M AcOH); TLC on Merck silica gel F-254, $R_f$ 0.23 (oxytocin, $R_f$ 0.19), in 4:1:1 1-BuOH/AcOH/$H_2O$, $R_f$ 0.57 (oxytocin, $R_f$ 0.61) in 15:3:10:6 1-BuOH/AcOH/pyridine/$H_2O$, $R_f$ 0.51 (oxytocin, $R_f$ 0.55) in 20:10:11 1-BuOH/pyridine/$H_2O$. Anal. ($C_{43}H_{66}N_{11}O_{13}S_2 \cdot CH_3CO_2H \cdot 2\frac{1}{2}H_2O$), C, H, N. Amino acid analysis[18] gave the following molar ratios: Cys($O_3$H),[19] 2.04; Asp, 0.90; Glu, 1.03; Pro, 1.00; Gly, 1.00; Ile, 0.96; Leu, 1.01; Tyr, 0.89; $NH_3$, 2.09.

In the in vitro rat uterotonic assay[20] [5-aspartic acid]-oxytocin possesses a potency of 20.3 ± 0.8 (mean ± SEM) units/mg in the absence of added $Mg^{2+}$; the comparable value for oxytocin is 546 ± 18 units/mg.[21] Dose-response studies on the isolated rat uterus with [5-aspartic acid]-oxytocin and oxytocin using the individual injection technique[22] in the presence of either 0.5 mM or 1.0 mM added $Mg^{2+}$ in the bathing medium or without added $Mg^{2+}$ and in the presence of either 0.5 mM $Ca^{2+}$ (standard assay conditions) or reduced $Ca^{2+}$ levels (0.3 and 0.15 mM) revealed identical intrinsic activities for the analogue compared with the hormone. In fact, the activity of [5-aspartic acid]-oxytocin is potentiated to such a degree by added $Mg^{2+}$ that the dose-response relationships of the analogue and oxytocin are virtually identical in the presence of 1.0 mM added $Mg^{2+}$. In addition, [5-aspartic acid]-oxytocin exhibits 41 ± 2 units/mg avian vasodepressor[23] and 0.14 ± 0.02 units/mg rat antidiuretic activities;[24] these values should be compared with 507 ± 15[25] and 2.7 ± 0.2,[25] respectively, for oxytocin.

Thus, [5-aspartic acid]-oxytocin retains not only a high affinity for the uterotonic receptor, but, more importantly, it exhibits an intrinsic activity identical with that of oxytocin under various experimental conditions. This result is significant in view of the proposed biologically active model of oxytocin where the side chain of the 5-position residue was assigned to contain an "active element" responsible for the intrinsic activity of the hormone when bound to the uterine receptor (Figure 1).[9]

The synthesis of [5-aspartic acid]-vasopressin is warranted in order to test the proposed biologically active model of vasopressin when bound to its antidiuretic receptor.[5]

**Acknowledgment.** This work was supported in part by Grant No. AM 18399 from the U.S. Public Health Service.

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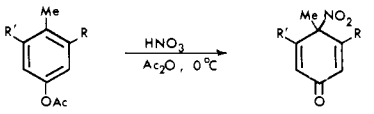
## Ipso Nitration. Characterization of Nitro Group Shifts in 4-Methyl-4-nitrocyclohexa-2,5-dienones[1]

*Sir:*

Aromatizations of 4-nitrocyclohexa-2,5-dienones by 1,3 shift of the nitro group are documented.[2,3] These observations stand in marked contrast to 1,2 shifts of nitro groups that have been observed with 4-alkyl-4-nitrocyclohexadienyl cations.[4,5] We report here some studies that aid differentiation and mechanistic characterization of these nitro group shifts with migration order [1,3].

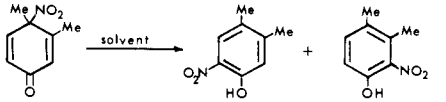
Nitration of 4-methylphenyl acetate, 3,4-dimethylphenyl acetate, or 3,4,5-trimethylphenyl acetate with nitric acid in acetic anhydride at 0 °C yields the corresponding 4-methyl-4-nitrocyclohexadienone (**1**, **2**, or **3**) in good yield, eq 1. In each




(1)

| | | % (NMR) |
|---|---|---|
| 1 | R = R' = H | 90 |
| 2 | R = Me, R' = H | 85 |
| 3 | R = R' = Me | 90 |

case the crystalline dienone may be isolated by low temperature precipitation and purified by low temperature crystallization. Earlier reports indicate that such dienones decompose in acidic or basic media to yield *o*-nitrophenols.[2,3] We find that **1**, **2**, or **3** rearomatize in all solvents tested to yield products of a formal 1,3 shift of a nitro group, eq 2, and that reaction rates are actually much slower in aqueous solvents than in nonpolar hydrocarbon solvents.




(2)

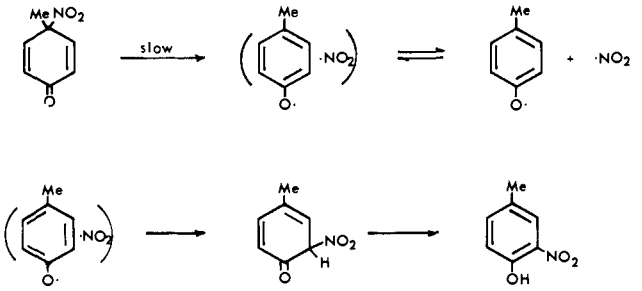
Rates of the reactions, eq 2, could be followed spectrophotometrically. Well-behaved first-order kinetics were observed for product formation and reactant disappearance. Table I lists

**Table I.** First-Order Rates of Reaction of **1**, **2**, and **3** in Various Solvents[a]

| Solvent | Temp, °C | $10^4k$, $s^{-1}$ 1 | 2 | 3 |
|---|---|---|---|---|
| Hexane | 45.0 | | 18.8 ± 1.1 | |
| | 40.0 | 31.1 ± 0.5 | 10.5 ± 0.5[b,c] | 0.42 ± 0.01 |
| | 30.0 | 8.90 ± 0.05 | 3.01 ± 0.05 | |
| | 15.0 | | 0.34 ± 0.01 | |
| Acetic acid | 45.0 | | 11.8 ± 0.2 | |
| | 40.0 | | 5.75 ± 0.05[c] | |
| | 30.0 | 4.70 ± 0.02 | 1.60 ± 0.01 | |
| | 15.0 | | 0.162 ± 0.03 | |
| Ethanol | 40.0 | | 8.70 ± 0.04[b] | |
| | 30.0 | 7.46 ± 0.10 | | |
| Water | 40.0 | | 2.00 ± 0.03 | |
| | 30.0 | 1.57 ± 0.03 | | |
| Dimethyl sulfoxide | 40.0 | | 1.00 ± 0.02 | |
| $\Delta H^{\ddagger}_{298}$ (hexane) | | 23.2[d] | 23.4[d] | |
| $\Delta H^{\ddagger}_{298}$ (HOAc) | | | 25.2[d] | |
| $\Delta S^{\ddagger}_{298}$ (hexane) | | 4[e] | 2.5[e] | |
| $\Delta S^{\ddagger}_{298}$ (HOAc) | | | 7.2[e] | |

[a] Kinetics were followed, except where noted, by development of 360-nm product absorption band. Data reported represent the average of at least two, normally four, independent runs. All data reported gave excellent first-order plots over more than 90% reaction. Normal substrate concentrations were ~$2 \times 10^{-4}$ M. [b] Rate of disappearance of dienone (230-nm band) gave rates of $10.5 \times 10^{-4}$ $s^{-1}$ and $8.5 \times 10^{-4}$ $s^{-1}$ (ethanol). [c] Addition of hydroquinone ($2 \times 10^{-4}$ M) reduced $A_\infty$ (360 nm) by ~50%, but rates were unchanged, $5.7 \pm 0.2 \times 10^{-4}$ $s^{-1}$ (acetic acid), $11.5 \pm 0.5 \times 10^{-4}$ $s^{-1}$ (hexane). [d] Kilocalories $mole^{-1}$. [e] Calories $degree^{-1}$ $mole^{-1}$.

Scheme I

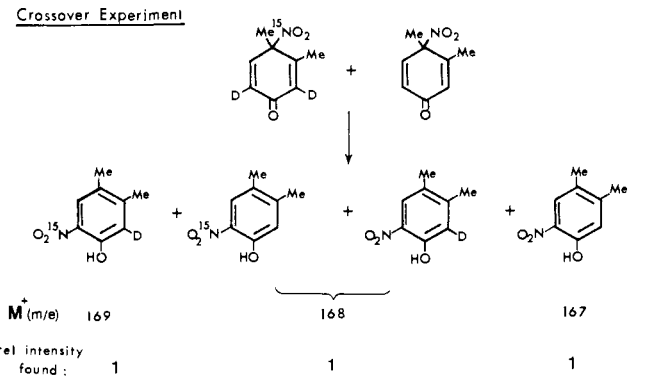


some kinetic data collected together with activation parameters. Products of rearrangement were shown by GLC analyses to be those derived from formal 1,3 shift.[6] No 1,2-shift products could be detected.

The data in Table I indicate the following reaction characteristics: (1) Rates of formation equal rates of reactant disappearance; (2) reaction rates decrease as polarity or hydrogen bonding ability of the solvent increases; (3) activation entropies are small but positive; (4) added radical scavengers do not alter reaction rates but do reduce the yield of nitrophenol products and increase yields of alkylphenol products; (5) the reactivity order **1** > **2** > **3** is observed,

These results indicate a radical dissociation-recombination mechanism as shown in Scheme I, where dissociation is rate limiting. Polar solvents presumably stabilize the reactant and reduce rearrangement rates. Observed activation entropies are consistent with rate-limiting dissociation and activation energies agree with thermochemical estimates.[7] Steric effects that increase on going from reactant to phenoxy radical may account for the reactivity order **1** > **2** > **3**. Formation of 3,4-dimethylphenol when **2** is allowed to react in the presence of hydroquinone reflects some diffusion of the radical pair from the solvent cage.[8]

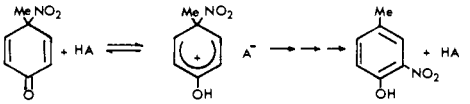
Scheme II




A test of this scheme was made by allowing an equimolar mixture of **2** and [$^{15}$N]-**2**-*2,6-d*$_2$ to react in dry *n*-hexane at 35 °C under kinetic conditions ($2 \times 10^{-4}$ M). The distribution of isotopic labels in the major product (>90% yield) was determined by mass spectrometry and the results are shown in Scheme II. Scrambling is substantial but far from complete. The extent of scrambling conforms to the results obtained with radical scavengers and leads to an estimated recombination rate to form product that is one half the rate of diffusion of radical pairs from the solvent cage.

We conclude that 4-methyl-4-nitrocyclohexadienones aromatize in a wide range of solvents by radical dissociation-recombination. Products that result from apparent 1,3 shifts of nitro groups in other ipso nitration products should be examined with this mechanism in view.

Perrin has suggested that certain rearomatizations of charged ipso nitration products, involving migration of the nitro group, may be best explained in terms of an intramolecular rearrangement via an aromatic radical cation-radical pair.[9]



We note that rates of aromatization of **1** and **2** give evidence of acid catalysis in sulfuric acid solutions that exceed 50 wt %. It seems reasonable to assume that under these strongly acidic conditions the oxygen conjugate acid is the reactant.[10] Products of the acid-catalyzed rearrangements of **1** and **2** include *o*-nitrophenols, phenols, and dinitrophenols. Detailed studies of this acid-catalyzed rearrangement are in progress and will be reported in due course.

**Acknowledgment.** We thank Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for grants supporting this work.

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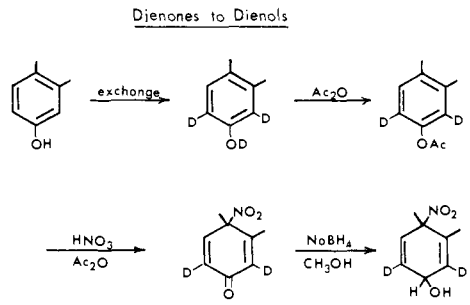
## Ipso Nitration. A Study of the Migratory Aptitude of the Nitro Group in the 1,2-Dimethyl-1-nitrocyclohexadienyl Cation

*Sir:*

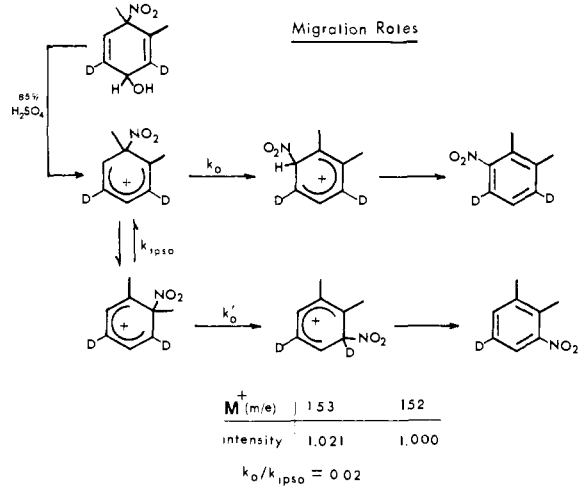
Trapping studies indicate that the ipso ion, 1,2-dimethyl-1-nitrocyclohexadienyl cation (**1**), is formed in >50% yield upon nitration of 1,2-dimethylbenzene.[1,2] Ion **1** is known to undergo nitro group migration to yield 1,2-dimethyl-3-nitrobenzene (**2**) in acidic, weakly nucleophilic media.[3,4] We report here results of labeling experiments designed to characterize the nitro group migrations in this cationic system.

This study required the development of a new method of synthesis, one that would yield an unambiguously labeled ipso adduct. 3,4-Dimethyl-4-nitrocyclohexadienone proved to be the key intermediate. As indicated in Scheme I, 3,4-dimethylphenol-*2,6-d*$_2$ was prepared by repeated exchange in acidified deuterium oxide. Nitration of the acetate derivative in acetic anhydride gave 3,4-dimethyl-4-nitrocyclohexadienone-*2,6-d*$_2$ in 80% yield.[5] Reduction of the labeled dienone with sodium borohydride in methanol at 0 °C gave crude 3,4-dimethyl-4-nitrocyclohexadienol-*2,6-d*$_2$.[6] The crude dienol was solvolyzed at 0 °C in 85 wt % sulfuric acid, Scheme II. 1,2-Dimethyl-3-nitrobenzene was isolated in 50% overall yield from the dienone.[7] Careful chromatographic analysis showed that the nitration product was isomerically pure. No 1,2-dimethyl-4-nitrobenzene could be detected with detection limits of <0.1%. Integration of the $^1$H NMR spectrum indicated equal amounts of 1,2-dimethyl-3-nitrobenzene-*4,6-d*$_2$ (**2**-$d_2$) and 1,2-dimethyl-3-nitrobenzene-*5-d*$_1$ (**2**-$d_1$). Low voltage (11 eV) mass spectrometry indicated a **2**-$d_2$:**2**-$d_1$ ratio of 1.021 ± 0.014.[8]

**Scheme I**




**Scheme II**




Earlier reports rule out intermolecular transfer of the nitro group during rearrangement in this system.[1,3,4] The present results confirm the absence of the 4-nitro isomer, and lower detection limits are established. An intramolecular 1,2 shift of the nitro group appears to summarize the data adequately. If this is granted, the distribution of labeled **2**-$d_2$ and **2**-$d_1$ provides a measure of the relative rate of migration of a nitro group to an equivalent ipso site vs. migration to an adjacent, open site bearing a hydrogen, Scheme II. With the assumptions that the isotopic isomers of **1** shown are steady-state intermediates and that $k_{ipso} = k_{ipso}'$ and $k_o = k_o'$, it may be shown that

$$k_o/k_{ipso} = [(\mathbf{2}\text{-}d_2/\mathbf{2}\text{-}d_1) - 1]$$

This leads directly to the conclusion that the rate of a 1,2 shift of a nitro group to an open position, $k_o$, is about one-fiftieth of the rate of migration to an equivalent ipso position, $k_{ipso}$. The nature of the competitive method is such that uncertanties in the ratio are quite large when rates compared are different. It should also be recognized that the scheme has neglected the difference in rates of $k_o$ and $k_o'$ that might be anticipated owing to hybridization changes in the migration transition state. Presumably this secondary isotope effect, $k_o/k_o'$, is less than unity, and correction of the equation shown above would increase $k_o/k_{ipso}$ estimates.[9] Despite numerical uncertainties, it seems safe to conclude that migration of a nitro group in **1** to an equivalent ipso site is sufficiently fast so that the isotopic isomers of **1** are nearly equilibrated before migration occurs to an open position.[10,11]

Are these results consistent with Perrin's suggestion that nitro group migrations occur via an aromatic radical cation-radical pair?[12] Perrin's model does predict a small $k_o$:$k_{ipso}$ ratio, since spin density of the *o*-xylene radical cation is large at the ipso positions (C-1 and C-2) and vanishingly small at the adjacent open positions (C-3 and C-6),[13] but, if this is granted, one must also expect that in the course of repeated dissociations and recombinations a reasonable fraction of the $\cdot NO_2$ would leak across the ring carbons of very low spin density to C-4 and C-5 where spin density is nearly as large as at C-1 and C-2. However, no trace of this leakage product, 1,2-dimethyl-4-nitrobenzene, has been found. It is most difficult to reconcile this result with Perrin's model without introducing very restrictive and cumbersome conditions involving highly oriented or strongly perturbed radical ion–radical pairs. Such conditions appear to be the operational equivalent of a two-electron three-center 1,2 shift.

It should be noted that the synthetic method used to prepare 1,2-dimethyl-3-nitrobenzene in this study may represent a generally useful procedure for conversion of *o*- and *p*-alkylphenols to isomerically pure *o*-alkylnitrobenzenes. The synthetic utility of this procedure is under active study.

**Acknowledgment.** We thank the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for grants supporting this work.

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