Table III. AM1 Energetics for Several Diels-Alder Reactions[a]

		transition state			
		H_f		H_{act}	
diene	dienophile	endo	exo	endo	exo
butadiene	maleic anhydride	-25.4	-26.8	21.0	19.7
cyclopentadiene	maleic anhydride	-13.8	-14.9	25.5	24.4
cyclopentadiene	cyclopentadiene	108.5	107.3	34.4	33.2

[a] AM1 heats of formation for the reagents: butadiene, 29.9; cyclopentadiene, 37.1; maleic anhydride, -76.4.[12]

the experimental observations, we decided to further investigate the exo/endo selectivity. First, we calculated the relative energies of the endo and exo transition states using the MMX molecular mechanics program[9] with inclusion of π-interactions, using bond orders of 0.4 and 0.5 for the bonds that are forming in the transition state. MMX, also, predicts the exo transition state to be of lower energy (0.9 and 1.0 kcal/mol for bond orders of 0.4 and 0.5, respectively). We then investigated the effect of imposing synchronicity upon the reaction. When a MNDO calculation is performed with the constraint of synchronicity (both bonds being formed constrained to be equal), the endo structure is 1.0 kcal/mol more stable than the exo. This observation loses much of its significance when one considers that the energies of these structures are 8-10 kcal/mol higher than the optimized transition states, which in turn, are already much too high to agree with experimental observation. The only molecular orbital study in which the transition states have been directly calculated suggests that the endo transition states are favored over the exo.[10] Unfortunately, the transition states in question were not completely optimized. We have optimized one of the transition states from ref 10 (dimerization of cyclopentadiene). The activation energies are approximately 30 kcal/mol lower than the reported values for this reaction. The exo transition state was predicted to be favored in this case as well as two others (see Table III), contrary to the previous report. The transition states were symmetrical for all of these reactions except for the dimerization of cyclopentadiene where the partial bonds differed by 0.28 and 0.11 Å for the endo and exo transition states, respectively.

One should consider the possibility that the experimental preference for the endo product might be due to the differences between the condensed phase environment at elevated pressure in which the experiments were performed and the low-pressure gas phase that are modeled by the calculations. Pressure is known to affect the product distributions of Diels-Alder reactions.[11] It is worthy of note that even at 1 atm of pressure, the internal pressure within the solution can be quite high. It is possible that the preference for endo product often (but not always) observed in solution might be largely due to the differences in the volume of activation for the endo and exo adducts. If this is the case, these differences will not be manifest in theoretical modeling of gas-phase reactions. While the present calculations are not at a sufficiently high level to allow one to conclude that the endo preference is due to these effects, the three methods used here are in reasonable internal agreement both qualitatively and quantitatively. Careful determination of the activation parameters of gas-phase retro-Diels-Alder reactions could provide evidence in this domain.

(9) Gajewski, J. J.; Gilbert, K. E., to be published.
(10) Fox, M. A.; Cardona, R.; Kiwiet, N. J. *J. Org. Chem.* **1987**, *52*, 1469.
(11) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999.
(12) These results are in agreement with those reported in ref 7. They do not agree with some values given in ref 10.

Conclusion

Although some discrepancies remain to be clarified (such as the endo/exo selectivity), AM1 (but not MNDO) seems to be a reasonably well suited method for modeling Diels-Alder reactions. In addition, RHF calculations seem adequate, at least for reactions that are not likely to progress via a diradical mechanism.

Acknowledgment. This work was supported in part by grants from the U.S.-Spain Cooperative Research Program, "Comision Asesora de Investigacion Cientifica y Tecnica" (PB85-0244), and the PSC-BHE.

Pathway of the Aluminum Chloride Induced Isomerization of *N*-(2-Hydroxyethyl)-2-phenylbenzylamine Hydrochloride

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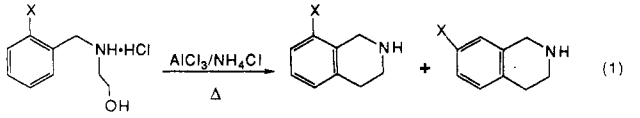
In previous work, we reported that the ring closure of **1b** in an aluminum chloride-ammonium chloride melt produced the 8-substituted 1,2,3,4-tetrahydroisoquinoline **2** (X = Cl) without any appreciable isomerization (eq 1).[1] When we applied the aluminum chloride cyclization to **1a**, however, we obtained 7-substituted 1,2,3,4-tetrahydroisoquinoline **3** (X = Ph) as the major product. This rearrangement raised two questions. Firstly, does the reorientation occur before or after cyclization? Secondly, is the migrating group the phenyl ring or the aminoalkyl side chain, or are both species involved in the transformation?



(1)

1a: X=Ph
1b: X=Cl

2 3

To address these questions, we explored the chemistry of *N*-(2-hydroxyethyl)-2-phenylbenzylamine hydrochloride (**1a**). Substituent-group migration occurred very readily in this compound (135 °C), whereas chlorination or cylization required more drastic temperature conditions (>180 °C). In fact, we were able to isomerize **1a** to obtain a mixture of *N*-(2-hydroxyethyl)-3- and -4-phenylbenzyl-

(1) Lam, B. L.; Mendelson, W. L.; Spainhour, C. B. U.S. Patent 4,251,660, 1981. Mendelson, W. L.; Spainhour, C. B.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* **1980**, *21*, 1393.

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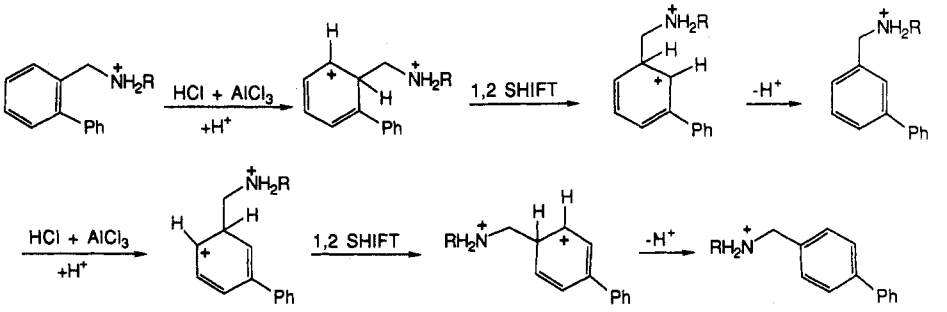
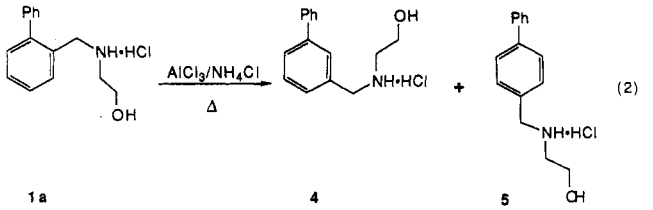
Scheme I



amines, **4** and **5**, without any ring closure to the tetrahydroisoquinoline (eq 2). This finding tended to rule out

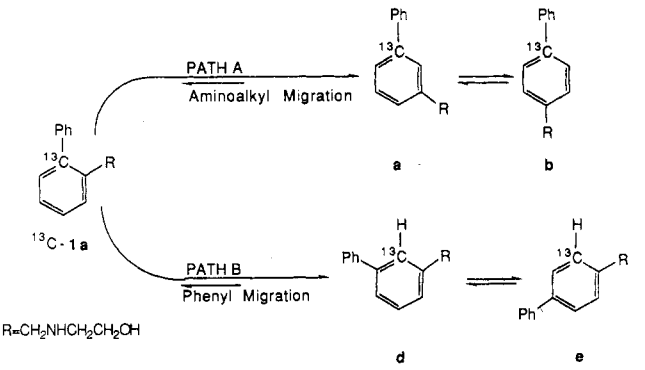


the intermediacy of a 8-substituted 1,2,3,4-tetrahydroisoquinoline **2** in the rearrangement to the 7-substituted isomer **3**. Thus, in answer to our first question, it appeared that some substituent reorientation must occur prior to cyclization.[2] The ratio of ortho/meta/para (**1a**/**4**/**5**) was 4/73/23 by GLC. These values compare well with previous literature reports on the aluminum chloride isomerization of diethylbenzenes, in which the ortho/meta/para ratio of the equilibrium mixture was reported to be 3/69/28.[3] Because of the simplicity of this system, compound **1a** seemed to be an appropriate model to address our second question, the identity of the migrating group.

Literature precedent alone did not give us a clear consensus as to the identity of the migrating group in the reorientation. One supposition was that the aminoalkyl moiety was undergoing a 1,2-migration as shown in Scheme I. The 1,2-migration of alkyl groups has been demonstrated,[4] and the Fries rearrangement of phenyl esters with aluminum chloride is a well-known phenomenon.[5] However, there is also literature precedence for aryl migration during aluminum chloride treatment, as in the case of ^{14}C-labeled biphenyl.[6] Since our system contains two potential migrating groups, we proposed that ^{13}C enrichment of the 2-position of the parent benzene ring would allow us to clearly differentiate between both proposed reaction pathways.

The rationale involved in ^{13}C labeling at C-2 is shown in Scheme II. Path A shows the course of reaction if the aminomethyl moiety is the migrating group. In this case,

Scheme II



the resultant meta and para isomers (a and b) should both have a ^{13}C NMR signal for the labeled carbon that is very similar to that of the starting ortho isomer **1a**; that is, a singlet without $^{1}J_{CH}$ coupling. Conversely, if phenyl positional isomerization is occurring (path B), the meta and para isomers that are formed (d and e) should exhibit strong ^{13}C–H splitting of the enriched carbon signal, in contrast to the ortho isomer **1a**. A combination of pathways A and B would result in complex spectra for both meta and para isomers. In any case, by subjecting **1a** with the appropriate carbon label to the conditions of the aluminum chloride melt and separating the resultant isomers, we could use ^{13}C NMR to provide the data necessary to define the reaction pathway.

The synthesis of *N*-(2-hydroxyethyl)-2-phenyl-2-^{13}*C*-benzylamine hydrochloride, hereafter called ^{13}C-**1a**, is shown in Scheme III. A 6% overall yield from 1,5-dibromopentane (**6**) was obtained. The labeled material was diluted with unenriched **1a** prior to treatment with the aluminum chloride melt. The resultant products, **4** and **5**, were separated by column chromatography and examined by ^{13}C NMR. **4** was the predominant product. *Only milligram quantities of both* **5** *and unreacted* **1a** *were isolated from the reaction mixture* (*eq* 2).

As expected, ^{13}C NMR of the starting ortho isomer **1a** showed a singlet in the C–H coupled spectrum at 142.36 ppm for the labeled carbon. If the reaction proceeded via path A, we would expect to see similar singlets for both the meta and para reorientation products. Instead, ^{13}C NMR of the meta isomer **4** clearly showed a ^{13}C–H split as a doublet of triplets. The chemical shift was 129.07 ppm, with the triplets centered at 133.05 and 125.14 ppm, respectively ($^{1}J_{CH}$ = 158.2 Hz; $^{3}J_{CH}$; $^{3}J_{CH}$ = 5.5 Hz). Similar findings were observed in the para case. A chemical shift of 130.89 ppm for the labeled carbon was observed. The minor para isomer **5** showed the ^{13}C–H split as a doublet of doublets with the bands centered at 134.89 and 126.90 ppm ($^{1}J_{CH}$ = 159.7 Hz; $^{3}J_{CH}$ = 5.0 Hz). The value of the coupling constant $^{1}J_{CH}$, in both **4** and **5**, compared well with a previously reported example of $^{1}J_{CH}$ = 158.5 Hz.[7]

(2) When the hydrochloride salt of **2a** (X = Ph) was subjected to the conditions of the aluminum chloride melt at 195–200 °C, rearrangement occurred to give **3a** and 6-phenyl-1,2,3,4-tetrahydroisoquinoline. Thus, when we applied these reaction conditions to **1a** (195–200 °C), the final product mixture of tetrahydroisoquinolines represented rearrangement occurring prior to and after cyclization.

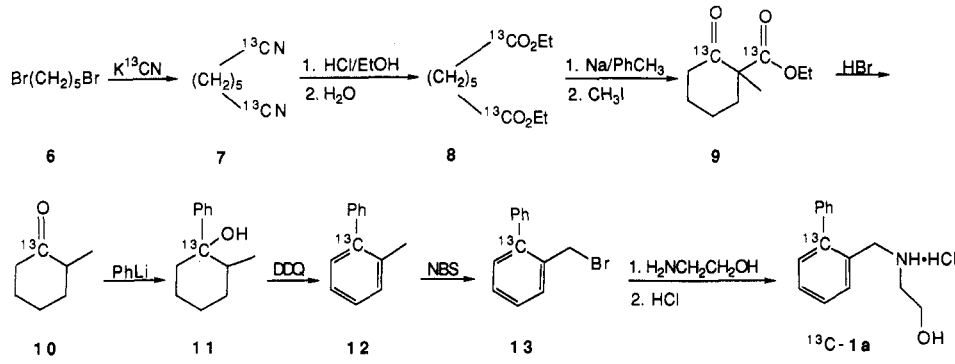
(3) Olah, G. A.; Meyer, M. W.; Overchuk, N. A. *J. Org. Chem.* **1964**, *29*, 2313. Olah, G. A. *Friedel Crafts Chemistry*; John Wiley and Sons: New York, 1973; pp 179–183. Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984; Chapter 7.

(4) Allen, R.. H. *J. Am. Chem. Soc.* **1960**, *82*, 4856.

(5) Martin, R. *Bull. Soc. Chim. Fr.* **1974**, 1519. Auwere, K.; Bundesmann, H.; Wieners, F. *Justus Liebigs Ann. Chem.* **1926**, *447*, 162. Chatterjea, J. N.; Gupta, S. N. P.; Mehrotra, V. N. *J. Indian Chem. Soc.* **1965**, *42*, 205. Cohen, N.; Lopresti, R. J.; Williams, T. H. *J. Org. Chem.* **1978**, *43*, 3723.

(6) Wynberg, H.; Wolf, A. P. *J. Am. Chem. Soc.* **1963**, *85*, 3308. Olah, G. A.; Meyer, W. M. *J. Org. Chem.* **1962**, *27*, 3682. Hay, A. S. *J. Org. Chem.* **1965**, *30*, 3577.

Scheme III



The conclusive demonstration of ^{13}C–H splitting in both the meta and para isomers umambiguously defines path B as the functioning pathway.

The simplicity of the ^{13}C NMR spectra in both examples demonstrated that only one route or rearrangement, path B, is operative. From this set of experiments, we may conclude that, prior to ring formation, the phenyl group of **1a** undergoes a series of 1,2-migrations, which contributes to the preponderant formation of 7-phenyl-1,2,3,4-tetrahydroisoquinoline **3**, rather than the anticipated 8-phenyl isomer **2**.

Experimental Section

General. All ^{13}C-labeled intermediates were identified by gas chromatographic comparison with their unlabeled analogues. The percentage of ^{13}C incorporation was determined by electron-impact mass spectroscopy. ^{13}C NMR experiments were performed at 20 MHz on a Varian FT-80A as gated decoupled spectra with full C–H coupling and retention of NOE. Tetramethylsilane was used as an internal standard. The ^{13}C NMR experiments were run on the hydrochloride salts in DMSO-d_6.

Synthesis of *N*-(2-Hydroxyethyl)-2-phenyl-*2*-^{13}C-benzylamine Hydrochloride (^{13}C-1a). The source of ^{13}C labeling was potassium cyanide-^{13}C obtained from Prochem/Isotopes. Steps in the synthesis of ^{13}C-**1a** are shown in Scheme III. All of the steps are from the literature and are not described here in detail. 1,5-Dibromopentane (**6**) was treated with potassium cyanide-^{13}C and heated under reflux in 4:1 (v/v) ethanol–water to form the labeled 1,5-dicyanopentane (**7**) in 87% yield.[8] Treatment with gaseous hydrogen chloride in ethanol formed the iminoester, and subsequent hydrolysis in water–ethanol gave diethyl pimelate (**8**) with the desired carboxyl label in 55% yield. Cyclization with concomitant methylation occurred with sodium metal and methyl iodide in refluxing toluene, forming labeled ethyl 2-methylcyclohexanone-2-carboxylate (**9**).[9] Upon heating in 48% aqueous hydrobromic acid, *1*-^{13}C-2-methylcyclohexanone (**10**) was formed. The yield from **8** to **10** was 40%. Reaction with phenyllithium in tetrahydrofuran at −78 °C gave 1-phenyl-1-hydroxy-*1*-^{13}C-2-methylcyclohexane (**11**). Aromatization by treating **11** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing toluene for 16 h yielded *1*-^{13}C-2-methylbiphenyl (**12**). Bromination of the methyl group with *N*-bromosuccimide in refluxing carbon tetrachloride gave **13**. Subsequent treatment with an excess of 2-aminoethanol in 1,2-dimethoxyethane and acidification with gaseous hydrogen chloride in ethanol gave ^{13}C-**1a** in 26% yield from **10**, without the necessity of purification of any intermediate. ^{13}C-**1a** was purified by the formation of the hydrochloride salt and the recrystallization from ethanol (mp 128 °C; isotopic enrichment: ^{13}C = 95.2%).

Aluminum Chloride Induced Migration of ^{13}C-1a. ^{13}C-labeled **1a** (0.42 g, 1.59 mmol) was diluted with unlabeled compound **1a** (0.33 g, 1.25 mmol) and intimately mixed with aluminum chloride (1.10 g, 8.25 mmol) and ammonium chloride (0.25 g, 4.67 mmol). This material was heated to a melt at 132 °C while being stirred for 45 min. After this time, TLC (Baker silica gel, EtOAc/MeOH/NH_4OH = 10/10/0.01) showed the reaction to be complete (**1a**, R_f = 0.57; **4**, R_f = 0.57; **5**, R_f = 0.53). The reaction was quenched in 12 N hydrochloric acid and diluted with water. Toluene and ammonium tartrate were added to the solution. Sodium hydroxide pellets were added to adjust the pH to 10. The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product mixture as an oil (0.55 g, 85%). The three isomers were separated by column chromatography (Baker silica gel; EtOAc/MeOH/NH_4OH = 93/7/1) and converted to their respective hydrochloride salts by treatment with gaseous hydrogen chloride in 2-propanol.

Acknowledgment. We acknowledge our indebtedness to David Staiger of the Physical and Structural Chemistry Department for NMR spectral data and interpretation and Lewis Killmer for GC/MS spectral data.

Supplementary Material Available: ^{13}C NMR spectra of compounds **1a**, **4**, and **5** (Figures 1–3) (2 pages). Ordering information is given on any current masthead page.

(7) Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*; John Wiley & Sons: New York, 1980; p 36.
(8) Murray, A.; Williams, D. L. *Organic Synthesis with Isotopes*; Interscience Publishers: New York, 1958; Part 1, pp 823–829.
(9) Nicole, L.; Berlinguet, L. *Can. J. Chem.* **1962**, *40*, 353.

Rate Constants for the Reactions of Tris(trimethylsilyl)silyl Radicals with Organic Halides[1]

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We recently discovered that organic halides can be reduced in good yields to their corresponding dehalogenated compounds by using tris(trimethylsilyl)silane.[3] The procedure is straight-forward and involves a two-step free-radical chain process, eq 1 and 2. These findings

$$R^\bullet + (Me_3Si)_3SiH \rightarrow RH + (Me_3Si)_3Si^\bullet \quad (1)$$

$$(Me_3Si)_3Si^\bullet + RX \rightarrow (Me_3Si)_3SiX + R^\bullet \quad (2)$$

suggest that tris(trimethylsilyl)silane might be an effective substitute for tributyltin hydride. The tin compound is used extensively in laboratory syntheses but is unsatisfactory for widespread use because of its toxicity.

In support of the concept, we have found that the bond dissociation energy of the silicon–hydrogen bond in

(1) Issued as NRCC publication No. 29996.
(2) (a) Consiglio Nazionale delle Ricerche. (b) National Research Council of Canada.
(3) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.*, in press.

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