# Cumulative Deuterium Isotope Effects on the Conformational Equilibria of Tribenzylamine

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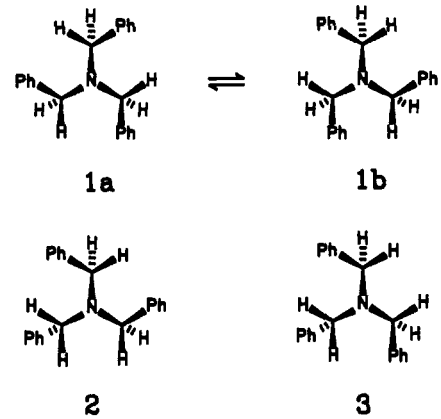
Conformational equilibrium isotope effects (CEIE) were measured for several α-deuteriated isotopomers of tribenzylamine via NMR isotope shifts. Unlabeled benzyl groups give an AB system of two doublets in the benzylic region of the $^1H$ NMR spectrum when the conformational equilibria are perturbed by labeling in another benzyl group. The benzylic proton signal of a monolabeled benzyl group is shifted upfield by an intrinsic deuterium isotope effect and may be additionally shifted by an equilibrium isotope effect. An equilibrium constant for the isotope effect, $K_{iso}$, derived from the isotope shift for a labeled benzyl group is the same as one derived from an unlabeled benzyl group of the same isotopomer. The CEIEs are cumulative for placing additional deuteriums to create additional chiral benzyl groups of the same configuration. Thus, a deuterium in one benzyl group appears to influence equally the average conformations of all three benzyl groups. The results are consistent with the expectations for CEIEs for a structure of $C_3$ symmetry, but a substantial contribution from a $C_1$ structure is also possible.

## Introduction

A substantial conformational equilibrium isotope effect (CEIE)[1] associated with deuterium substitution at a carbon adjacent to the nitrogen in an amine was first reported in 1974 in an infrared and microwave study of methyl-*d*-amine and methyl-*d*-amine-$d_2$.[2] The conformation with deuterium gauche to the lone pair was found to be lower in energy than the anti conformation. Since then, several NMR studies of tertiary, cyclic amines have found analogous preferences. The equatorial rather than the axial site is favored for deuterium in *N,N'*,5,5-tetramethylhexahydropyrimidine-2-$d_1$[3] and in *N*-methylpiperidine-2-$d_1$.[4] A similar preference was found for *N*-methyl-3-azabicyclo[3.2.2]nonane-2-$d_1$.[5] Isotope effects on equilibria involving the side chains of *N*-alkylpiperidines have also been reported.[6,7] In these studies of CEIEs in tertiary amines, deuterium is found to prefer the gauche alignment over the anti alignment by 50–70 cal/mol$^{-1}$.

The specific objective of the present NMR study of CEIEs in tribenzylamine was to examine a case where a deuterium placed in the methylene of a benzyl group (α-deuteriation) might influence not only the conformation of that benzyl group but possibly also the conformation of the other benzyl groups. It was anticipated that the extent of this influence could be detected by the pattern of equilibrium NMR isotope shifts observed for several α-deuteriated tribenzylamine isotopomers.

Tribenzylamine was chosen for study because an earlier investigation by Bushweller et al. showed that the predominant conformation had $C_3$ symmetry and interconverted by C–N bond rotation between two such enantiomeric structures, **1a** and **1b**.[8] Indeed, if the only possible conformers were **1a** and **1b**, then an isotopic influence on the preferred alignment of one benzyl group would necessarily influence each of the other benzyl groups. Appropriate placement of an additional deuterium in each of the other groups could be expected to have a cumulative influence on the overall conformation of the molecule. In the other extreme, if all possible conformers of tribenzylamine had the same energy content, then the benzyl orientations would be essentially independent of each other and the isotope effects should be noncumulative and local. Bushweller et al. did show that a second type of conformer, **2**, was present at very low temperature (101 K); perhaps more than two would be populated at higher temperatures. A third conformational type, **3**, was predicted in molecular mechanics calculations (MM2)[9] to be only 1.98 kcal/mol higher in energy than **1**.[8,10] Thus, the immediate goal of the research reported here was to determine the magnitude and additivity properties of CEIEs in tribenzylamine and relate them to possible conformations.




The general objective of the present study was to explore further the potential for deuterium isotope effects to control conformation. In a sense, any time there is an isotope effect on a conformational equilibrium, conformation is being controlled. However, these effects are usually rather small. If a second deuterium can be placed in an equivalent position in the equilibrating structure, for instance, in cis-labeled *N*-methylpiperidine-*cis*-2,6-$d_2$, the isotope effect can be doubled.[4] The opportunities for placing more deuteriums are usually very limited and, until now, the placement has been in the same group, e.g., the piperidine ring. The ultimate control of conformation would be expected in systems that have a large number of repeating structural features that have mutual influence

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(9) For a discussion of the MM2 method applied to amines, see: Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907.
(10) We have repeated the calculations using the MMX force field (Allinger[9] parameters for amines) in the PCMODEL program from Serena Software and find slightly larger energy differences among the three lowest energy structures. Our result for relative energy content (kcal/mol) of **1**:**2**:**3** is 0.00:1.27:2.42; Bushweller's[8] is 0.00:1.17:1.98.

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on each other. Such an outcome has recently been reported in a finding of an apparent cooperative deuterium isotope effect that resulted in a large optical rotation for poly((*R*)-1-deuterio-*n*-hexyl isocyanate).[11] The repeating amide backbone of the poly(*n*-alkyl isocyanates) adopts helical conformations in solution. The isotope effect controls which sense of the helix is dominant. However, no direct measurement of the isotope effect on a local conformational feature is available for the poly(isocyanate). In the present examination of the more simple tribenzylamine, it is possible to measure the isotope effect on the conformation of one benzyl group separately from the effect on the overall conformation of the molecule.

## Results

**Preparation of α-Deuteriated Tribenzylamines.** The synthetic approach to α-deuteriated tribenzylamines was planned with the idea of preparing mono-, di-, and trideuteriated isotopomers with the option of control of configuration at the labeled benzylic carbon. Although optically pure tribenzylamine-$\alpha,\alpha',\alpha''$-$d_3$, TBA-$d_3$, in which all labeled benzyl groups have the same configuration, was not obtained, the synthesis did give a sample enriched in (*S,S,S*)-TBA-$d_3$. For the NMR study, samples of high optical purity are not required; indeed, the NMR isotope shift measurements need to be performed on mixtures of isotopomers for accurate measurements of small chemical shift differences.

The outline of the planned preparation is shown in Scheme I, and details of the reactions are given in the Experimental Section. Optically active benzyl-α-$d_1$ chloride and bromide were prepared by a series of literature procedures[12-15] for use as alkylating agents. A two-stage alkylation procedure was chosen in order to use the benzyl-α-$d_1$ halides efficiently and to allow the option of introducing one, two, or three deuteriums. The first stage was dialkylation of cyanamide,[16] followed by hydrolysis to give dibenzylamine.[17] The second stage was benzylation carried out via the amide salt of dibenzylamine in order to get monoalkylation instead of dialkylation.

**Scheme I**

$$2\,(R)\text{-PhCHDCl} \xrightarrow{H_2NCN} (S,S)\text{-}(PhCHD)_2NCN \xrightarrow{H_3O^+}$$

$$(S,S)\text{-}(PhCHD)_2NH \xrightarrow[(2)\ (R)\text{-PhCHDBr}]{(1)\ n\text{-BuLi}} (S,S,S)\text{-}(PhCHD)_3N$$

The synthesis of (*S,S,S*)-TBA-$d_3$ was not entirely successful because of extensive racemization of the final benzyl group in the last benzylation step. Also, there was some loss of configurational integrity and a lesser loss of label at the dibenzylation stage. However, the reactions of Scheme I were entirely successful at providing the mono-, di-, and trideuteriated species needed in the NMR study. As described briefly in the following text, five samples containing different proportions of isotopomers were prepared: racemic tribenzylamine-α-$d_1$, TBA-$d_1$; racemic tribenzylamine-$\alpha,\alpha'$-$d_2$, TBA-$d_2$; TBA-$d_2$ enriched in the *S,S* isotopomer, (*S,S*)-TBA-$d_2$; racemic TBA-$d_3$; and a sample enriched in (*S,S,S*)-TBA-$d_3$.

Racemic TBA-$d_1$ was prepared by alkylation of the amide salt of unlabeled dibenzylamine with racemic benzyl-α-$d_1$ bromide. Racemic TBA-$d_2$ was prepared by dialkylating cyanamide with racemic benzyl-α-$d_1$ and carrying out the final alkylation with unlabeled benzyl bromide. This sample of TBA-$d_2$ contains an equal ratio of *R,R* + *S,S* to *R,S* + *S,R* isotopomers.

Chirally labeled TBA-$d_2$ was made by carrying out the dialkylation step with (*R*)-benzyl-α-$d_1$ chloride (99% ee) and using unlabeled benzyl bromide in the final alkylation. Evidence from the $^1$H NMR study to be described later shows that the dialkylation does not give complete inversion of the two alkyl groups and there is some loss of label as revealed in the $^1$H spectrum of the dibenzyl cyanamide that shows a triplet for benzyl-α-$d_1$ protons (shifted upfield by an intrinsic isotope effect of −0.016 ppm) and a singlet for the protons of unlabeled benzyl groups, estimated at 6%. After hydrolysis of the cyanamide, the $^1$H spectrum of the dibenzylamine showed the same pattern of a small singlet and a triplet (shifted upfield by −0.020 ppm). The ratio of *S,S* to *S,R* isotopomers is assumed to be ~4:1 on the basis of the ratio found in the final TBA-$d_2$ mixture.

The dialkylation of cyanamide is a two-phase process employing 50% aqueous sodium hydroxide and catalytic amounts of Aliquat 336. The partial racemization probably occurs because the strongly basic conditions cause some epimerization and loss of label by proton or deuteron removal from the benzyl chloride (or possibly the dibenzylcyanamide product), followed by delivery of a proton back from the solvent. Obviously, this point could be made more clear by further experiments and perhaps the conditions could be improved for obtaining inversion by using a more weakly basic solution or less contact time. Actually, no loss of label was seen in the repetition of the procedure in the preparation of racemic TBA-$d_2$, so the problem may lie in part with the reproducibility of reaction conditions in the two-phase process. There is no loss of label in the hydrolysis of the dibenzylcyanamide to dibenzylamine.

The preparation of racemic TBA-$d_3$ employed racemic benzyl-α-$d_1$ bromide in the alkylation of the amide salt of racemic dibenzylamine-$\alpha,\alpha'$-$d_2$. In terms of compounds distinguishable by ordinary NMR, this sample contains a 1:3 ratio of the *S,S,S* + *R,R,R* enantiomeric pair to the isotopomers of the *R,S,S* or *S,R,R* type, i.e., *S,R,R* + *R,S,R* + *R,R,S* + *S,S,R* + *S,R,S* + *R,S,S*.

The synthesis of TBA-$d_3$ enriched in the *S,S,S* isotopomer was achieved by alkylation of the amide salt of chirally labeled dibenzylamine-$\alpha,\alpha'$-$d_2$ (4:1 *S,S* to *S,R*) with (*R*)-benzyl-α-$d_1$ bromide. The ratio of *S,S,S* compound to *S,S,R* + *S,R,R* compounds is estimated to be ~1:1 from the $^1$H NMR spectra. Obviously, the last benzylation step results in a major loss of configurational integrity in the final benzyl group. The anhydrous tetrahydrofuran solvent used for this reaction is good for carbanion ion pair formation as well as $S_N2$ reactions. Thus, a possible mechanism is the epimerization of the benzyl-α-$d_1$ bromide by the very strongly basic $R_2NLi$, followed by an $S_N2$ reaction with the largely racemized alkylating agent.

**Equilibrium NMR Isotope Shifts.** At ambient temperature, all conformational changes in tribenzylamine are fast on the NMR time scale and a single peak is observed for the methylene protons. However, several peaks are observed in the methylene region of $^1$H spectra of α-deuteriated tribenzylamines. These signals arise from a com-

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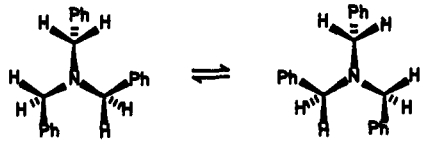
bination of upfield intrinsic isotope shifts, at protons geminal to deuterons in labeled benzyl groups, and equilibrium isotope shifts, which arise because the isotope perturbs the conformational equilibria and thereby creates different time-averaged environments for the two methylene hydrogens in a benzyl group.

Isotopic perturbation of rapid degenerate equilibria can effectively be analyzed by measuring the separation of NMR signals that were time-averaged to equivalence in the absence of the isotopic label.[18] The chemical shift separation, or equilibrium isotope shift, $\delta_{eq}$, between such signals is used to calculate the equilibrium constant, $K_{iso}$, for the perturbed equilibrium by comparison with the maximum possible separation of the signals, $\Delta$, obtained from an NMR spectrum of the unlabeled compound at the slow exchange limit. For exchange between two sites, the $K_{iso}$ is calculated from Saunders' equation (eq 1):[19]

$$K_{iso} = (\Delta + \delta_{eq})/(\Delta - \delta_{eq}) \quad (1)$$

Bushweller's $^1$H NMR study[8] of tribenzylamine provides the $\Delta$ value needed in eq 1. Low-temperature spectra showed decoalescence into two subspectra due to slowed N–$CH_2$ rotation.[8] (Inversion is invisible in dynamic NMR spectra due to the symmetry.) The major subspectrum (71% at 101 K) consisted of an AB system of two doublets ($^2J_{AB}$ = −13 Hz) separated by 0.89 ppm for the diastereotopic $NCH_2$ protons of three equivalent benzyl groups, consistent with the $C_3$ symmetry of structure 1. The enantiomers **1a** and **1b** interconvert slowly at low temperature. The other subspectrum (29%) was assigned to structure 2, which lacks symmetry ($C_1$ point group) but was suggested to rapidly equilibrate between enantiomers **2a** and **2b** for time-averaged $C_s$ symmetry. On the NMR



**2a** **2b**

time scale at 101 K, one phenyl in 2 is static in an anti orientation to the lone pair and the other two gauche benzyl groups rapidly rotate past the lone pair. Again, the coupling of −13 Hz was observed in the gauche benzyl groups, but a much smaller separation of only 0.04 ppm for the benzylic protons was seen. The smaller separation arises because the gauche and anti environments are averaged for these benzylic protons in the rapid **2a**, **2b** equilibrium, and other environmental influences on the shifts are small. On the assumption that any such influences on the chemical shifts will be much smaller than the gauche–anti influence, the $\Delta$ value of 0.89 ppm will be assumed to be general for the purpose of our analysis of CEIEs in tribenzylamine.

The equilibrium isotope shifts, $\delta_{eq}$, to be evaluated in eq 1 are easily obtained from the $^1$H signals of unlabeled benzyl groups. If the single isotopic label in one benzyl group influences the conformation of the other benzyl groups, their methylene protons, CHH, will become chemical shift nonequivalent. They are formally diastereotopic, but the methylene protons are unlikely to exhibit a chemical shift separation unless the equilibrium is perturbed. The intrinsic effect should be negligible at four-bonds distance from the deuteron, so the CHH signals

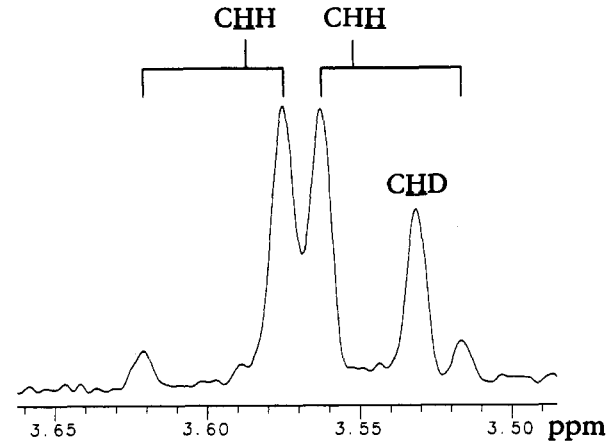
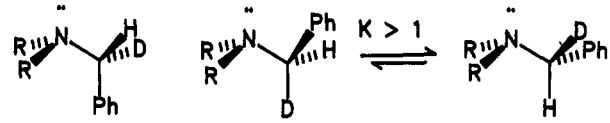



**Figure 1.** Benzylic proton region of a 300-MHz $^1$H NMR spectrum of tribenzylamine-$\alpha$-$d_1$ in $CDCl_3$ at 215.7 K. A resolution-enhancing weighting function was applied before Fourier transformation.

should separate symmetrically about the averaged position of the unlabeled compound. Geminal coupling, $^2J_{HH}$, will also become evident and the two proton signals will be seen as an AB system of doublets positioned symmetrically with respect to the position of the unlabeled compound. Their chemical shift separation can be used directly as $\delta_{eq}$ values.

Obtaining the $\delta_{eq}$ values from the $^1$H signal of a labeled benzyl group is slightly more complex because, obviously, only the proton and not the deuteron signal is observed in the spectrum and because an intrinsic isotope effect also influences the signal position. An individual benzyl group in tribenzylamine is in an anti, A, or either of two gauche




**A** **G** **G′**

conformations, G and G′, defined by the alignment of the phenyl ring relative to the nitrogen lone pair. An equilibrium NMR isotope shift will occur if there is unequal weighting of the two gauche conformers G and G′ due to the expected isotope effect, which will favor G′, with deuterium in a gauche rather than anti alignment with the lone pair. Half of the usual NMR isotope shift will be seen in the $^2$H spectrum, with the CHD deuteron shifted downfield because it is more often in the gauche alignment. The proton, which is more often in the anti alignment, will be shifted upfield by an equivalent number of ppm in the $^1$H NMR spectrum, i.e., $-^1/_2\delta_{eq}$. However, the CHD proton will also be shifted upfield by an intrinsic NMR isotope shift due to the geminal deuterium. The intrinsic shift, $\delta_{int}$, is expected to be about the same magnitude as observed in methane, −0.019 ppm,[20] or in dibenzylamine, −0.020 ppm. In fact, the apparent value found from the spectrum of (*R*,*S*)-TBA-$d_2$ is −0.019 ppm (vide infra). Thus, for a labeled benzyl group, the observed proton chemical shift, $\delta_{obs}$, relative to the reference signal for unlabeled tribenzylamine must be corrected for the $\delta_{int}$ of −0.019 ppm as in eq 2.

$$-\tfrac{1}{2}\delta_{eq} = \delta_{obs} - \delta_{int} \quad (2)$$

Figure 1 shows the benzylic region of a resolution-enhanced 300-MHz $^1$H NMR spectrum of TBA-$d_1$ taken at

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**Table I. Equilibrium Isotope Shifts and Apparent CEIEs in α-Deuteriated Tribenzylamines**

| compd[a] | temp, K | $\delta_{eq}$,[b] ppm | $K_{iso}$[c] | $-\Delta G°_{iso}$, cal/mol |
|---|---|---|---|---|
| (PhC*H*D)N($CH_2$Ph)$_2$ | 294.0 | 0.028 | 1.064 | 36.2 |
| | 255.8 | 0.032 | 1.075 | 36.8 |
| | 235.9 | 0.034 | 1.079 | 35.6 |
| | 217.0 | 0.035 | 1.082 | 34.0 |
| | 215.7 | 0.036 | 1.084 | 34.6 |
| (PhCHD)N(*$CH_2$*Ph)$_2$ | 294.0 | 0.028 | 1.064 | 36.2 |
| | 235.9 | 0.033 | 1.077 | 34.8 |
| | 217.0 | 0.035 | 1.082 | 34.0 |
| | 215.7 | 0.036 | 1.084 | 34.6 |
| (*S,S*)-(PhCHD)$_2$N*$CH_2$*Ph | 294.0 | 0.054 | 1.130 | 71.4 |
| (*S,S*)-(PhC*H*D)$_2$N$CH_2$Ph | 294.0 | 0.056 | 1.135 | 74.0 |
| (*S,R*)-(PhC*H*D)$_2$N$CH_2$Ph | 294.0 | 0.000 | 1.000 | 0.0 |
| (*S,R*)-(PhCHD)$_2$N*$CH_2$*Ph | 294.0 | 0.000 | 1.000 | 0.0 |
| (*S,S,S*)-(PhC*H*D)$_3$N | 294.0 | 0.081 | 1.201 | 107.0 |
| | 225.2 | 0.103 | 1.261 | 103.8 |
| (*S,S,R*)-(PhC*H*D)$_3$N | 294.0 | 0.026 | 1.061 | 34.6 |
| (*S,S,R*)-(PhC*H*D)$_3$N | 294.0 | 0.028 | 1.064 | 36.2 |

[a] Italics indicate nucleus observed for $\delta_{eq}$ measurement. [b] For $CH_2$ group, measured directly from separation of doublets; for CHD group, obtained from eq 2 with $\delta_{int}$ = −0.019 ppm. [c] From eq 1.

215.7 K in $CDCl_3$. The unlabeled methylenes give rise to an AB pattern of two doublets ($|^2J_{HH}|$ = 14.0 Hz). The center of the pattern is equivalent in chemical shift to the reference signal of unlabeled tribenzylamine (the sample for Figure 1 contains no unlabeled amine). The separation of the doublets, $\delta_{eq}$, is 0.036 ppm. A singlet signal is seen for the CHD proton, upfield from the reference position by −0.037 ppm. The expected triplet for coupling to deuterium is not resolved because the line widths are comparable to the coupling constant; in some spectra, the CHD signals are clearly broader than the CHH signals. After correcting for the intrinsic effect of −0.019 ppm in eq 2, the CHD signal also gives a $\delta_{eq}$ of 0.036 ppm.

The $\delta_{eq}$ values obtained for TBA-$d_1$ from Figure 1 and from spectra at other temperatures are listed in Table I. As expected for an equilibrium isotope effect, the $\delta_{eq}$ values are temperature dependent. The doublet separation becomes difficult to resolve in 300-MHz spectra as the temperature increases, but the separation was measured at 294 K in a 400-MHz spectrum. The apparent $K_{iso}$ values calculated from eq 1 with Δ = 0.89 ppm, and the derived $\Delta G°$ values, are also given in Table I. The $K_{iso}$ data were used in a van't Hoff plot that gave $\Delta H°$ = −30 cal/mol and $\Delta S°$ = 0.02 eu.

Table I includes CEIE data derived from 400-MHz spectra of other isotopomeric mixtures of tribenzylamine at 294 K. The types of benzylic proton spectra given by the various isotopomers are summarized briefly in the following text. Fundamentally, the features are those expected from the analysis of Figure 1: unlabeled benzyl groups give an AB system of two doublets if the equilibrium is perturbed and just a singlet if there is no equilibrium isotope effect; the proton signals of CHD groups are broad singlets shifted upfield by an intrinsic shift and additionally shifted by an equilibrium isotope shift if it is present. Signal assignments to the various isotopomers were verified by changing the ratio of isotopomers through use of the mixtures containing different ratios of isotopomers prepared as described previously.

Multiple benzylic signals were also found for the two samples of TBA-$d_2$ isotopomers. The *R,R* and *S,S* enantiomers will give the same spectra and have the same chemical shifts. The *R,S* and *S,R* enantiomers will also give identical spectra, but the *R,R* + *S,S* spectra differ from the *R,S* + *S,R* spectra. The CHH signals of (*S,S*)-TBA-$d_2$ divide into two doublets ($|J|$ = 13.7 Hz) separated symmetrically about the reference signal ($\delta_{eq}$ = 0.054 ppm). The CHD proton signal in (*S,S*)-TBA-$d_2$ is a singlet shifted upfield by −0.047 ppm at 294 K, giving $\delta_{eq}$ = 0.056 ppm from eq 2. In contrast, (*R,S*)-TBA-$d_2$ gives only two singlet signals: the CHD signal that is shifted upfield by −0.019 ppm and the $CH_2$ signal that is coincident with the signal of unlabeled TBA. Thus, there is no apparent CEIE involved in (*R,S*)-TBA-$d_2$, and the shift of the CHD signal is attributed entirely to the intrinsic isotope shift.

The enantiomeric *S,S,S* and *R,R,R* isotopomers of TBA-$d_3$ are indistinguishable by ordinary NMR but give a different spectrum than for the *S,S,R* and *R,R,S* type. Only one signal is given by (*S,S,S*)-TBA-$d_3$ for the CHD protons, and that is shifted upfield by −0.059 ppm from the reference signal at 294 K. Correcting for the intrinsic effect in eq 2 gives $\delta_{eq}$ = 0.081 ppm at 294 K. The signal position is temperature dependent, as expected, appearing −0.070 ppm upfield of the reference at 225.2 K.

Two signals with relative areas of 2:1 are found for (*S,S,R*)-TBA-$d_3$. The large signal ($\delta_{obs}$ = −0.032 ppm at 294 K) belongs to the two CHDs of the (*S*)-benzyl groups and gives $\delta_{eq}$ = 0.026 ppm from eq 2. The small signal for the CHD of the benzyl group of *R* configuration appears at only −0.005 ppm upfield from the reference. This is too small a shift to include upfield shifts by both the intrinsic effect (−0.019 ppm) and the equilibrium effect. Clearly, the influence of the equilibrium effect must be in the opposite, downfield direction in this case; application of eq 2 gives $-^1/_2\delta_{eq}$ = +0.014 rather than the usual negative value. The $\delta_{eq}$ must have a positive sign, so clearly $\delta_{eq}$ = 0.028 ppm, which is essentially the same as that obtained from the CHD signals of the (*S*)-benzyl groups. In other words, the usual preference for deuterium in the gauche position is reversed for the (*R*)-benzyl group because of the influence of the *two* (*S*)-benzyl groups in which the deuterium is found preferentially in the gauche position.

## Discussion

Table I summarizes the observed isotope effects on the conformational equilibria in tribenzylamine. The apparent $K_{iso}$ values and the associated $\Delta G°_{iso}$ values for the various isotopomers are listed for comparison. Several points are clear from the NMR study of CEIEs in tribenzylamine: (1) The signal separation for diastereotopic benzyl protons is temperature dependent. For example, the $\delta_{eq}$ separating the benzyl proton signals in TBA-$d_1$ increases from 0.028 ppm at 294 K to 0.036 ppm at 225 K. At the least, the temperature dependence verifies the origin from a perturbed equilibrium and indicates the presence of rapid degenerate conformational equilibria in the unlabeled compound. (2) A deuterium in one benzyl group influences the average conformation not only of that benzyl group but also equally the conformations of the others. This is indicated most simply in TBA-$d_1$, where the $K_{iso}$ value derived from the isotope shift for the labeled benzyl group is the same as the $K_{iso}$ value derived from the unlabeled benzyl groups. (3) The effects on energy are cumulative for placing additional deuteriums to create additional chiral benzyl groups of the same configuration. The additive $\Delta G_{iso}$ are reflected in the relationship between the $K_{iso}$ values for one, two, and three deuteriums: $K_{iso}(1) = (K_{iso}(2))^{1/2} = (K_{iso}(3))^{1/3}$. (4) If two benzyl groups of opposite configuration are present, the net influence on conformation is zero. No equilibrium isotope effect is apparent in the (*R,S*)-TBA-$d_2$ spectra, and in (*S,S,R*)-TBA-$d_3$ a CEIE of the same size as in the monolabeled compound is seen. (5) The apparent isotope effect per deuterium is ~−36 cal/mol ($\Delta G°$ at 294 K) favoring the

gauche alignment of deuterium with the lone pair.

The first four observations listed are entirely consistent with an equilibrium between two conformers of $C_3$ symmetry, as discussed in more detail in the following text. However, the magnitude of the isotope effect is smaller than expected, i.e., −36 cal/mol is smaller than the −50 cal/mol estimated for gauche–anti fractionation of a benzylic C–D bond in a G ⇌ G′ type equilibrium.[6] A possible explanation for the reduced magnitude can be summarized by saying that other conformations are present that have the phenyl ring of the benzyl group in an anti alignment with the lone pair. A similar suggestion accounted for the small isotope effect associated with deuteriation of the single benzyl group in *N*-benzylpiperidine.[6] However, the greater number of possible conformations and the interactions between benzyl groups in TBA create a more complex situation. Therefore, the relation the observed isotope effects to effects expected for each of the three types of TBA structures, **1**–**3**, will be discussed in the following text. Other possible conformations are considerably higher in energy.[10]

***$C_3$* Tribenzylamine.** The case of the $C_3$ structure, **1**, is quite simple. Because none of the benzyl groups has the phenyl oriented anti to the lone pair, **1** equilibrates by C–N bond rotation between only the two enantiomeric conformers, **1a** and **1b**. (Inversion at N creates two more, but these are equivalent by symmetry to the first two and can be ignored in analyzing the NMR spectra.) When a deuterium is introduced, as in (*S*)-TBA-$d_1$, it equilibrates between an anti and a gauche alignment. The isotope effect favors the gauche alignment, as shown in Figure 2. With only two conformers available, the isotope effect from labeling one benzyl group will be evident equally in the positioning of all three benzyl groups. Introduction of a second deuterium to give a second PhCHD group of the same configuration as the first should simply double the energy of the isotope effect. As shown in Figure 2, in (*S*,*S*)-TBA-$d_2$ the conformational exchange switches two anti deuteriums to two gauche deuteriums. Similarly, in (*S*,*S*,*S*)-TBA-$d_3$, three anti deuteriums become gauche deuteriums in the exchange. Thus, the isotope effects are expected to be additive and consistent with the observations.

It is also obvious from Figure 2 that the net isotope effect will be zero for two PhCHD groups of opposite configuration. The equilibrium between the two conformers of (*S*,*R*)-TBA-$d_2$ is degenerate, as the two conformers are enantiomeric and each has one anti and one gauche deuterium.

***$C_s$* Tribenzylamine.** The case of the $C_s$ structure, **3**, is somewhat more complicated. However, the conclusion is simple, namely that the observed isotope effects are not compatible with expectations of **3** and it cannot be present to any appreciable extent. The analysis is more complex because there are three conformers of $C_s$ symmetry interconverting by C–N bond rotation (six if you include inverted structures). The phenyl group of one benzyl group is anti to the lone pair, and the other two benzyl groups are enantiotopic. Each of the three benzyl groups can be the anti-oriented group, for a total of three conformers.

Figure 3 outlines the possibilities for fractionation of deuterium labels among the three conformers. Several expectations for this system are incompatible with observed isotope effects. For (*S*)-TBA-$d_1$, an isotope effect is expected to favor the two conformers with a gauche deuterium over the one with an anti deuterium. For (*S*,*S*)-TBA-$d_2$, one structure with two gauche deuteriums would be favored over either of two structures having an anti–gauche combination of deuterium alignments. However, the magnitude of the effect for (*S*,*S*)-TBA-$d_2$ should be about the same as for (*S*)-TBA-$d_1$, because the net result would be an isotope effect based on the change of one anti aligned deuterium to a gauche alignment. In other words, two deuterons would not produce twice the effect of one, in contrast to observation. Further, the NMR signal of one CHD proton in (*S*,*S*)-TBA-$d_2$ should move upfield while the other CHD proton moves downfield because the favored conformation has one PhCHD proton anti to the lone pair and the other PhCHD proton is gauche. In the experiment, only one CHD proton signal is observed.

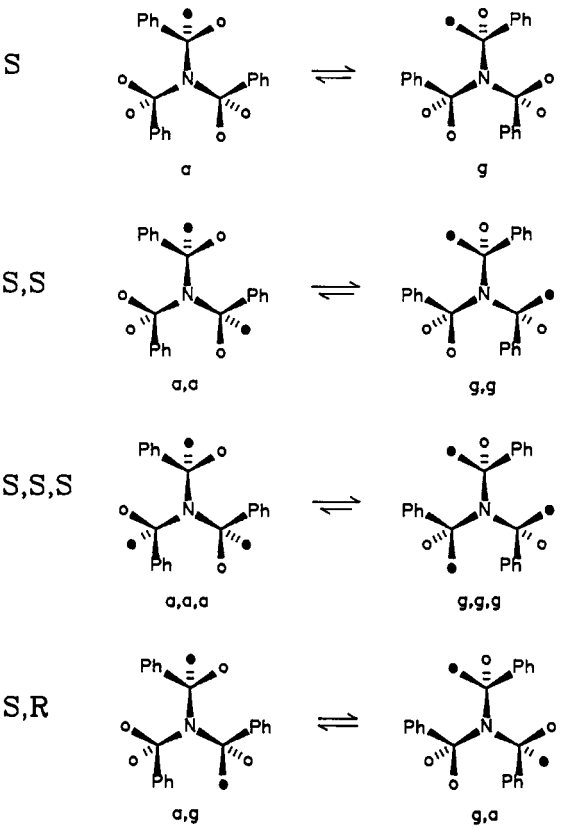


**Figure 2.** Conformational possibilities for various α-deuteriated tribenzylamines within the $C_3$ structural type **1**. Open circles (○) indicate protons and closed circles (●) represent deuterons. Below each conformer, the alignment of the deuterons with the lone pair is indicated by a for anti or g for gauche, starting with the top position and proceeding clockwise.

Another incompatibility with experiments is that no equilibrium isotope effect is expected for (*S*,*S*,*S*)-TBA-$d_3$. Each conformation has two gauche deuteriums and one anti; in fact, all three structures are entirely equivalent and superimposable. This expectation of no isotope effect for (*S*,*S*,*S*)-TBA-$d_3$ for structure **3** is not compatible with the observation of additivity of effects, since, to the extent that the $C_s$ conformer is populated, the $d_3$ isotope effect would be reduced and nonadditivity would result.

Finally, the expectations for (*S*,*R*)-TBA-$d_2$ in the $C_s$ structure also do not match experiment. One of the features is that twice the isotope effect of a single deuterium is expected, whereas no isotope effect is observed.

***$C_1$* Tribenzylamine.** The case of the unsymmetrical $C_1$ structure, **2**, is considerably more complex because there are six conformers of the same $C_1$ type that can interconvert via C–N bond rotations (12 total including inverted structures). The conclusion is that the expected pattern of isotope shifts of **2** is probably compatible with the observed pattern, but the apparent magnitude of the effects

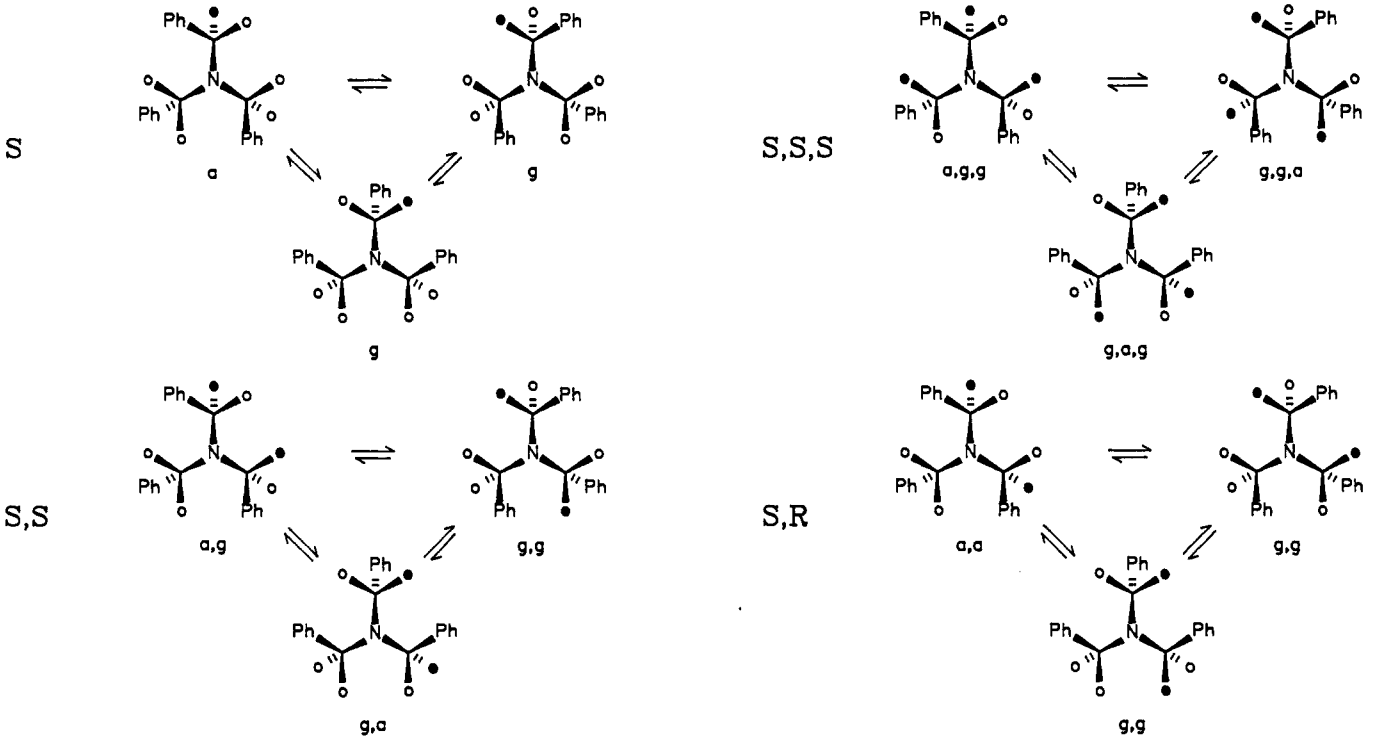


**Figure 3.** Conformational possibilities for $\alpha$-deuteriated tribenzylamines within the $C_s$ structural type, **3**. Notation as in Figure 2.

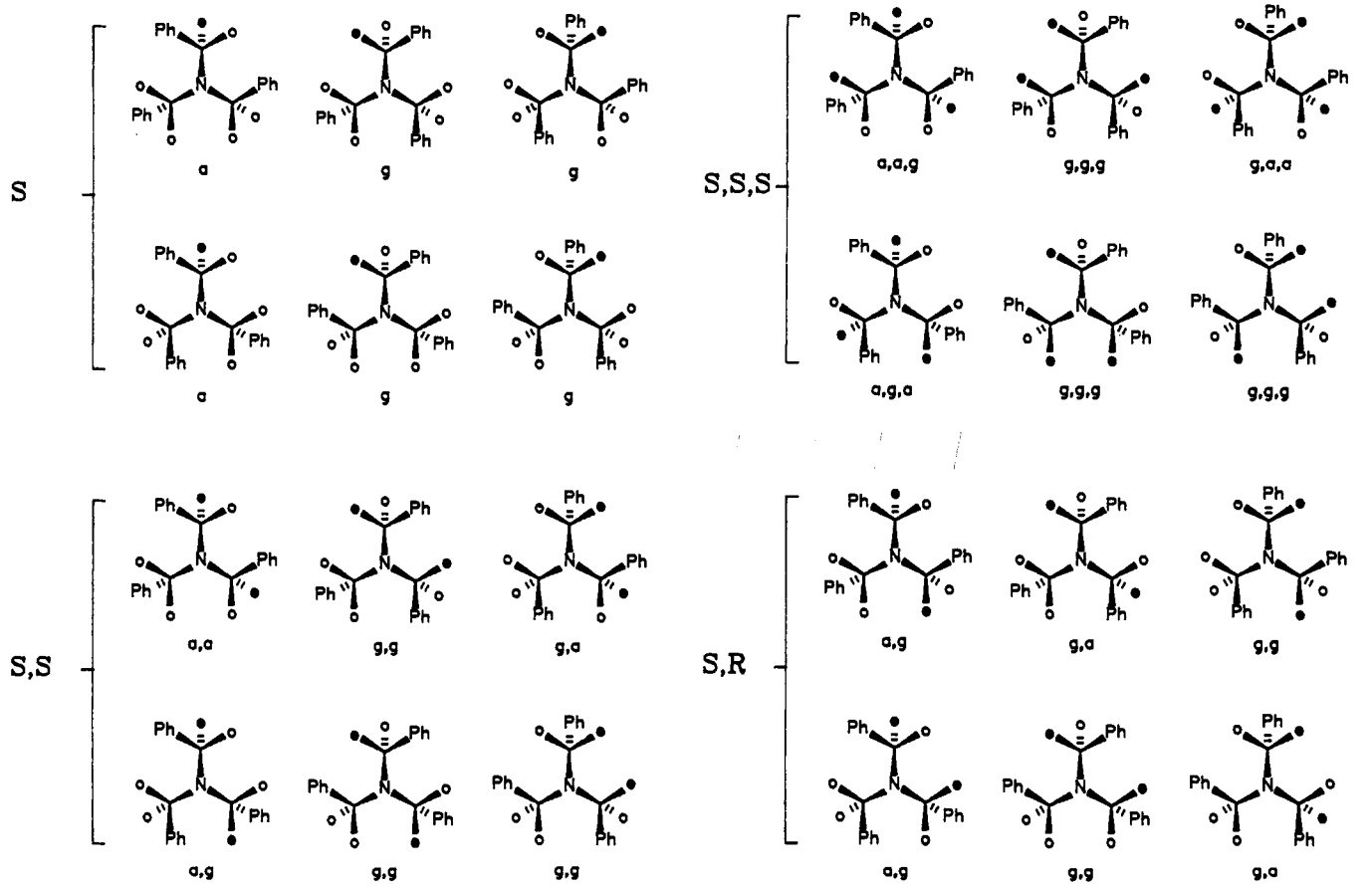


**Figure 4.** Conformational possibilities for $\alpha$-deuteriated tribenzylamines within the $C_1$ structural type, **2**. Notation as in Figure 2.

should be smaller than for **1**. Figure 4 shows the possibilities for fractionation of deuterium labels among the six conformers.

A single deuterium, as in (*S*)-TBA-$d_1$, would produce an isotope effect similar in energy content to that expected for **1** and **3**. Here, there are two conformers with anti alignments of the deuterium and four favored conformers with gauche alignments. However, the magnitude of the NMR isotope shift observed for the CHD proton signal is expected to be less than that for **1**. The reasoning is as follows. In unlabeled **1**, the average environment of a benzylic proton is 50% anti and 50% gauche. A deuterium

label will shift the percentages, with the maximum possible effect ($K_{iso}$, large) resulting in the CHD proton being 100% in the anti alignment. On the other hand, in **2**, the time-averaged benzylic proton environment has 33% anti and 67% gauche character. The maximum possible isotope effect favoring the two conformers with gauche deuteriums would result in only 50% anti character for the CHD protons (see Figure 4), i.e., the maximum effect on the chemical shift that is only $^1/_3$ that for **1**. Thus, while the energy content of the isotope effect might be the same, the observed NMR isotope shifts and the *apparent* $K_{iso}$ derived from eq 1 will be smaller. It should be noted that eq 1 is derived for an equilibrium between two structures and is suitable for **1** but not for equilibria among the six conformers of **2**.

In the dilabeled (*S,S*)-TBA-$d_2$ version of **2**, the net isotope effect in terms of energy should be less than double that expected of a single deuterium. The most favored conformers would be those three with gauche–gauche combinations of C–D alignments, but two with anti–gauche combinations should be favored also, to a lesser extent, over the one with the anti–anti alignment of the two deuteriums. On the other hand, in the favored three conformers with gauche–gauche deuterium alignments, four of the six (or 67%) CHD proton alignments are anti to the lone pair. Thus, the change in anti character from the 33% in the unperturbed equilibrium is potentially three times larger in (*S,S*)-TBA-$d_2$ than in (*S*)-TBA-$d_1$. This larger potential change in average environment could compensate for a smaller energetic effect, resulting in apparent isotope effects that are approximately additive.

The apparent isotope effects for (*S,S,S*)-TBA-$d_3$ in the $C_1$ structure should be larger than in the $d_1$ and $d_2$ cases. Three conformers with anti–anti–gauche combinations of deuterium alignments are in equilibrium with three having gauche–gauche–gauche alignments. The net energetic effect should be $^2/_3$ that expected for **1**, which would equilibrate between one conformer having all anti deuteriums to one having all gauche. The maximum possible change in CHD proton environment (from average of 33% anti to maximum of 67% anti) is similar to that for **1** (from average of 50% anti to maximum of 100% anti). Thus, the (*S,S,S*)-TBA-$d_3$ effect in structure **2** is expected to be larger than the $d_2$ and $d_1$ effects, but smaller than in **1**. Approximate additivity may occur.

Finally, in the isotopomers of **2** with PhCHD groups of opposite configuration, the expected NMR isotope shifts would be small but not nonexistent. In (*S,R*)-TBA-$d_2$, there are four structures with anti-gauche combinations of deuterium alignments and two with favored gauche-gauche alignments (Figure 4). However, even though there would be an isotope effect on the conformational equilibrium, no NMR signal separation for the benzylic protons of the unlabeled benzyl group would occur. The two favored conformers are isoenergetic enantiomers, with the same average environment for each proton of the benzyl group, e.g., the *pro-R* proton is anti in one conformer and gauche in the other. Any change in average environment would affect each proton equally. Furthermore, the largest effect of an exchange between two conformers can only be a net change of one deuterium from an anti to a gauche alignment, so the energy difference should thus be no larger than in the monolabeled compound, and there is an opposite 1:2 rather than 2:1 statistical preference for the lower energy conformers. Since only 50% of the CHH proton alignments are anti in the energetically favored two conformers, the maximum change in average environment relative to the average 33% anti alignment in the unlabeled case would be only $^1/_3$ that of the (*S*)-TBA-$d_2$ isotopomer of **1**. A similar analysis indicates that the equilibrium isotope effect would also have only a small effect on the average CHD proton environment of the (*R,S*)-TBA-$d_2$ isotopomer of **2**.

The expectation of some equilibrium-based isotope effect on the signal position for the unlabeled benzyl group of the (*R,S*)-TBA-$d_2$ isotopomer of **2** does not appear at first glance to be consistent with the experimental result of no observed shift. However, displacement of ~0.003 ppm or less from the reference position could pass unnoticed (a signal separation of 0.005 ppm was resolved). The expected magnitude of the effect is at most $^1/_3$ that for the equilibrium effect on the CHD proton of the (*S*)-TBA-$d_1$ isotopomer of **1**. The equilibrium portion of the upfield shift observed for the CHD proton of (*S*)-TBA-$d_1$ was derived as −0.018 ppm at 294 K (Table I). Thus, perhaps as much as ~50% of **2** could be present with no discernible effect on the benzyl proton signals of (*R,S*)-TBA-$d_2$.

## Conclusion

The pattern of NMR isotope shifts of the benzylic proton signals observed for various α-deuteriated tribenzylamines is dominated by the CEIEs for the conformation of $C_3$ symmetry, **1**. The local preference in a single benzyl group for a gauche rather than anti alignment of a deuterium label appears to enforce a conformational preference equally for the other benzyl groups. The apparent cumulative character of the isotope effects with additional chiral benzyl groups of the same configuration also indicates mutual interaction of the benzyl groups. However, these results may be misleading in the sense of indicating perfect fidelity in the mutual influence. While the presence of the $C_s$ conformation, **3**, can be ruled out, the results probably hide the amount of the $C_1$ conformation, **2**. The equilibrium NMR isotope shifts for **2** are expected to increase in the order $d_1 < d_2 < d_3$; i.e., they would appear to give roughly cumulative CEIEs, but they are also expected to be smaller in magnitude than for **1**. Thus, the observed pattern could include substantial contributions from **2**, which would reduce the magnitude of the observed effects, but not be otherwise detectable up to about a coequal concentration with **1**.

## Experimental Section

**Materials.** Literature methods were followed in the preparation of the known (*R*)-(−)-benzyl-α-$d_1$ bromide and (*R*)-(−)-benzyl-α-$d_1$ chloride[14,15] from (*S*)-benzyl-α-$d_1$ alcohol; (*S*)-benzyl-α-$d_1$ alcohol[13] from benzaldehyde-α-$d_1$; and benzaldehyde-α-$d_1$ from 2-phenyl-1,3-dithiane-2-$d_1$.[12] Deuterium incorporation was >99% in all of these compounds by $^1$H and $^{13}$C NMR analysis. Examination of (*S*)-benzyl-α-$d_1$ alcohol in the presence of Eu(hfc)$_3$ indicated >98% ee (no detectable signal for the *R* isomer). Also, about 99% ee for (*R*)-(−)-benzyl-α-$d_1$ chloride was indicated by optical rotation: $[\alpha]^{25}_D$ −1.53 (neat, $l$ = 1) (lit.$[\alpha]^{25}_D$ −1.530). Racemic benzyl-α-$d_1$ alcohol from the LiAlD$_4$ reduction of benzaldehyde was used to prepare racemic benzyl-α-$d_1$ bromide and chloride.

**Dibenzylcyanamide (4) Isotopomers.** The literature procedure[16] was followed for the preparation of unlabeled **4**, and also 4-α,α-$d_2$ as an isotopomeric mixture enriched in (*S,S*)-4-α,α′-$d_2$ by using (*R*)-benzyl-α-$d_1$ chloride and racemic 4-α,α′-$d_2$ by using racemic benzyl-α-$d_1$ chloride. The procedure for the *S,S*-enriched material is described.

Cyanamide (0.63 g, 0.015 mol) was added to stirred 50% aqueous NaOH (10 mL) (*caution: exothermic reaction*). The mixture was cooled, and 0.1 g of Aliquat 336 (Aldrich) and (*R*)-benzyl-α-$d_1$ chloride (3.83 g, 0.030 mol) were added. The mixture was stirred at 50 °C for 3 h, then diluted with water (30 mL), and extracted with ether. The organic extracts were washed

with aqueous NaCl, dried ($MgSO_4$), and concentrated (rotary evaporator). The residue was recrystallized from ethanol to obtain 4-$\alpha,\alpha'$-$d_2$ (1.85 g, 0.0083 mol, 55%, 94% D), mp 53–54 °C. $^1$H NMR ($CDCl_3$/TMS): $\delta$ 4.10 (t, 2 H, $J_{HD}$ = 1.8 Hz), 4.11 (small s, for 6% unlabeled benzyl group of 4-$\alpha$-$d_1$), 7.35 (m, 10 H). $^{13}$C NMR ($CDCl_3$/TMS): $\delta$ 54.0 (t, CHD, $J_{CD}$ = 20 Hz), 128.6 ($C_3$, $C_5$), 134.4 ($C_1$), 128.6 ($C_4$), 128.9 ($C_2$, $C_6$).

**Dibenzylamine (5) Isotopomers.** Hydrolysis[17] of isotopomers of 4 proceeded with no loss of label to give the corresponding isotopomers of 5 following the method given here for the preparation of the sample enriched in (*S,S*)-5-$\alpha,\alpha'$-$d_2$. A mixture of 2 g of sulfuric acid (96%) in 12 mL of water and (*S,S*)-4-$\alpha,\alpha'$-$d_2$ (1.12 g, 0.0050 mol) was refluxed for 22 h. After initial cooling, 50% NaOH was added while the mixture was cooled to bring the pH to 11–12. The solution was extracted with ether, and the combined extracts were washed with saturated NaCl solution, dried ($Na_2SO_4$), and concentrated (rotary evaporator) to give a colorless oil of 5-$\alpha,\alpha'$-$d_2$ (0.95 g, 0.004 75 mol, 95%, 94% D). $^1$H NMR ($CDCl_3$/TMS): $\delta$ 3.79 (t, 2 H, $J_{HD}$ = 1.8 Hz), 3.81 (small s, for 6% 5-$\alpha$-$d_1$), 7.33 (m, 10 H). $^{13}$C NMR ($CDCl_3$/TMS): $\delta$ 52.7 (t, CHD, $J_{CD}$ = 20.4 Hz), 126.9, 128.1, 128.4 ($C_{2-6}$), 140.2 ($C_1$).

**Tribenzylamine (TBA) Isotopomers.** Five different isotopomeric mixtures of TBA, plus unlabeled TBA, were prepared by the procedure described below for the sample enriched in (*S,S,S*)-TBA-$d_3$. The variations were introduced by the following combinations: 5 with racemic benzyl-$\alpha$-$d_1$ bromide; *S,S*-enriched 5-$\alpha,\alpha'$-$d_2$ with benzyl bromide; racemic 5-$\alpha,\alpha'$-$d_2$ with benzyl bromide; racemic 5-$\alpha,\alpha'$-$d_2$ with racemic benzyl-$\alpha$-$d_1$ bromide; and *S,S*-enriched 5-$\alpha,\alpha$-$d_2$ with (*R*)-benzyl-$\alpha$-$d_1$ bromide.

To a flame-dried 50-mL 3-neck flask equipped with a stopper, condenser, nitrogen inlet, and magnetic stir bar were added 27 mL of dry THF and 2.56 mL (0.0041 mol, 1.6 M in hexane) of *n*-butyllithium. Then, *S,S*-enriched 5-$\alpha,\alpha'$-$d_2$ (0.808 g, 0.0041 mol) was added to this stirred solution, which became red. After the solution was stirred for 3 h, (*R*)-benzyl-$\alpha$-$d_1$ bromide was added, and the mixture was refluxed for 4 h. After being cooled, the mixture was concentrated (rotary evaporator) and the residue was extracted with ether. The ether extracts were washed twice with saturated NaCl solution, dried ($Na_2SO_4$), and concentrated. The residue was recrystallized from ethanol to give TBA-$d_3$ as a white solid (0.77 g, 0.0027 mol, 65%), mp 93–95 °C, $[\alpha]^{25}_D$ + 0.64° (*c* 0.0188, ethanol, *l* = 1). $^1$H NMR ($CDCl_3$/TMS): $\delta$ 3.4–3.6 (CHD signals, see text for analysis; unlabeled TBA signal at 3.55), 7.25 (t, 3 H, $H_p$), 7.34 (t, 6 H, $H_m$), 7.44 (d, 6 H, $H_o$). $^{13}$C NMR ($CDCl_3$/TMS): $\delta$ 57.5 (t, CHD, $J_{CD}$ = 19 Hz), 126.8, 128.2, 128.7 ($C_{2-6}$), 139.8 ($C_1$).

**NMR Spectroscopy.** Routine $^1$H and $^{13}$C NMR spectra were obtained at 299.9 and 75.4 MHz, respectively, on a Varian Model XL-300 spectrometer with a broad-band tunable probe. Isotope shift measurements in $^1$H spectra were obtained under temperature control, for $CDCl_3$ solutions, and from resolution-enhanced spectra, on the Varian XL-300 and also at 399.9 MHz on a Varian Model VXR-400 spectrometer. Temperatures were read directly from the calibrated ($CH_3OH$) thermocouple monitor and varied less than 0.5 °C during each acquisition. Some additional measurements were carried out in $CFCl_3$ solution, with no significant change in results.

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# On the Origin of Substituent Effects in Electrophilic Addition: Evidence from Core-Electron Spectroscopy

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The rate-determining step for electrophilic reactions involves the formation of a charged intermediate by addition of a positively charged species at a site in the molecule. Since core ionization involves the addition of a positive charge by removal of an electron, both processes are governed by the same factors: the initial-state charge distribution and the final-state charge rearrangement. Combining core-ionization energies with Auger energies provides direct experimental information on the relative importance of these factors. Core-electron energies have been measured for sulfur in a series of 2-substituted thiophenes. The substituents comprise $CH_3$, $OCH_3$, I, Br, Cl, CHO, CN, and $NO_2$ and possess a wide range of electron-donating and electron-withdrawing properties. The results show that the variation in substituent effect is predominantly determined by the initial-state charge distribution and that the final-state charge rearrangement is very little influenced by the nature of the substituent. These conclusions are supported by correlations of the core-electron energies with electronic substituent parameters, which show that resonance delocalization contributes significantly to the initial state but has virtually no effect on the final state. This result challenges the traditional view since resonance stabilization of the transition state (the final state of the charge addition) for electrophilic addition reactions is considered to be crucial to the understanding of both reactivity and orientation effects in aromatic rings. Ab initio calculations have been performed for all thiophene derivatives and support the experimental results. In addition they show that the conclusions are not limited to the sulfur atom, but are equally applicable to the ring carbons. Thus, the sulfur atom is a suitable probe for substituent effects in the aromatic thiophene ring.

## Introduction

The effects of substituents on chemical properties such as equilibria, reaction energies, and reaction rates are of continuing interest. The rate-determining step for electrophilic reactions involves the formation of a charged intermediate by addition of a positively charged species at a site in the molecule. The rates for such reactions and the competition between different paths depends on the energy of these transition states.[2] Varying the substituents

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