methylindole picrate, mp 159-160 °C. A mixture with the picrate prepared below melted at 159-161 °C.

**2-Ethyl-3,5,6,7-tetramethylindole and Its Picrate.** A solution of 3-pentanone (1.70 g, 0.0195 mol) and 2,3,4-trimethylphenylhydrazine (obtained by hydrolysis of 0.0195 mol of *N,N'*-dicarbethoxy-2,3,4-trimethylphenylhydrazine) in 19 mL of acetic acid was refluxed for 0.5 h. A solution of 6.7 g (0.029 mol) of picric acid containing 10% $H_2O$ in 11.5 mL of hot acetic acid was added, and the flask containing the picric acid solution was washed with an additional 10 mL of acetic acid, which was added to the reaction mixture. Hot $H_2O$ (ca. 3 mL) was added to the solution, which was cooled and filtered. The black residue was boiled in $H_2O$, filtered, and dried in air to give 4.0 g (0.093 mol, 47.7%) of 2-ethyl-3,5,6,7-tetramethylindole picrate as black crystals, mp 161-162 °C (from benzene). Anal. Calcd for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.55; H, 5.39; N, 12.75.

A sample (0.080 g) of the picrate was shaken with aqueous potassium hydroxide solution, and the mixture was extracted with methylene chloride, washed three times with aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left 2-ethyl-2,5,6,7-tetramethylindole as a tan oil which could not be crystallized.

**2-Ethyl-3,4,5,7-tetramethylindole and Its Picrate.** 3-Pentanone (2.92 g, 0.034 mol) and 2,4,5-trimethylphenylhydrazine (prepared from 0.034 mol of *N,N'*-dicarbethoxy-2,4,5-trimethylphenylhydrazine) in 15 mL of acetic acid were reacted as described for preparation of 2-ethyl-3,5,6,7-tetramethylindole. After addition of 7.79 g of picric acid in 18 mL of hot acetic acid, the product was worked up as previously described and recrystallized from benzene to give 1.71 g (0.0040 mol, 12%) of **2-ethyl-2,3,4,5-tetramethylindole picrate** as a reddish-brown solid. Anal. Calcd for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15; N, 13.02. Found: C, 56.02; H, 5.19; N, 12.48.

A sample of the picrate was converted to the free indole as described above to give a dark brown oil which did not crystallize.

Physical properties are given in Tables III and IV.

**Acknowledgments.** We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant in support of this work.

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# Carbon Isotope Effects in Proton Abstraction from 2-Nitropropane-*2*-$^{14}C$ by Pyridines. The Contribution of Tunneling[1]

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**Abstract:** The large kinetic isotope effects in the reaction of 2-nitropropane-*2-d* and 2-nitropropane-*2-t* with 2,6-dimethylpyridine are frequently cited as evidence for tunneling. We have found that 2-nitropropane-*2*-$^{14}C$ reacts with 2,6-dimethylpyridine in 60% *tert*-butyl alcohol-40% water to give a $^{14}C$ isotope effect, $k_{12}/k_{14}$, of 1.096 ± 0.003. The same reaction with pyridine gives $k_{12}/k_{14}$ of only 1.037 ± 0.002. Comparison with model calculations suggests that both carbon isotope effects contain a contribution from tunneling, and that the larger isotope effect with 2,6-dimethylpyridine as base arises from a larger tunnel correction. The calculations also suggest that significant rehybridization at C-2 has occurred in the transition state for the proton abstraction.

We recently reported evidence that tunneling contributes to carbon isotope effects on proton abstraction from carbon in E2 reactions of 2-phenylethyldimethylsulfonium and 2-phenylethyltrimethylammonium ions.[2,3] In order to obtain further evidence on this matter, we chose to study carbon isotope effects in a reaction for which a small change in the attacking base produces a dramatic change in the hydrogen isotope effect. This reaction is the pyridine-promoted ionization of 2-nitropropane. In 60% *tert*-butyl alcohol-40% water at 24.88 °C, the reaction with pyridine occurs with a $k_H/k_D$ of 9.8, but the reaction with 2,6-dimethylpyridine occurs with a $k_H/k_D$ of 24.1.[4] Although the reaction of 2-nitropropane-*2-d* with 2,6-dimethylpyridine is slow and difficult to follow, any doubt that the large isotope effect is essentially correct is allayed by the observations that $k_H/k_D$ is consistent with $k_H/k_T$[5] and that it agrees rather well with $k_H/k_D$ measurements by Bell and Goodall in aqueous solution.[6] In addition, a large $k_H/k_D$ value is found for the reaction of methyl 4-nitrovalerate with 2,4,6-trimethylpyridine.[7]

The tendency of 2,6-disubstituted pyridines to give unusually large isotope effects in proton abstractions has been ascribed to tunneling promoted by steric hindrance in the transition state.[4] The steric hindrance was suggested to lead to a high and narrow potential-energy barrier, a situation particularly favorable for tunneling. The temperature dependence of the isotope effect ($A_H/A_D$, the ratio of Arrhenius preexponential factors, is 0.15) with 2,4,6-trimethylpyridine was cited as additional support for tunneling. Later it was pointed out that the steric effect could also operate by hindering solvation of the proton in transit, thereby reducing the effective mass along the reaction coordinate and favoring tunneling.[8-10]

Coupling of internal heavy-atom motion with the proton transfer may have the same depressive effect as solvation on the isotope effect and the tunnel effect.[11,12] An unusually large isotope effect

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[1] This work was supported by the National Science Foundation.

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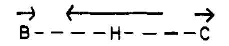
**Table I.** $^{14}$C Isotope Effects in the Reaction of 2-Nitropropane-2-$^{14}$*C* with Pyridine Bases in 60% *tert*-Butyl Alcohol–40% Water at 30 °C[a]

| base | $R_0$, µCi/mmol | $R_p$, µCi/mmol | $F_1$ | $k_{12}/k_{14}$ |
|---|---|---|---|---|
| pyridine | 0.065 80 | 0.063 65 | 0.0876 | 1.035 |
| pyridine | 0.065 80 | 0.063 26 | 0.0537 | 1.041 |
| pyridine | 0.065 80 | 0.063 59 | 0.0741 | 1.036 |
| | | av | | 1.037 ± 0.002[b] |
| 2,6-lutidine | 0.070 05 | 0.064 46 | 0.0565 | 1.089 |
| 2,6-lutidine | 0.064 88 | 0.059 64 | 0.126 | 1.094 |
| 2,6-lutidine | 0.223 2 | 0.202 8 | 0.0957 | 1.106 |
| 2,6-lutidine | 0.059 1 | 0.054 3 | 0.123 | 1.094 |
| 2,6-lutidine | 0.039 75 | 0.036 42 | 0.139 | 1.099 |
| | | av | | 1.096 ± 0.003[c] |

[a] See Experimental Section for details of concentration and time. [b] Standard deviation of mean; 95% confidence limit ±0.008. [c] Standard deviation of mean; 95% confidence limit ±0.008.

can in this view be taken as evidence for minimal heavy-atom involvement in the reaction coordinate motion, either from solvation of the proton or internal heavy-atom motion. Bordwell and Boyle have suggested that rehybridization at carbon (and hence heavy-atom motion) is slight in the rate-determining step of proton abstraction from nitroalkanes.[13]

If motion of the α carbon really makes an insignificant contribution to the reaction coordinate motion in proton abstraction from nitroalkanes, the marked difference in the hydrogen isotope effects between the reactions with pyridine and 2,6-disubstituted pyridines should not be reflected in the carbon isotope effects. The qualitative basis of this statement can be outlined as follows. The p*K*s of pyridine (5.17), 2,6-dimethylpyridine (6.75), and 2,4,6-trimethylpyridine (7.59) are all fairly close to that of 2-nitropropane (7.7).[4,14,15] The range of Δp*K* is only 0.1–2.5, and a transition state with an almost symmetrically located proton is expected with all three bases according to the criterion of Bell and Goodall.[6] If the proton transfer can be described by a simple three-center model, the motion along the reaction coordinate will in such a case consist almost entirely of proton motion (**1**).



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Changing the carbon mass will have little influence on the reaction coordinate frequency, and the tunnel correction to the rate of proton transfer should be almost the same for the $^{12}$C and $^{14}$C species. Only if carbon motion is a significant contributor to the reaction coordinate motion, either in an unsymmetrical three-center transition state or in a more complex reaction coordinate that couples the proton transfer with carbon motion, is a sizable tunnel correction to the carbon isotope effect expected.

The results reported in Table I show that the carbon isotope effects parallel the hydrogen isotope effects. In both cases, there is a large increase when pyridine is replaced by 2,6-dimethylpyridine as base. The $^{14}$C isotope effect of 3.7% with pyridine as base corresponds to a $^{13}$C effect of about 1.9%.[16] This is of the same order of magnitude as we observed earlier for $^{13}$C isotope effects in E2 reactions,[2,3] which we took as indicative of a modest but significant contribution of tunneling to the isotope effect. The 9.6% $^{14}$C isotope effect with 2,6-dimethylpyridine (corresponding to a $^{13}$C isotope effect of 4.9%[16]) is, however, larger than any of our previous values.[2,3]

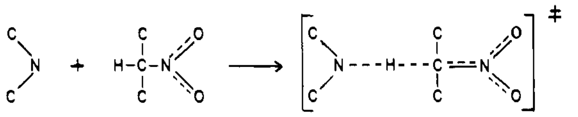
**Table II.** Force Constants for Reactant and Transition State for Pyridine + 2-Nitropropane[a,b]

| type of force constant | value in reactant | value in transition state[c,d] |
|---|---|---|
| C==N (pyridine) str | | 8.0 |
| N---H str | 6.5 | $6.5n_{NH}$ |
| H---C str | 4.7 | $4.7n_{CH}$ |
| C–C str | 4.7 | 4.7 |
| C==N str | 4.7 | $4.7n_{CN}$ |
| N==O str | 8.6 | $5.7n_{NO}$ |
| C==N--H bd | | $0.64n_{NH}n_{CN}$ |
| C–N–C (pyridine) bd | | 0.40 |
| H--C–C bd | 0.40 | $0.40n_{CH}$ |
| C–C–C bd | 0.35 | 0.35 |
| C–C==N bd | 0.40 | 0.40 |
| N--H--C lin bd | | $0.32n_{NH}n_{CH}$ |
| C==N==O bd | 0.80 | 0.80 |
| O==N==O bd | 1.20 | 1.20 |
| H–NC$_2$ oop bd | 0.35 | 0.35 |
| C==NO$_2$ oop bd | 0.35 | 0.35 |
| CC==NO tors | 0.20 | 0.20 |
| CN--H--CC tors | 0.02 | 0.02 |

[a] Values in mdyn Å$^{-1}$ for stretching and mdyn Å$^{-1}$ rad$^{-1}$ for bending force constants. The bending force constants were multiplied by $r_1r_2$, the equilibrium bond lengths of the respective bonds, before the calculation. [b] See text and ref 20–26 for sources of the values. [c] $n_{ij}$ refers to the order of the *ij* bond in the particular model. In all models $n_{CH} = 1.0 - n_{NH}$ unless otherwise noted. [d] In the sp$^3$ model $n_{CN} = 1.0$ and $n_{NO} = 1.5$ for all values of $n_{CH}$, but for the variable-geometry model $n_{CN} = 1.0 + n_{NH}$ and $n_{NO} = 1.5 - 0.5n_{NH}$.

In view of the fact that Δp*K* changes by only 1.6 units when the base changes from pyridine to 2,6-dimethylpyridine, it does not seem reasonable to ascribe the change in $k_{12}/k_{14}$ (or in $k_H/k_D$) to a change in transition-state symmetry. An increase in the tunnel correction is a much more likely source of the increase in isotope effect. If tunneling is a significant contributor to the carbon isotope effect, at least some contribution of carbon motion to the reaction coordinate is implied.

In order to test our qualitative reasoning on the effect of heavy-atom motion, we carried out calculations on the model reaction shown in eq 1. The partial structures meet the two-bonds-removed rule for cutoff models[17,18] with respect to isotopic substitution at the hydrogen being transferred, but not with respect to isotopic substitution at C-2 of the 2-nitropropane. The frequencies lost by omission of the methyl hydrogens should, however, be little dependent on the mass of C-2 and change little from reactant to transition state. The C–N–C angle of the "pyridine" was taken as 120° and the C–N bond length as 1.47 Å. For the substrate, C-2 was taken as tetrahedral, the O–N–O angle as 127°, the C–N bond as 1.47 Å, the N–O bond as 1.22 Å, the C–C bond as 1.54 Å, and the C–H bond as 1.09 Å. Most of these values are based on the corresponding ones for nitromethane.[19]



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The valence force constants of the reactant and transition state are listed in Table II. They were derived in part from general compilations[20–23] and in part from published vibrational analyses

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of nitroalkanes.[24-26] Some of the force constants from the last of these investigations were used as guides to relative magnitudes rather than directly, as they are derived from a force field with rather large off-diagonal elements.[26] The force constants and other basic features of our models are not dissimilar from those used by Melander and Bergman[27] in their calculations of deuterium isotope effects in the reaction of hydroxide ion with nitromethane and 2-nitropropane, though we diverge from their models to a considerable extent in the ways in which transition-state force constants and geometry are treated. The dependence of transition-state force constants on bond order is given in the last column of Table II. The CCN, CNO, and ONO bending force constants were not varied even though bond orders involving these bonds are changing in one set of our models. When they are varied in a manner analogous to that used for other bends in Table II, unrealistically large force constants result as the CN bond approaches a full double bond. One set of calculations in which they were varied showed that the only effect on the final outcome was to make both $k_H/k_D$ and $k_{12}/k_{14}$ somewhat smaller, as might be expected for transition states that place more constraint on the motion of the isotopic atoms.

The only off-diagonal elements were those used to generate the reaction coordinate frequency in the transition state. Two different sets of models were used. One, the sp$^3$ model, kept the sp$^3$ hybridization at C-2 constant for all extents of proton transfer, and left the bonding to and within the nitro group unchanged. For this model the single off-diagonal element was that connecting the N---H and C---H stretches, given by

$$F_{NH,CH} = A(F_{NH}F_{CH})^{1/2} \tag{2}$$

where $A$ is an arbitrary parameter. The second, the variable geometry model, allowed C-2 to go from sp$^3$ to sp$^2$ as the proton transfer proceeded. Simultaneously the C–NO$_2$ bond went from single to double, and the NO bonds from 1.5-order to single. The CH stretch was coupled to the CN stretch, and it in turn to the NO stretches, introducing the additional off-diagonal elements

$$F_{CH,CN} = B(F_{CH}F_{CN})^{1/2} \tag{3}$$

$$F_{CN,NO} = C(F_{CN}F_{NO})^{1/2} \tag{4}$$

The relation between values of $A$, $B$, and $C$ for any given value of the curvature parameter, $D$, was derived as previously described[28] and is given by

$$1 - A^2 - B^2 - 2C^2 + 2A^2C^2 = D \tag{5}$$

Only those solutions to eq 5 that give positive values of $A$, $B$, and $C$ were used so as to keep the stretching motions of the reacting bonds in the proper phases for a realistic reaction coordinate motion. For lack of any good reason for doing otherwise, we arbitrarily set $B = C$ in all of our calculations.

The general approach in the choice of parameters was to look for sets that gave overall isotope effects similar to the observed ones for $k_H/k_D$, and then to see whether reasonable adjustments could also reproduce $k_{12}/k_{14}$. A further constraint was that calculated tunnel corrections to $k_H/k_D$ should be of roughly the same size as tunnel corrections estimated from the observed magnitude and temperature dependence of $k_H/k_D$. This serves to set realistic limits for the curvature parameter $D$.

The tunnel corrections were calculated from the first term of the Bell equation[29]

$$Q_t = \frac{u_t/2}{\sin (u_t/2)} \tag{6}$$

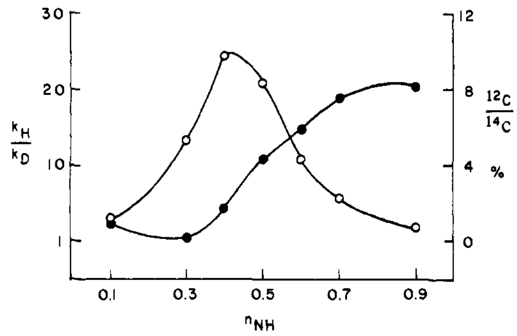

**Figure 1.** Calculated isotope effects as functions of the NH bond order (extent of H transfer) for the reaction of pyridine bases with 2-nitropropane. Open circles, $k_H/k_D$; closed circles, $(k_{12}/k_{14} - 1) \times 100$. sp$^3$ model (see text), $A = 1.15$. Tunnel corrections included.

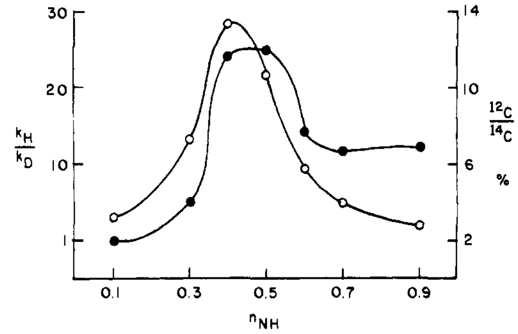

**Figure 2.** Calculated isotope effects as functions of the NH bond order (extent of H transfer) for the reaction of pyridine bases with 2-nitropropane. Open circles, $k_H/k_D$; closed circles, $(k_{12}/k_{14} - 1) \times 100$. Variable geometry model (see text), $A = 1.11$, $B = C = 0.427$, $D = -0.33$. Tunnel corrections included.

where $u_t = h|\nu_L^{\ddagger}|/kT$ and $\nu_L^{\ddagger}$ is the reaction coordinate frequency obtained in the isotope-effect calculations. The overall isotope effects then are

$$\frac{k_H}{k_D} = \frac{Q_{tH}}{Q_{tD}}\left(\frac{k_H}{k_D}\right)_s \tag{7}$$

and

$$\frac{k_{12}}{k_{14}} = \frac{Q_{t(12)}}{Q_{t(14)}}\left(\frac{k_{12}}{k_{14}}\right)_s \tag{8}$$

were the subscript s signifies semiclassical isotope effect, or the isotope effect in the absence of tunneling. Except as otherwise noted, isotope effects in the following discussion are overall effects. The BEBOVIB-IV program was used to perform the calculations.[30]

The results for the sp$^3$ model are shown in Figure 1. The model gives a maximum $k_H/k_D$ of 24, but the $^{14}C$ isotope effect corresponding to this value is less than 2%. If all $^{14}C$ effects corresponding to $k_H/k_D > 20$ are considered as possibilities, the largest value is still less than 5%. Using the sp$^3$ model it was not possible to achieve a $^{14}C$ isotope effect anywhere near the 9.6% observed with 2,6-dimethylpyridine, except at large values of $n_{NH}$ (large extents of hydrogen transfer) where $k_H/k_D$ was small.

The variable-geometry model, on the other hand, easily permits the generation of $^{14}C$ isotope effects of 10% or more at or near the $k_H/k_D$ maximum. One set of results is shown in Figure 2, where a maximum $k_H/k_D$ of 28 is accompanied by a $^{14}C$ effect of 12%. This increase in the carbon isotope effect arises from the tunnel correction, which goes from 0.5% for the sp$^3$ model to 12%

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Table III. Calculated Isotope Effects as Functions of the NH Bond Order for the Reaction of Pyridine Bases with 2-Nitropropane. Influence of Solvation and Total Bond Order to Hydrogen[a,b]

| | | | |
|---|---|---|---|
| | Unsolvated[c] | | |
| $n_{NH}$ | 0.3 | 0.4 | 0.5 |
| $k_H/k_D$ | 13.10 | 28.56 | 21.36 |
| $^{12}C/^{14}C$, % | 4.06 | 11.73 | 11.93 |
| | Water Solvated, $n_{OH} = 0.1$ | | |
| $n_{NH}$ | 0.3 | 0.4 | 0.5 |
| $k_H/k_D$ | 9.46 | 19.88 | 15.02 |
| $^{12}C/^{14}C$, % | 2.73 | 9.84 | 10.34 |
| | Water Solvated, $n_{OH} = 0.2$ | | |
| $n_{NH}$ | 0.3 | 0.4 | 0.5 |
| $k_H/k_D$ | 7.41 | 15.40 | 11.67 |
| $^{12}C/^{14}C$, % | 2.59 | 9.54 | 10.11 |
| | Water Solvated, $n_{OH} = 0.2$, $n_{NH} + n_{CH} = 0.8$ | | |
| $n_{NH}$ | 0.2 | 0.3 | 0.4 |
| $k_H/k_D$ | 5.42 | 9.27 | 8.66 |
| $^{12}C/^{14}C$, % | 0.83 | 2.94 | 5.05 |
| | Unsolvated, $n_{NH} + n_{CH} = 0.8$ | | |
| $n_{NH}$ | 0.2 | 0.3 | 0.4 |
| $k_H/k_D$ | 9.80 | 17.09 | 16.10 |
| $^{12}C/^{14}C$, % | 2.13 | 4.24 | 6.27 |

[a] $n_{NH} + n_{CH} = 1.0$ unless otherwise noted. The variable-geometry model and the parameters $A$, $B$, $C$, and $D$ are the same as for Figure 2. All values include tunnel corrections. [b] The water-solvated models contain an $H_2O$ molecule with its oxygen immediately above the proton in transit and bound to it by a bond of order $n_{OH}$. [c] The isotope effects reported in Figure 2.

for the variable-geometry model. The major factor in this change is the increased isotopic sensitivity of the reaction-coordinate frequency. The ratio $\nu^{\ddagger}_{L(12)}/\nu^{\ddagger}_{L(14)}$ is 1.000 58 for the sp$^3$, but 1.007 13 for the variable-geometry model. This greatly increased isotopic sensitivity undoubtedly results from the increased involvement of carbon in the reaction-coordinate motion produced by coupling the C–H stretch with the C–N stretch.

Comparison of the calculated and experimental carbon isotope effects shows that there must be a significant contribution of tunneling even to the smaller of the two measured isotope effects. In the vicinity of the $k_H/k_D$ maximum, the sp$^3$ model predicts a semiclassical carbon isotope effect of a little over 1%, while the variable-geometry model predicts an *inverse* semiclassical effect of about 0.5%. The models thus suggest that at least 2–3% of the 3.7% effect with pyridine, and 8–9% of the 9.6% effect with 2,6-dimethylpyridine, arise from tunneling. Tunnel corrections of 1.5–2.5% are needed to explain our $^{13}C$ isotope effects in E2 reactions of 2-phenylethyl derivatives[2,3] (2.9–4.8% for the corresponding $^{14}C$ effects, since our model calculations show that the same relation[16] applies to the tunnel corrections as to the semiclassical isotope effect). Thus the tunnel correction for the reaction of 2-nitropropane with pyridine seems to be a little less than those for the E2 reaction.

The observation of sizable tunnel corrections to the carbon isotope effects indicates that heavy-atom motion arising from rehybridization must be significant in the transition states for these reactions. Some doubt is thus cast on the suggestion of Bordwell and Boyle,[13] though we cannot specify quantitatively how extensive the rehybridization need be. Neither can we specify a precise reason for the greater tunnel correction to the carbon isotope effect with 2,6-dimethylpyridine than pyridine. It could arise from increased rehybridization in the transition state, but it is also possible that steric hindrance acts primarily by increasing the curvature of the potential barrier.

We noted above that steric hindrance to solvation of the proton in transit has been predicted to promote tunneling.[8-10] The influence of solvation was explored in calculations reported in Table III, where the unsolvated model of Figure 2 is compared to models in which a water molecule is bonded via its oxygen atom to the proton in transit. Comparison of the unsolvated, $n_{OH} = 0.1$, and $n_{OH} = 0.2$ models shows that solvation without any other adjustments in force constants decreases $k_H/k_D$ substantially, but has relatively little influence on the carbon isotope effect. The model for the fourth set of entries in the table is perhaps more realistic, for the total bond order to the proton in transit is kept at 1.0 by the requirement that $n_{NH} + n_{CH} = 0.8$ when $n_{OH} = 0.2$. This model does produce substantial decreases in both the hydrogen and carbon isotope effects.

Comparison of the fourth and fifth sets of entries in Table III permits some more specific conclusions about the sources of the changes in the calculated hydrogen and carbon isotope effects. In the fifth entry, simply decreasing the total bond order to the proton in transit to 0.8, without introducing any water of solvation, depresses the carbon isotope effect to about the same extent as in the solvated model of the fourth set of entries. Furthermore, the decreases in both cases are the consequence of smaller tunnel corrections—the semiclassical carbon isotope effects actually *increase* slightly. When $n_{NH} + n_{CH} < 1.0$, the force constants $F_{NH}$, $F_{CH}$, and $F_{NH,CH}$ (eq 2) are decreased, which decreases the absolute value of the reaction coordinate frequency and hence the tunnel corrections. Solvation of the proton in transit thus can markedly reduce the carbon isotope effect only if it reduces the sum of bond orders, $n_{NH} + n_{CH}$.

Finally, the first and last sets of entries in Table III show that 2,6-dimethylpyridine cannot be exerting a steric effect that simply causes the CH and NH bonds to be longer and weaker in the transition state. Such an effect obviously decreases rather than increases both the hydrogen and carbon isotope effects.

## Experimental Section

**Materials.** *tert*-Butyl alcohol and pyridine were distilled prior to use. 2,6-Dimethylpyridine was distilled from boron trifluoride etherate.[31]

**2-Nitropropane-*2*-$^{14}$*C*.** The general procedure of Barnes and Patterson[32] was followed. Acetone-*2*-$^{14}$*C* (ICN Chemical and Radioisotope Division, Cleveland, Ohio) was diluted to 14 g (0.24 mol) and mixed with 30 mL of water and 21.8 g of hydroxylamine hydrochloride. To this mixture was added with stirring over 1 h 14.8 g of sodium carbonate, and stirring continued for another 3 h. The solution was continuously extracted with ether for 30 h, the ether solution dried over magnesium sulfate, and the ether removed. Further drying in a vacuum desiccator yielded 16 g (91%) of crude oxime that was used directly in the next steps. The oxime was dissolved in 250 mL of methylene chloride and chlorine gas passed through the solution at 0 °C until a greenish color persisted. Flushing with oxygen to remove excess chlorine was followed by treatment with a stream of ozone in oxygen until the blue color disappeared (6–48 h in different experiments). The solvent was removed on a rotary evaporator and the residue treated with 14.4 g of sodium hydroxide in 180 mL of water and 1 g of 5% palladium on carbon. The mixture was hydrogenated at 30 psi initial pressure of hydrogen until uptake ceased (ca. 5 h). The mixture was then filtered, and cooled to 0 °C, and 25 g of hydroxylamine hydrochloride was added. The resulting mixture was left standing overnight in the refrigerator, saturated with sodium chloride, and extracted several times with pentane. The extracts were dried over sodium sulfate, the pentane removed by distillation, and the residue distilled, bp 120.5–121.5 °C. The 2-nitropropane-*2*-$^{14}$*C* was chased with inactive material to increase recovery of activity. Yields in cold runs ran 30–55%.

**Determination of $k_{12}/k_{14}$ for the Reaction of 2-Nitropropane-*2*-$^{14}$*C* with Pyridine Bases.** A 500-mL solution in 60% *tert*-butyl alcohol–40% water 0.1–0.15 M in 2-nitropropane-*2*-$^{14}$*C*, 0.13–0.18 M in pyridine or 2,6-dimethylpyridine, 0.04 M in bromine, and 0.035 M in potassium bromide was kept in a constant-temperature bath at 30 °C until 5–10% reaction had occurred (119–164 h with pyridine, 95–190 h with 2,6-dimethylpyridine). The solution was then poured into ice and water containing enough Dowex W-X8 acid ion exchange resin to neutralize the excess base. A solution of sulfur dioxide in water was added to destroy the remaining bromine. The mixture was filtered and extracted several times with pentane. The combined pentane extracts were washed with water and dried over sodium sulfate. The fraction of reaction, $F_1$, was determined by analyzing the pentane solution for 2-nitropropane and 2-bromo-2-nitropropane by GLC on a $^1/_8$ in. × 6 ft column of Chromosorb 101 (column temperature 140 °C, detector temperature 200 °C, injector temperature 150 °C, flow rate 70 mL/min), taking the molar

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(31) Lewis, E. S.; Allen, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2022–2024.
(32) Barnes, M. W.; Patterson, J. M. *J. Org. Chem.* **1976**, *41*, 733–735.

response factors of the two compounds into account.

The pentane was removed by distillation and the 2-nitropropane and 2-bromo-2-nitropropane were separated by preparative GLC on a $^1/_4$ in. × 12 ft column of SF-96 on Chromosorb W (column temperature 85 °C, detector temperature 180 °C, injector temperature 110 °C, flow rate 60 mL/min). The purity of the 2-bromo-2-nitropropane was checked by GLC. Analyses for radioactivity were conducted on a Beckman LS-100C liquid scintillation counter on 50-mg samples in 15 mL of scintillation cocktail (26.50 g of butyl-PBD scintillator in 8 pints of toluene). Three samples were counted for each run to ±0.2% ($2\sigma$) precision.

Isotope effects were calculated from the equation[33]

$$\frac{k_1}{k_2} = \frac{\log (1 - F_1)}{\log [1 - F_1(R_p/R_0)]} \qquad (9)$$

where $F_1$ is the fraction of reaction, $R_0$ is the molar activity of the original 2-nitropropane, $R_p$ is the molar activity of the 2-bromo-2-nitropropane isolated from the reaction mixture, and $k_1/k_2$ is $k_{12}/k_{14}$. The data and the derived isotope effects are listed in Table I.

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[33] Melander, L.; Saunders, W. H., Jr. "Reaction Rates of Isotopic Molecules"; Wiley-Interscience: New York, 1980; p 100.

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# Optical Rotary Dispersion Studies. 129.[1] Conformational Isotope Effects and Octant Contributions of $CD_3$ and $^{13}CH_3$ Groups in Cyclohexanone

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**Abstract**: Through the variable-temperature circular dichroism measurements of (2*S*)-2-methyl-$d_3$-2-methylcyclohexanone (**3**) and (2*S*)-2-methyl-$^{13}C$-2-methylcyclohexanone (**4**), quantitative values for the conformational isotope effect are obtained. The chair conformation with the heavier isotope in the equatorial position is found to be energetically preferred by 3.4 and 1.5 cal/mol for **3** and **4**, respectively, and empirical force-field calculations qualitatively confirm this view. The $CD_3$ and $^{13}CH_3$ groups act as weaker octant perturbers compared to $CH_3$.

## Introduction

The investigation of steric isotope effects, i.e., the effect of differences in the "effective size" between different isotopes, has been investigated primarily through kinetic studies where this phenomenon is most easily measurable.[2] The conformation of the transition state has to be known to obtain quantitative values through this method, as for example the difference in van der Waals radii, information which is rarely available. A more direct approach to this question would be the determination of the effect which an isotopic substitution exerts on the composition of a dynamic conformational equilibrium. Experimental verification for the existence of this "conformational isotope effect" has only recently become available.

Using $^{13}C$ NMR chemical shifts, Baldry and Robinson[3] concluded that for *trans*-1-methyl-$d_3$-3-methyl substituted cyclohexanes (e.g., compound **1**, Scheme I) the conformation with the $CD_3$ substituent in the axial position is favored by ca. 11 cal/mol. This value corresponds to an equilibrium shift of 0.6% toward **1**-ax (Scheme I) at room temperature. Two other studies[4,5] have interpreted the unusually large NMR chemical shifts introduced through deuterium substitution in terms of conformational isotope effects but did not attempt to evaluate the conformational-energy differences.

From our studies,[6,7] using variable-temperature circular dichroism measurements, we have shown that for 2,2-dimethylcyclohexanones, substituted with deuterium in various ring positions (e.g., compound **2**, Scheme I), the conformer with the deuterium in the axial position is energetically more stable by 2 to 7 cal/mol, which corresponds to a 0.09 to 0.30% equilibrium shift towards **2**-ax (Scheme I). Therefore, the results of both these studies are consistent in that deuterium is found to occupy preferentially the position of higher strain (e.g., axial), which is in agreement with the results from the kinetic investigations that deuterium is of "smaller size" compared to hydrogen. The high sensitivity of the circular dichroism measurements toward such small changes in a conformational equilibrium was achieved by dimethylation of the $\alpha$ position. While the *gem*-dimethyl group does not contribute by itself to any preference of one conformer over the other, it causes the rotational strengths of both conformers to be large numbers of opposite sign (see Scheme I); therefore we have termed this group a "chiral probe".

By applying the same principle, we report here the conformational isotope effects for the equilibria of (2*S*)-2-methyl-$d_3$-2-methylcyclohexanone (**3**), (2*S*)-2-methyl-$^{13}C$-2-methylcyclohexanone (**4**), and (3*R*)-3-methyl-$d_3$-3-methylcyclohexanone (**5**). These compounds can be assumed to exist exclusively in a dynamic equilibrium between two chair conformations, which are reproduced in Scheme I together with their octant representations. As has been observed for **1** and **2**, the isotopic "size difference" is expected to bias the equilibria of **3**–**5** slightly toward one or the other side. Quantitative evaluation of the energy differences from the temperature-dependent circular dichroism spectra requires a knowledge of the rotational strengths of the specific conformers. For **3** we obtained these values from conformationally rigid (2*S*,4*R*)-2-methyl-$d_3$-2-methyl-4-*tert*-butylcyclohexanone (**6**) and (2*R*,4*R*)-2-methyl-$d_3$-2-methyl-4-*tert*-butylcyclohexanone (**7**) with the $CD_3$ substituent in the axial and equatorial position, respectively. A comparison of the circular dichroism spectra of these two compounds with that of the previously reported[1] (4*R*)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**8**) allows us to obtain values for the relative octant contributions of the $CD_3$ group in various positions of the cyclohexanone ring—a subject which is discussed in detail in the present paper.

**Synthesis.** The synthesis of compounds **3** and **5**–**8** starting with (+)-nopinone (**10**) of known optical purity was achieved by the reaction steps outlined in Scheme II. Stepwise alkylation under

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[1] For preceding paper see: Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.*, **1980**, *102*, 2737–45.

[2] For a recent review on this subject see: Carter, R. E.; Melander, L. *Adv. Phys. Org. Chem.* **1973**, *10*, 1–27.

[3] Baldry, K. W.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1663–1668.

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[7] Lee, S.-F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 8010–8012.

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