Table IX. Kinetic Parameters for Ring Inversion of Piperidine-3,3,5,5-d_4 (I) and Its N-Methyl (II) and N-*t*-Butyl (III) Derivatives in Methanol-d_4

I			II		III	
Temp, °C	$\tau(\alpha)$,[a] sec	$\tau(\gamma)$, sec	Temp, °C	$\tau(\gamma)$,[a,b] sec	Temp, °C	$\tau(\alpha)$,[a,c] sec
-50 ± 1[d]	0.0020	0.0015	−10.5	0.0015	−16.5	0.00040
−55	0.0045	0.0040	−17	0.0030	−22	0.00090
−60	0.0090	0.0085	−22	0.0070	−28	0.0018
−62.5	0.0150	0.013	−28	0.012	−34.5	0.0040
−65	0.022	...	−33	0.020	−39	0.0060
−70	0.045	0.035	−38.5	0.040	−44	0.012
−75	0.150	0.090	−44.5	0.090	−49	0.025
−80	0.30	...	...	...	−53.5	0.045
					−58	0.095

[a] Mean lifetime, *i.e.*, the reciprocal of the first-order rate constant; the error is generally about 10% of the value quoted. [b] The changes in the α-proton resonances could not be analyzed because of overlap of the methyl resonance. [c] The resonance of the *t*-butyl group obscures the γ resonances sufficiently to preclude an accurate kinetic analysis. [d] The temperature was determined at each point by measurement of the distance between the methanol peaks.

heated at 110° for 3 hr in a sealed ampoule. The tube was cooled and opened and the excess ammonia removed by forced effervescence. The methanol was removed by bulb-to-bulb distillation. The white solid was taken up in 3 ml of water and placed in a small test tube. Pellets of potassium hydroxide were added slowly until two layers separated. The upper layer was removed and purified by bulb-to-bulb distillation to give essentially pure piperidine-3,3,5,5-d_4 (140 mg).

N-Methylpiperidine-3,3,5,5-d_4 (II) and **N-*t*-butylpiperidine-3,3,5,5-d_4** (III) were prepared from 1,5-dibromopentane-2,2,4,4-d_4 and methanol containing methylamine and *t*-butylamine, respectively, in the same manner as piperidine (I).

3-Azabicyclo[3.3.1]nonane (IV). Dimethyl isophthalate was converted to a mixture of *cis*- and *trans*-dimethyl 1,3-cyclohexanedicarboxylate by hydrogenation at room temperature over Adams catalyst.[29] Treatment of the corresponding diacid with ammonium hydroxide according to the method of Komppa[30] produced 1,3-cyclohexanedicarboximide which, upon reaction with lithium aluminum hydride, gave 3-azabicyclo[3.3.1]nonane.[31]

3-Methyl-3-azabicyclo[3.3.1]nonane (V). To a stirred solution of 3.0 g of 3-azabicyclo[3.3.1]nonane in 25 ml of methanol, refluxing gently, was added 5.2 g of methyl iodide in small portions through the condenser. Five minutes after completion of addition, the solution was cooled to room temperature, and 70 ml of dry ether was added. The resulting suspension was filtered, and the precipitate was washed with 100 ml of dry ether. The precipitate was dissolved in 100 ml of water and treated with 1 g of sodium hydroxide in 10 ml of water. The oily upper layer was removed and dried with potassium hydroxide pellets to give 3-methyl-3-azabicyclo[3.3.1]nonane, mol wt 139 by mass spectroscopy (calcd 139.24).

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Acidity of Hydrocarbons. XXV. Secondary Isotope Effects in the Lithium Cyclohexylamide Catalyzed α-Deuterium Exchange of Ring-Deuterated Toluenes[1]

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Abstract: The protodedeuteration rates of toluene-α,4-d_2, -α,2,4,6-d_4, and -α,2,3,4,5,6-d_6 with lithium cyclohexylamide–cyclohexylamine at 50° are dissected to the following isotope effects per ring deuterium: *ortho*, −2.4%; *meta*, −0.4%; *para*, −1.8%. These rate retardations are in the direction and of the order of magnitude expected for deuterium as an electron-donating substituent but the variations with position are not explicable on any simple general basis.

Isotope effects are generally explicable by statistical mechanical treatments of the entire molecular systems involved. Since, in general, this is difficult or impossible, the total system is usually truncated to the region of isotopic change.[3] In some secondary deuterium isotope effects this type of simplication is not feasible because the effects are small, and there are no obvious simple changes in force constants. In such cases deuterium has been treated as a substituent of a subtle type, and its effects have been discussed with the language of substituent effects. For example, a number of previous studies have shown that deuterium exhibits a small but definite electron-donating "inductive effect"

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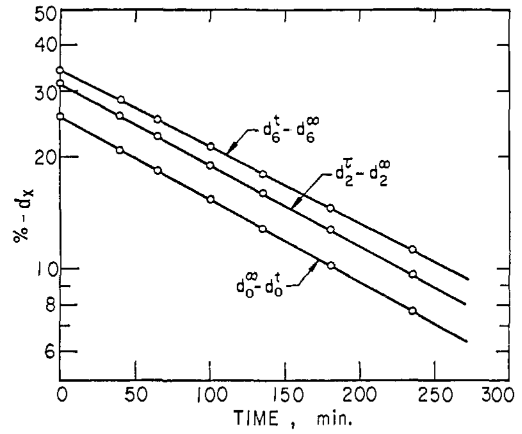

Figure 1. First-order kinetic plot of data from Table I. For the competitive exchange between toluene-d_6, -d_2, and -d_1 with cyclohexylamine using lithium cyclohexylamide as catalyst.

relative to hydrogen.[4] Substituent effects are well developed for benzenoid systems, and nuclear deuteration effects have been amply demonstrated: the acidities of benzoic acid[5] and anilinium ions,[6] the reactions of pyridine with methyl iodide,[7] π-complex equilibria,[8] the ionization equilibrium of triphenylmethyl chloride,[9] and the solvolyses of benzhydryl chloride,[10] but only in the latter two systems are accurate data available for the orientation effects of deuterium substitution. In both of these carbonium ion systems a single deuterium enhances carbonium ion formation by 1–2%; the order of magnitude of the effect is the same at all ring positions but there are subtle variations among the *ortho*, *meta*, and *para* positions. To study these variations as potential tools in evaluating electronic structure it was important to complement the above carbonium ion systems with a corresponding carbanion example. This paper presents a study of the α-deuterium exchange of ring-deuterated toluenes with lithium cyclohexylamide, a reaction for which normal substituents have been studied and whose transition state is known to have a high degree of benzyl anion character.[11,12]

Experimental Section

Toluene-α-*d* of 98% isotopic purity was prepared as described previously.[13]

Toluene-α-4-d_2 and **-α,2,4,6-d_4** were prepared from the corresponding deuterated bromobenzenes.[10] The synthetic sequence for the toluene-d_4 is illustrative. Quenching the ethereal Grignard reagent (0.1 mole) of bromobenzene-2,4,6-d_3 with Dry Ice afforded a 61% yield of the benzoic-d_3 acid. Lithium aluminum hydride reduction of the d_3-acid gave a 67% yield of benzyl-2,4,6-d_3 alcohol, bp 113° (26 mm). Conversion of the d_3-alcohol to the corresponding chloride in 45% yield, bp 93° (21 mm), was effected by boiling with an excess of thionyl chloride. The toluene-d_4 was obtained as a concentrated ethereal solution by quenching the Grignard reagent of benzyl-2,4,6-d_3 chloride with deuterium oxide; final purification was by preparative glpc and yielded material which gave the following mass spectrum: (*m*/*e*) 94, 2.45%; 95, 22.80%; 96, 74.75%. The toluene-d_2 so prepared gave the following mass spectral distribution: (*m*/*e*) 93, 87.5%; 94, 12.5%.

Toluene-α,2,3,4,5,6-d_6 was prepared in high isotopic purity, *m*/*e* 98, 91.6%; 97, 8.4%, by the gallium bromide catalyzed exchange of toluene-α-*d* with deuterium chloride. A deuterium chloride generator[14] was connected in series to three tubes (20 × 300 mm), each of which was constructed with a filter stick extending to the bottom. About 10 g of toluene-α-*d* was mixed with a small amount (*ca.* 0.1 g) of freshly sublimed gallium bromide,[15] and equal portions of the solution were placed in each of the three tubes. A large excess of deuterium chloride was bubbled through the solutions at a positive pressure of about 40 mm over a period of 10 hr. The tubes containing the reaction mixture were then attached to a vacuum line and thoroughly degassed, and the volatile material was transferred into another flask. Preparative glpc was necessary to purify samples for the kinetic experiments.

Kinetics. The procedures were similar to those developed in earlier work[13] except that no base concentrations were determined. Total toluene-d_x concentration in each kinetic experiment was about 0.1 *M*, and the lithium cyclohexylamide concentration varied from run to run but was always in the range 0.03–0.04 *M*. Toluene-α-*d* was mixed with an appropriate amount of the ring-deuterated derivative to give a distribution of isotopic masses such that the d_1 and d_x components of interest (x = 6, 4, or 2) were of comparable intensities. The temperature bath was maintained at 50.00 ± 0.02°. In general, eight kinetic aliquots were collected, representing about 75% reaction. Each quenched aliquot was extracted with 1 ml of cyclohexane in the usual procedure, and the toluene-d_x mixture was isolated for mass spectrometric assay by preparative glpc. Care was taken to collect the entire toluene band to avoid fractionation. Low-voltage mass spectra were taken with a CEC-21-130 instrument. All samples from a given kinetic run were analyzed on the same day under identical conditions. No tropylium ion formation was observable at the conditions selected, and careful checks for background contamination preceded each analysis. Reproducibility of the mass spectral data for duplicate samples of a given kinetic aliquot indicated that the combined error due to the isolation and assay techniques is about ±0.15%. Primary data (corrected for ^{13}C) for the competitive exchange between the toluenes-d_6, -d_2, and- d_1 are shown in Table I. Note that because d_2 is converted to d_1, the rate of d_1 was determined as the rate of formation of d_0.

Table I. Primary Data for the Competitive Kinetic Run between Toluene-d_6, -d_2, and -d_1, Run 10

Time,	Relative % d_x						
	x =						
min	0	1	2	3	4	5	6
0	0.77	27.33	32.69	0	0.38	3.32	35.50
40	5.41	28.51	26.85	0.09	0.70	8.81	29.64
65	7.93	29.01	23.88	0.09	0.93	11.85	26.31
100	10.92	29.83	20.17	0.08	1.19	15.27	22.55
135	13.48	30.31	17.10	0.14	1.42	18.31	19.23
180	16.03	30.80	14.09	0.17	1.77	21.27	15.86
235	18.63	31.32	10.85	0.41	2.05	24.26	12.49
∞	26.23	32.94	1.25	0.31	4.37	33.57	1.33

Pseudo-first-order rate coefficients were evaluated from the nonlinear least-squares fit[16] of log [% $d_x(t)$ − % $d_x(\infty)$] *vs.* time correlations using either calculated or experimental infinity values. For a given competitive determination, these rate constants yield directly the isotope effects. Figure 1 presents the kinetic correlations for the data in Table I. The isotope effects quoted in Table II come from computer-evaluated rate constants for runs with six

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Table II. Summary of Isotope Effects

Run	k_0/k_6[a]	k_0/k_2[a]	k_0/k_4[a]
5	1.074	. . .	. . .
6	(1.076)[b]	. . .	. . .
7	(1.076)[b]	. . .	. . .
10	1.073	1.018	. . .
9	. . .	. . .	1.066
13	. . .	. . .	1.066

[a] Ratio of rate of appearance of unlabeled toluene to the rate of disappearance of toluene-α,2,3,4,5,6-d_6 (k_6), toluene-α,4-d_2 (k_2), or toluene-α,2,4,6-d_4 (k_4). [b] Evaluated graphically for five-point kinetic plots.

points except as noted. The standard deviations of the least-squares-evaluated rate constants were all less than 1%. From the reproducibility of the k_0/k_6 isotope effect (Table II) in four different experiments, an experimental uncertainty of ±0.2% is indicated.

Cognizance was taken of possible exchange of ring protons. The partial rate factors for ring *vs.* benzylic exchange are 6×10^{-4} for the *ortho* position of toluene and 4×10^{-3} for *meta* and *para*;[17] hence, the correction of loss of ring deuterium even after ten half-lives for benzylic exchange is less than estimated experimental uncertainties.

Results and Discussion

The data in Table II suffice to assign a net isotope effect to each ring position if the effects are assumed to be additive. Additivity has been shown to hold approximately in the solvolysis of deuterated benzhydryl chlorides in aqueous acetone.[10] The directly measured effect of a *p*-deuterium is a rate retardation of 1.8%. Subtracting this from the total effect given by the *ortho* and *para* positions (k_4) gives 2.4% for each *ortho* position. Finally, the fully ring-deuterated effect (k_6) gives a *meta* effect of 0.4%. The estimated errors in these numbers is ~±0.3%. All positions show a rate-retarding effect, the direction expected for an inductive effect of an electron-donating deuterium.

The *ortho* and *para* positions show the largest effect and these positions are also expected to have more negative charge than the *meta* position; however, this parallelism between charge density and isotope effect is not found for the carbonium ion reactions. These comparisons are summarized in Table III. The effect found in this work for the *meta* position is actually substantially smaller than that expected for a normal inductive effect. Using $\rho = 4$[12] and $\sigma_I(D) = \sigma_m = -0.0012$,[5] the calculated effect for the meta position is a retardation of −1.1%.

Table III. Net Isotope Effects in Various Reactions

	Carbanion	Carbonium ion	
	$PhCH_2D$	Ph_2CHCl	Ph_3CCl
	LiCHA, 50°	Aqueous acetone, 25°	Ionization in SO_2, 0°
	% per deuterium		
ortho	−2.4	1.8	1.2
meta	−0.4	1.5	1.5
para	−1.8	1.0	1.1

In the solvolysis of deuterated benzhydryl chlorides it was recognized that a possible contributor to the relatively high *ortho* effect was the smaller effective volume of deuterium that would allow greater conjugation.[10] Indeed, Brown has taken the extreme position that steric effects are the cause of all secondary deuterium isotope effects.[18] In the present case such a steric effect increasing the conjugation to the exocyclic carbon of the developing benzyl anion would operate to *increase* the rate of the *o*-deuterated toluene and would result in a less negative or positive isotope effect in this position. Experimentally, an *o*-deuterium causes a larger *decrease* in rate than any other position. The magnitude and direction of this isotope effect is such that it *cannot* be due to a conventional steric hindrance effect. Consequently, it seems probable that the *o*-hydrogens in benzylic systems do not interfere significantly in preventing coplanarity. This conclusion may also be derived from some recent secondary deuterium isotope effects of Karabatsos, *et al.*[19]

Kresge, Rao, and Lichtin[9a] have emphasized the possible importance of the reduced interaction upon deuteration between the π system and the out-of-plane bending vibration of the aryl hydrogen. Halevi[4] later pointed out that the remarkable sensitivity of the stretching frequency between the aromatic and α-carbon atoms to deuterium substitution in the triphenylmethyl system might also be interpreted in the direction favoring the deuterated material. Emphasizing the out-of-plane bending vibration in a different fashion, Karplus, Lawler, and Fraenkel[20] point out that to the extent that the p orbital of aromatic carbon atom *r* follows this motion, deuteration at site *r* produces an effectively larger resonance effect or overlap with the adjacent skeletal carbons than for the nonisotopic parent system. Such a resonance integral perturbation appears to explain the observed effects of deuteration upon the esr hyperfine constants of aromatic radicals, and we may now examine its application to the present isotope effects.

The effect of such a perturbation on the π-energy change from benzene to benzyl anion is given by

$$\Delta\Delta\epsilon_r = 2[\Delta p_{r,r-1} + \Delta p_{r,r+1}]\delta\beta$$

in which

$$\Delta p_{r,s} = p_{r,s}(\text{benzyl}) - p_{r,s}(\text{benzene})$$

The Δp sum has the following values: *ortho*, −0.106; *meta*, +0.007; *para*, −0.063. Using $\delta\beta/\beta_0 = 0.0025$[20] and $\beta_0 = -49$ kcal/mole[21] this treatment gives calculated isotope effects of magnitude 0.2–3.5%. Although this order of magnitude is correct, the reversal of sign for the *meta* position is not, unless it is superimposed on an inductive effect. Thus, this treatment could account for the present data alone but, unfortunately, the carbonium ion results do not then agree. The bond orders for odd-alternant anions and cations are the same; hence, this treatment predicts the same isotope effects for benzyl cation and anion reactions. The carbonium ion studies with the benzhydryl and triphenylmethyl systems gave isotope effects of the same

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order of magnitude of the present benzyl anion studies, but *opposite in sign*. We conclude that the orbital following perturbation as proposed is too large by at least an order of magnitude. We also conclude that although deuterium substitution has some of the properties of a normal electron-donating substituent in terms of gross direction and order of magnitude, variations of magnitude cannot be analyzed as simple substituent effects and have limited usefulness as probes of electronic structure.

Acidity of Hydrocarbons. XXVI. Rates of Exchange of *m*- and *p*-Trimethylsilyltoluene-α-*d* and -α-*t* with Lithium Cyclohexylamide in Cyclohexylamine[1,2]

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Abstract: Deuterium and tritium exchange rates were determined for *m*- and *p*-trimethylsilyltoluenes in cyclohexylamine catalyzed by lithium cyclohexylamide at 25°. Tritium exchange rates relative to toluene-α-*t* are: *meta*, 1.01, $k_D/k_T = 3.3 \pm 0.3$; *para*, 4.57, $k_D/k_T = 3.0 \pm 0.1$. These results confirm the conjugative electron withdrawal of a silyl group. Equivalent σ^- values are: *m*-$(CH_3)_3Si$, 0.00; *p*-$(CH_3)_3Si$, +0.17.

Because silicon is more electropositive than carbon, it is expected to have an electron-donating inductive effect.[4,5] Several studies, however, have demonstrated that a conjugating trimethylsilyl group can have an electron-withdrawing effect.[6] From a study of the acidities of substituted anilinium ions and phenols, for example, Benkeser and Krysiak[7] found an enhancement of acidity by a *p*-trimethylsilyl group equivalent to σ^- values of +0.07 to +0.11. Similarly, in a study of base-catalyzed cleavages of substituted benzylsilanes, Eaborn and Parker[8] found a ninefold rate acceleration by a *p*-trimethylsilyl group that further demonstrates this electron-withdrawing effect.

These results prompted the present study of base-catalyzed exchange of trimethylsilyl-substituted toluenes with lithium cyclohexylamide (LiCHA) in cyclohexylamine. Our previous studies of isotope effects,[9,10] mechanism,[11] and substituent effects[12] have shown that this reaction proceeds through a benzyllithium intermediate and that the transition state is highly carbanionic. Hence, this system is well suited for a further characterization of the electrical effects of a silyl group.

Results and Discussion

The *m*- and *p*-trimethylsilyltoluene-α-*d*(*t*)'s were prepared by straightforward syntheses. The kinetic determinations were patterned after our previous vacuum-line procedures. Because of the difficulty of assaying the base concentration accurately, the pseudo-first-order experimental rate constants are always more accurate than the second-order rate constants. Accordingly, our current practice is to include some standard compound in every kinetic run in order to obtain relative rates directly. In addition, a mixture of deuterated and tritiated compounds is used, and the exchange of both isotopes is followed in order to obtain two independent relative rates and to obtain directly the primary isotope effect, k_D/k_T. A high value for this ratio provides a monitor for the absence of internal return which could render less significant the derived relative substituent rates.[12-14]

In the present study *o*-fluorotoluene was used as the internal standard for *p*-trimethylsilyltoluene; its rate relative to toluene, 12, has been determined previously.[12] It was desirable not to have toluene itself in the system in at least one case because it would be the product of a nucleophilic reaction of cyclohexylamide ion on silicon with subsequent cleavage of the silicon–aryl bond. The importance of such a cleavage reaction had to be determined. In fact, this cleavage does occur but at a rate an order of magnitude slower than the benzylic hydrogen exchange.

The results are summarized in Table I. The primary isotope effects indicate the mechanism is the same as for toluene for which $k_D/k_T = 2.8$; that is, that the carbon–hydrogen bond is largely broken at the transi-

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