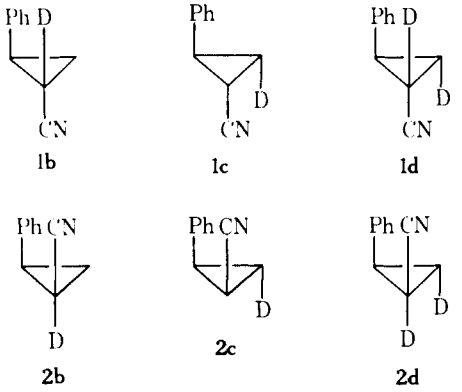
Table I. Rate Constants for Thermal Trans to Cis Isomerizations of Deuterium-Labeled 1-Cyano-2-phenylcyclopropanes

reaction	T, °C	$(k_1 + k_2)$, 10^{-5} s^{-1}	C(1)(k^H/k^D)	C(1)(k^H/k^D)C(3)(k^H/k^D)	C(3)(k^H/k^D)
1a → 2a	242.1	1.30 ± 0.02			
1b → 2b	242.1	1.22 ± 0.01	1.07 ± 0.02		
1d → 2d	242.1	1.09 ± 0.04[a,b]		1.19 ± 0.05	1.13 ± 0.05[c]
1a → 2a	246	1.58 ± 0.04			
1c → 2c	246	1.40 ± 0.03			1.13 ± 0.04

[a] $k_1 = 0.76 \pm 10^{-5}$ s^{-1}; $k_2 = 0.33 \times 10^{-5}$ s^{-1}. [b] Observed; 90% d_1 at C(1). [c] Corrected for incomplete labeling at C(1).



1i or **2i** in 1-methylnaphthalene solutions were followed by GLC on a Carbowax 20M column, with 8 to 12 kinetic points per system. Deuterated and unlabeled samples were pyrolyzed simultaneously in the kinetic bath in sealed ampules. The concentration vs. time data gave rise to the rate constants and isotope effects summarized in Table I.

Substitution of deuterium for hydrogen at C(1) leads to a normal secondary isotope effect, $(k_1 + k_2)^H/(k_1 + k_2)^{D\ C(1)} = 1.07 \pm 0.02$; if the entire change in rate constant with deuterium substitution is due to k_1, and k_1 for **1b → 2b** is ~70% of $(k_1 + k_2)$ as it is for the reaction **1d → 2d**, then $k_1{}^H/k_1{}^{D\ C(1)} = 1.09 \pm 0.02$. The magnitude of the isotope effect associated with deuterium substitution at C(3) is larger; the two independent determinations of $(k_1 + k_2)^H/(k_1 + k_2)^{D\ C(3)}$ in Table I average to 1.13 ± 0.02. This large β secondary deuterium isotope effect points to a high degree of interaction between C(1) and C(2) with the H-C(3) bonds in the transition state.[4]

Crawford and Mishra[5] and Al-Sader and Crawford[6] have observed β deuterium isotope effects of 1.06 ± 0.03 for pyrolytic decomposition of 4-methyl-1-pyrazoline and the 4-deuterio derivative, and for 1-pyrazoline and 4-deuterio-1-pyrazoline, at temperatures between 225 and 245 °C, and have noted that the effects may be due to hyperconjugative interactions in a *O,O*-trimethylene or π-cyclopropane species.

It may be that a π-cyclopropane serves as an entity through which the k_1, k_2, and k_{12} epimerizations of cyclopropanes such as **1** occur; the relative values of these rate constants would then depend on partitionings between conrotatory and disrotatory modes of ring opening and ring closing or on kinetic competition between single 180° rotations of terminal groups in the trimethylene species and ring closure.[4,7]

The kinetic isotope effect observed for D-C(3) substitution on the reaction **1 → 2** is relatively large even though the system bears substituents that one may presume are effective in delocalizing and stabilizing a *O,O*-trimethylene species; less substituted cyclopropanes might exhibit still larger β deuterium kinetic isotope effects. This possibility is relevant to a recent kinetic study of the thermal stereomutations of optically active *trans*-1,2-dideuteriocyclopropane, which recognized the likelihood of and assumed the kinetic consequences of a normal isotope effect for cleavage of a C-C bond α to a deuterium atom, but which did not consider β secondary deuterium isotope effects.[8] If there is a substantial β isotope effect on k_{12} and k_{13} of 1,2-dideuteriocyclopropane, k_1 might be a larger fraction of k_{12} than has been suggested. If, for example, k_{12}/k_{13} were 1.05, then k_1 would be 19 ± 5% of k_{12}; the assumption[8] that $k_{13}/k_{12} = 1.1$ and the experimental rate constants[8] for racemization and cis-trans isomerization give k_1 equal to 4 ± 5% of k_{12}.

There are clear and challenging experimental tasks ahead: determination of α and β secondary deuterium isotope effects on individual k_i and k_{ij} rate constants in appropriate representative substituted cyclopropanes and in isotopically labeled cyclopropane itself.

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

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Reduction of Nitrate Ion by $(bpy)_2pyRu(OH_2)^{2+}$

Sir:

The oxy anions NO_3^- and ClO_4^- are strongly oxidizing[1] and yet are sufficiently unreactive under normal conditions that they are frequently used as the anion in "inert" electrolytes or as the counterion in the preparation of metal complex salts. Facile reduction of NO_3^- is a particularly interesting mechanistic problem because (1) NO_3^- is a key source of inorganic nitrogen in biological systems via the molybdenum-based enzyme nitrate reductase,[2] and (2) NO_3^- represents a source of stored chemical oxidizing energy which may be useful in the oxidation of organic compounds[1b] or possibly in fuel-cell applications.[3] In the course of our studies on aquo and related 2,2′-bipyridine complexes of ruthenium for use in redox catalysis,[4] we have observed some remarkable chemistry in which aquo complexes of ruthenium are oxidized in solution by NO_3^- or ClO_4^- at room temperature.[5] Earlier studies[6] have shown that ruthenium complexes can be especially reactive toward ClO_4^-, and our initial results on the reduction of NO_3^- by

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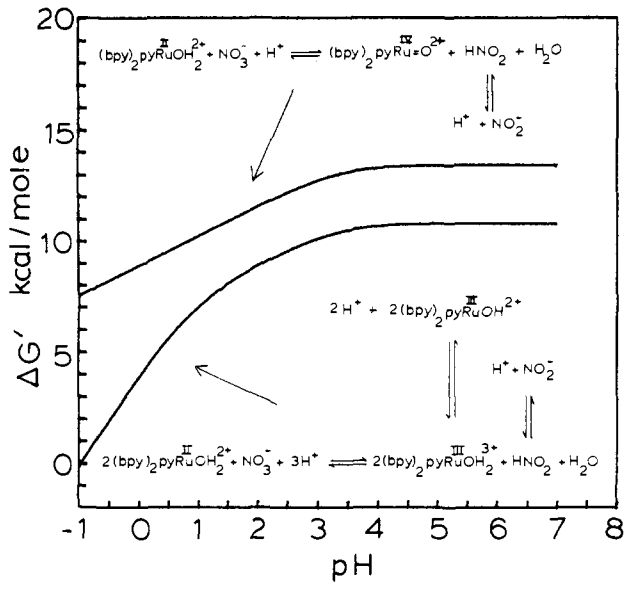

Figure 1. Free-energy dependence of the reduction of NO_3^- by Ru(II). The lower portions of the curves correspond to the equations as indicated (see eq 1 and 2) and level off as $(bpy)_2pyRu^{III}(OH)^{2+}$ and NO_2^- become the predominant products at higher pH values ($pK_a(HNO_2) = 3.35$[1a] and $pK_a((bpy)_2pyRu^{III}(OH_2)^{3+} \approx 0.85$[4b]). The upper curve does not represent the observed reaction at $[H^+] \geq 1$ M but would represent the minimum activation barrier if Ru(IV) is an intermediate.

$(bpy)_2pyRu(OH_2)^{2+}$ suggest that this reactivity extends to NO_3^- in a general way that may be of value in understanding a great many related reactions.

Previously,[4b] we reported the existence of reversible Ru(III)/Ru(II) and Ru(IV)/Ru(III) couples based on the ion $(bpy)_2pyRu^{II}(OH_2)^{2+}$. Two-electron oxidation of the Ru(II) ion gives the isolable Ru(IV) "ruthenyl" ion, $(bpy)_2pyRu^{IV}O^{2+}$, which is stabilized by the loss of two protons. From available redox potential data,[1a,4b] the oxidation of $(bpy)_2pyRu^{II}(OH_2)^{2+}$ to the corresponding Ru(III) complex by NO_3^- in 1 M acid (eq 1) is only slightly disfavored under standard conditions but can readily be made spontaneous with appropriate adjustment in relative concentrations. Oxidation to give Ru(IV) is less favored thermodynamically (eq 2).

$$2(bpy)_2pyRu^{II}(OH_2)^{2+} + NO_3^- + 3H^+ \longrightarrow 2(bpy)_2pyRu^{III}(OH_2)^{3+} + HNO_2 + H_2O \quad (1)$$

$$\Delta G^0 \geq 0.09\text{V (3.9 kcal/mole)}^7$$

$$(bpy)_2pyRu^{II}(OH_2)^{2+} + NO_3^- + H^+ \longrightarrow (bpy)_2pyRu^{IV}O^{2+} + HNO_2 + H_2O \quad (2)$$

$$\Delta G^0 = 0.19\text{V (8.9 kcal/mole)}^7$$

In 1 M HNO_3 at room temperature, $(bpy)_2pyRu^{II}(OH_2)^{2+}$ undergoes a reaction with NO_3^- which is complete within 90 min. The reaction products include $(bpy)_2pyRu^{III}(OH_2)^{3+}$ (57 ± 7%) and $(bpy)_2pyRu(NO)^{3+}$ (33 ± 8%) as shown by cyclic voltammetry ($E_{1/2}$ = +0.79 and +0.29 V for the couples $(bpy)_2pyRu(OH_2)^{3+/2+}$ and $(bpy)_2pyRu(NO)^{3+/2+}$ vs. SCE in 1 M HNO_3, respectively) and spectral measurements. A slow, competitive solvolysis reaction which yields *cis*-$(bpy)_2Ru(OH_2)_2^{3+}$ as shown electrochemically ($E_{1/2}$ = +0.63 V vs. SCE for the *cis*-$(bpy)_2Ru(OH_2)_2^{3+/2+}$ couple in 0.5 M $HClO_4$)[8] accounts for the remainder of the initial complex. The net chemistry appears to involve initial reduction of NO_3^- to HNO_2 (eq 3) followed by capture of the HNO_2 by Ru(II) (eq 4).[9]

Previous work[10] has demonstrated that the nitrosation of $(bpy)_2ClRu(OH_2)^+$ by HNO_2 in acidic aqueous solution gives

$$2(bpy)_2pyRu^{II}(OH_2)^{2+} + NO_3^- + 3H^+ \rightleftharpoons 2(bpy)_2pyRu^{III}(OH_2)^{3+} + HNO_2 + H_2O \quad (3)$$

$$(bpy)_2pyRu^{II}(OH_2)^{2+} + HNO_2 + H^+ \longrightarrow (bpy)_2pyRu^{II}(NO)^{3+} + 2H_2O \quad (4)$$

$(bpy)_2ClRu(NO)^{2+}$ stoichiometrically. In the case of the nitrosation of $(bpy)_2pyRu^{II}(OH_2)^{2+}$ by HNO_2 in 1 M $HClO_4$, the formation of the expected product $(bpy)_2pyRu(NO)^{3+}$ also occurs stoichiometrically and is complete on a time scale comparable with the disappearance of $(bpy)_2pyRu^{II}(OH_2)^{2+}$ in 1 M HNO_3. Thus, although eq 3 tends to a true equilibrium in the thermodynamic sense, eq 4 drives the oxidation of Ru(II) to Ru(III) to completion by removing HNO_2 as it is formed.

In order to avoid unwanted complications arising from further reactions of HNO_2,[11] we have carried out a series of experiments in the presence of sulfamate ion which is a quantitative scavenger of HNO_2 (eq 5).[12] With added sulfa-

$$HNO_2 + NH_2SO_3^- \longrightarrow N_2 + HSO_4^- + H_2O \quad (5)$$

mate, $(bpy)_2pyRu^{II}(OH_2)^{2+}$ is oxidized to Ru(III) in 1 or 2 M HNO_3, but, as shown by cyclic voltammetry, the nitrosyl complex $(bpy)_2pyRu(NO)^{3+}$ is not a product. As expected from eq 3 and 5 and verified by GC analysis of evolved N_2 and by spectrophotometric measurements, the net reaction becomes eq 6. If reaction 6 is carried out in an electrochemical cell, $(bpy)_2pyRu^{III}(OH_2)^{3+}$ can be electrolytically reduced (eq 6a) back to $(bpy)_2pyRu^{II}(OH_2)^{2+}$, and the net process becomes

$$2(bpy)_2pyRu^{II}(OH_2)^{2+} + NO_3^- + 3H^+ + NH_2SO_3^- \longrightarrow 2(bpy)_2pyRu^{III}(OH_2)^{3+} + N_2 + HSO_4^- + 2H_2O \quad (6)$$

$$+2e^- \quad (6a)$$

the chemically catalyzed net electrochemical reduction of NO_3^-.[13] The catalytic scheme represents the NO_3^-/HNO_2 part of a fuel cell which operates essentially at the thermodynamic potential of the NO_3^-/HNO_2 couple, but it is not yet practical since the useful chemicals, HNO_2 and $NH_2SO_3^-$, are irreversibly consumed to give N_2.

From our earlier study[4b] of the chemical reduction of $(bpy)_2pyRu^{IV}O^{2+}$ by $P(C_6H_5)_3$ to form $OP(C_6H_5)_3$, it is known that $(bpy)_2pyRu^{IV}O^{2+}$ can function as a net oxygen atom transfer reagent where the metal acts as a two-electron acceptor (eq 7). We do not yet have detailed kinetic and

$$(bpy)_2pyRu^{IV}O^{2+} + PPh_3 \xrightarrow{\text{fast}} (bpy)_2pyRu^{II}(OPPh_3)^{2+} \xrightarrow[\text{slow}]{CH_3CN} (bpy)_2pyRu^{II}(CH_3CN)^{2+} + OPPh_3 \quad (7)$$

mechanistic information about the reaction with NO_3^- but a reaction analogous to the microscopic reverse of eq 7 could provide a pathway for NO_3^- reduction. In such a scheme an initial substitution (eq 8) is required, followed by an intramolecular redox reaction (eq 9), giving free HNO_2 with uptake of one proton. Ru(III) would appear via eq 10 which is rapid

$$(bpy)_2pyRu^{II}(OH_2)^{2+} + NO_3^- \rightleftharpoons (bpy)_2pyRu^{II}(ONO_2)^+ + H_2O \quad (8)$$

$$(bpy)_2pyRu^{II}(ONO_2)^+ + H^+ \rightleftharpoons (bpy)_2pyRu^{IV}O^{2+} + HNO_2 \quad (9)$$

$$(bpy)_2pyRu^{IV}O^{2+} + (bpy)_2pyRu^{II}(OH_2)^{2+} + 2H^+ \longrightarrow 2(bpy)_2pyRu^{III}(OH_2)^{3+} \quad (10)$$

as shown by simple mixing experiments. The intermediate nitrato complex $(bpy)_2pyRu(ONO_2)^+$ has been prepared by a photochemical reaction,[15] and we find that it is unstable with added acid in polar organic solvents. A mechanism similar to eq 8–10 has been proposed for the reduction of ClO_4^- by $Ru(OH_2)_6^{2+}$ where the initial reduced oxy anion product is ClO_3^-.[6b]

From known pK_a and redox potential data,[1a,4b] the profile of the pH dependence of $\Delta G°$ for eq 1 and 2 is given in Figure 1. The change in ΔG with pH is complicated by the equilibria involving the HNO_2/NO_2^- and $(bpy)_2pyRu^{III}OH_2^{3+}/(bpy)_2pyRu^{III}OH^{2+}$ acid-base pairs. Except in extremely strong acid, the plot shows that eq 1 and 2 are both thermodynamically spontaneous in the reverse direction and predict that HNO_2 or NO_2^- should be capable of reducing $(bpy)_2pyRu^{IV}O^{2+}$ to $(bpy)_2pyRu^{II}(OH_2)^2$

In a $H_2PO_4^-/HPO_4^{2-}$ buffer at neutral pH, $(bpy)_2pyRu^{IV}O^{2+}$ is, in fact, reduced by NO_2^- to give $(bpy)_2pyRu^{II}(OH_2)^{2+}$. Since the reaction is slow, excess NO_2^- is required to achieve a reasonable rate, and a subsequent substitution of the aquo ligand by NO_2^- yields $(bpy)_2pyRu(NO_2)^+$ as the final ruthenium product. In acidic solution, the reaction between HNO_2 and $(bpy)_2pyRu^{IV}O^{2+}$ is rapid and gives rise to the nitrosyl complex $(bpy)_2pyRu(NO)^{3+}$ as shown by electrochemical and spectral experiments. The nitrosyl complex is the expected product in acidic solution since for the nitro-nitrosyl equilibrium in eq 11, $pK_a = 3.8$.[4a]

$$(bpy)_2pyRu(NO_2)^+ + 2H^+ \rightleftharpoons (bpy)_2pyRu(NO)^{3+} + H_2O \qquad (11)$$

We view the preliminary results reported here to be significant because (1) they suggest possible approaches to the catalytic use of HNO_3 as a chemical oxidant in synthesis or fuel cell applications, (2) combined with the earlier work on the reactivity of the $(bpy)_2pyRu^{IV}O^{2+}$ ion, they suggest the existence of a general type of multiple-electron, atom-transfer reactivity in this and related systems, and (3) detailed kinetic studies may give further insight into related processes in biological systems.

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(7) Potentials were measured potentiometrically vs. the SCE (saturated calomel electrode) in 1 M $HClO_4$ as formal potentials[4b] and are converted here for convenience to the NHE (normal hydrogen electrode) by adding 0.24 V.
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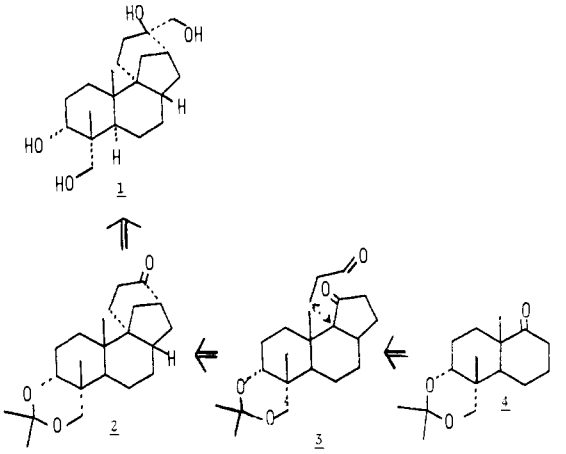
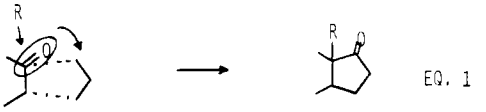
A Total Synthesis of Aphidicolin

Sir:

Aphidicolin (**1**), isolated from the fungus *Cephalosporium aphidicola* Petch, is an antibiotic that reduces the mitotic rate of mouse "L" cells and inhibits the growth of *Herpes simplex* type 1.[1] For a synthesis of this most unusual structure, some simplification in the target can be accomplished since the ketone **2**, which is obtained by degradation of **1**, has already been reconverted into aphidicolin. We analyzed the synthetic problem represented by **2** in terms of a regiocontrolled alkylation of a cyclopentanone as represented in formula **3**. Such



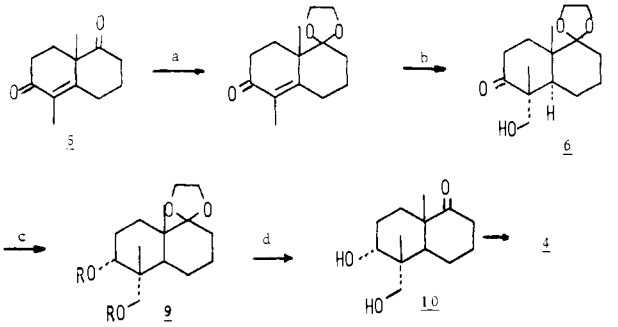
an analysis takes advantage of our recently described cyclopentanone annulation (eq 1) which allows adding a cyclopentanone ring onto a carbonyl compound with migration of the carbonyl group and with the ability of adding a new alkyl residue selectively at the carbon of the former carbonyl group.[2,3] Using such a strategy, the key intermediate becomes ketone **4**.



EQ. 1

The synthesis of ketone **4** (see Scheme I) begins with Δ^4-4,10-dimethyloctalin-3,9-dione (**5**)[4] which is chemoselectively ketalized. Reductive formylation[5] is best achieved by quenching the intermediate enolate in the dissolving metal reduction with chlorotrimethylsilane, regenerating the enolate in ether, and then bubbling in gaseous formaldehyde to give **6**,[6,7] mp 110–112 °C. Strikingly a single stereoisomer results

Scheme I. Synthesis of 4β,10β-Dimethyl-3α,11-isopropylidenedioxy-*trans*-decalin-9-one (4)[a]



[a] (a) $HOCH_2CH_2OH$, TsOH, PhH, reflux, Dean-Stark, 79%. (b) [i] Li, NH_3, THF, 0.8 equiv of t-C_4H_9OH, −78 °C, quench with isoprene and then $(C_2H_5)_3N$, $(CH_3)_3SiCl$; [ii] CH_3Li, ether, room temperature and then −78 °C, HCHO, 68%. (c) $(i\text{-}C_4H_9)_2(t\text{-}C_4H_9)AlH^-Li^+$, hexane, heptane, ether, −78 °C, 99%. (d) 3 N HCl, THF, room temperature, 100%. (e) CH_3COCH_3, TsOH, reflux, 92%.

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