after the first small portion of our reactions.

For our data to be consistent with the gas-phase data,[1-5] two conditions must be met.

First, the reaction with $N_2O_4$ observed in solution must be absent or minor in the gas phase. This is reasonable if solvation is considered: The $NO_2/N_2O_4$ equilibrium constant favors the monomer in the gas phase (particularly at the low concentrations studied in that medium), and the dimer is favored in solution.[21]

Second, the allylic hydrogen atom abstraction pathway observed in solution must be minor or absent in the gas phase, and the addition mechanism observed in the gas phase must be less important in solution. Our calculated first-order rate constant for cyclohexene (0.63 $M^{-1}$ $s^{-1}$ at 30 °C; Table I) is similar to the rate of reaction of *cis*-2-butene with $NO_2$ in the gas phase (0.15 $M^{-1}$ $s^{-1}$ at 25 °C),[1] suggesting that the rate of the forward reaction in eq 1 is similar in the gas phase and in solution. However, at atmospheric pressures of air, the intermediate radical **1** is scavenged by $O_2$; therefore, eq 1 becomes irreversible and the contribution of eq 5 is minor. (This is consistent with the gas-phase studies.)[1-5] In solution eq 1 should be more reversible, allowing the irreversible hydrogen atom abstraction pathway (eq 5–8) to dominate.[6,7]

The partitioning between the two first-order pathways also may be explained in terms of solvation. Solvation should shift the equilibrium in eq 1 to favor the starting materials. In addition, for highly electrophilic species like $NO_2$ or $N_2O_4$, it is likely that solvation would allow polar contributions to the transition states for eq 1 or 2 that would significantly lower their energy barriers. In endothermic reactions such as these, any lowering of the transition-state energy will have a much greater impact on the reverse reaction rate than on the forward rate. In addition, polar effects could also be invoked to argue that abstraction of an allylic hydrogen by $NO_2$ would be facilitated in solution compared to the gas phase. Thus, we suggest that the net effect of solvation is to make the abstraction pathway more favorable in solution.

**Relevance to Biological Systems.** The decrease in the kinetic order in $NO_2$ of these nitration reactions at low $NO_2$ concentrations is of interest to us for several reasons. First, low concentrations of $NO_2$ are present in the environment, i.e., outdoors from smog and indoors from cigarette smoke, space heaters, et al. Since it is useful to be able to estimate the susceptibility of biological targets toward $NO_2$, rate constants determined at low N(IV) are of value. In fact, on the basis of our findings, rate constants measured at high concentrations of N(IV) cannot be used to calculate the likelihood of biological target molecules reacting with environmental $NO_2$. Second, it is under low-$NO_2$ conditions that we observe allylic substitution products that can be rationalized by a hydrogen atom abstraction mechanism.[6,7,15] This not only is of mechanistic interest but also suggests that substrates with doubly allylic hydrogen atoms, such as polyunsaturated fatty acids, may be more reactive than rate constants measured at high $NO_2$ concentrations or in the gas phase would indicate. Indeed, we find that substrates with readily abstractable hydrogen atoms are more reactive at low $NO_2$ concentrations relative to simple alkenes. This may be of particular importance in biological systems, where polyunsaturated fatty acids are vital to the integrity of lipid membranes.

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**Registry No.** $H_2$, 1333-74-0; $NO_2$, 10102-44-0; $N_2O_4$, 10544-72-6; $O_2$, 7782-44-7; cyclohexene, 110-83-8; cyclopentene, 142-29-0; 1,4-hexadiene, 592-45-0; 2,3-dimethyl-2-butene, 563-79-1; 2,5-dimethyl-2,5-hexadiene, 927-97-9; allyl cyanide, 109-75-1; 3,3-dimethyl-3-phenylpropene, 18321-36-3; allyl chloride, 107-05-1; 3,3-dimethyl-1-butene, 558-37-2; allyl bromide, 106-95-6; 1-octene, 111-66-0; 1-hexene, 592-41-6; methyl oleate, 112-62-9; cyclooctene, 931-88-4; α-pinene, 80-56-8; β-pinene, 127-91-3; norbornene, 498-66-8; 2-methyl-2-pentene, 625-27-4; diphenylmethane, 101-81-5; triphenylmethane, 519-73-3; allylbenzene, 300-57-2.

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# Studies on the Deconjugation–Epimerization Strategy en Route to Avermectin $B_{1a}$: Problems and Solutions

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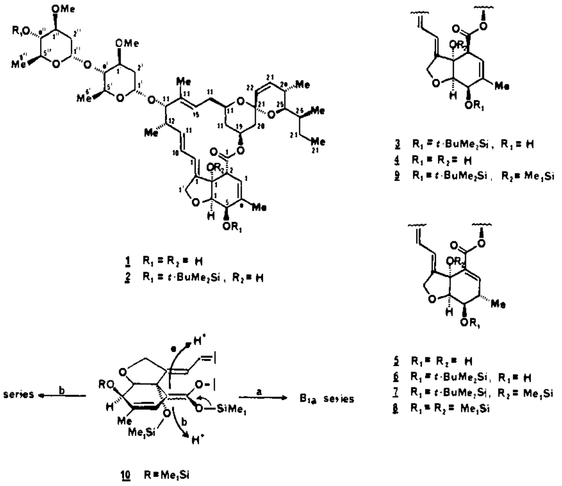
**Abstract:** A method is presented whereby $\Delta^2$-4(*R*)-avermectin $B_{1a}$ is converted in a two-step process into avermectin $B_{1a}$, first by deconjugation to 2-epiavermectin $B_{1a}$ and then by partial epimerization in the presence of imidazole.

Since their discovery,[1] the avermectins have been the subject of intensive investigations on several fronts.[2,3] Our studies[4] in this area have focused on the development of strategies and methodology for the synthesis of appropriate optically pure subunits. A culminating point in such synthetic studies was the first synthesis[5] of avermectin $B_{1a}$ (**1**) (Scheme I) from a totally synthetic $C_{11}$–$C_{28}$ extended spiroacetal subunit and an oxahydrindene derivative obtained from the degradation of the natural product.[6,7] Because of the tendency for aromatization of the oxahydrindene subunit, our original strategy was based on producing a $\Delta^2$-avermectin derivative such as **7** or **8** and effecting a critical deconjugation to the desired target in a penultimate step based on known precedents.[8,9] We had reasoned[4,5] that upon treatment with acid a dienolate species or the ketene acetal intermediate

Scheme I



**1** $R_1 = R_2 = H$
**2** $R_1 = t\text{-}BuMe_2Si$, $R_2 = H$

**3** $R_1 = t\text{-}BuMe_2Si$, $R_1 = H$
**4** $R_1 = R_2 = H$
**9** $R_1 = t\text{-}BuMe_2Si$, $R_2 = Me_3Si$

**5** $R_1 = R_2 = H$
**6** $R_1 = t\text{-}BuMe_2Si$, $R_1 = H$
**7** $R_1 = t\text{-}BuMe_2Si$, $R_2 = Me_3Si$
**8** $R_1 = R_2 = Me_3Si$

**10** $R = Me_3Si$

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