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Acid-Catalyzed Degenerate Isomerization of Biphenyl[1]

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[1-^{13}C]Biphenyl (**1**) has been synthesized in four steps from [7-^{13}C]benzoic acid. Treatment of **1** with AlX_3/H_2O (X = Cl or Br) in benzene under a variety of conditions scrambles the isotopic label in the biphenyl. With 10:1 $AlBr_3/H_2O$ as the catalyst, complete equilibration of the label to all positions in the biphenyl could be achieved even at room temperature. Monitoring the progress of the reaction established that the label begins to appear first in the *ortho* position, then in the *meta* position, and finally in the *para* position, *i.e.*, the migration is stepwise, one position at a time, and not random. A mechanism involving *ipso* protonation of the biphenyl, followed by 1,2-migration of a phenyl group *via* the novel phenonium ion **3** and rearomatization, reasonably explains all the experimental facts.

In 1963, Wynberg and Wolf published a short communication on the discovery of an intriguing acid-catalyzed degenerate isomerization of biphenyl at 80−100 °C, the evidence being derived from ^{14}C-labeling experiments.[3] They proposed as "the simplest explanation" for this unusual reaction a mechanism involving proton addition to a quaternary carbon to develop a positive charge on the *ortho* carbon, followed by a 1,2-shift of phenyl and subsequent proton loss. Such *ipso* additions of protons and other electrophiles to halogenated, silyl-substituted, or alkyl-substituted aromatic rings, followed by a 1,2-shift or loss of the original substituent, are well-documented,[4] but the *ipso* protonation of biphenyls remains rare,[5] and the cases in which it appears to occur require reaction conditions far more brutal[5] than those reported by Wynberg and Wolf for the parent system.

Since the use of radioactive ^{14}C labeling to follow acid-catalyzed rearrangements of aromatic hydrocarbons is known to be fraught with experimental pitfalls,[6] it is unfortunate that the original communication on the degenerate isomerization of biphenyl[3] was never followed by a full paper with more complete experimental details, especially considering the high current level of research activity on *ipso* substitution,[4] arenium ions,[7a−g] and degenerate isomerizations of carbocations.[7h] Our own interest in the acid-catalyzed rearrangements of aromatic hydrocarbons[4c,8] and in degenerate isomerization reactions more generally[9] prompted us to reexamine the biphenyl degenerate isomerization using ^{13}C labeling and NMR spectroscopic analysis methods not available to Wynberg and Wolf in 1963. We considered it important to establish in this the most unfettered biaryl system whether *ipso* protonation and aryl migration really can occur and, if so, under what conditions. For this purpose, we developed a short new synthesis of [1-^{13}C]biphenyl (**1**).

Results

Synthesis of [1-^{13}C]Biphenyl (1). Scheme 1 outlines the route by which [1-^{13}C]biphenyl (**1**) was synthesized. Thus, [7-^{13}C]benzoic acid (99% ^{13}C-enriched) was prepared by carboxylation of phenylmagnesium bromide with $^{13}CO_2$, which was generated from ^{13}C-enriched barium carbonate by treatment with sulfuric acid in an apparatus we have described previously[10] (90% yield based on $BaCO_3$). Esterification of this acid (CH_3OH, H^+, 86% yield) followed by reaction with the di-Grignard reagent obtained from 1,5-dibromopentane[11] gave 1-phenyl[1-^{13}C]cyclohexanol, which was dehydrated with iodine at 140 °C[12] (55% overall yield from methyl benzoate). The

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[1] Part 3 in the series Catalytic Degenerate Isomerization Reactions. For Part 2, see ref 4c.

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[11] Fields, M.; Leaffer, M. A.; Rothchild, S.; Rohan, J. *J. Am. Chem. Soc.* **1952**, *74*, 5498.

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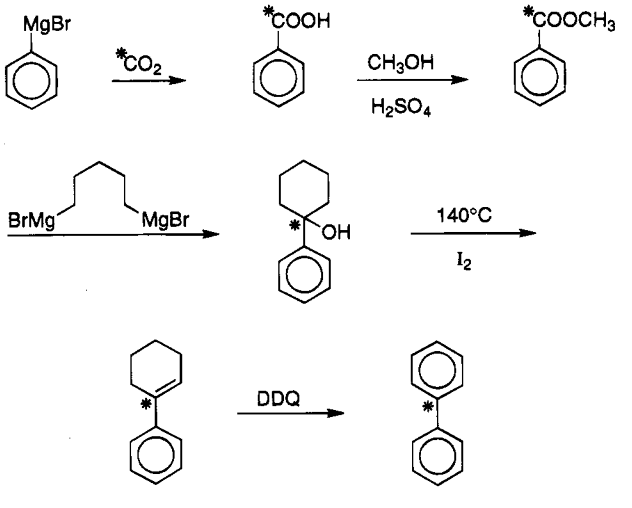
Scheme 1



resulting 1-phenyl[1-^{13}C]cyclohexene was aromatized to [1-^{13}C]biphenyl (**1**) with DDQ in refluxing benzene[13] (64% yield).

Degenerate Isomerizations. Solutions of [1-^{13}C]biphenyl (**1**) in benzene were treated with varying amounts of AlX_3/H_2O (X = Cl or Br) as summarized in Table 1; entry 1 cites the results reported by Wynberg and Wolf[3] for reference. The intentional addition of small, but measured, amounts of water has long been a standard procedure for ensuring reproducibility in such AlX_3-promoted reactions.[3,4c,5] Distribution of the label in the recovered [^{13}C]biphenyl was determined by integration of the ^{13}C NMR spectrum, correcting for the inherent differences in NMR peak intensities for carbons in the different positions under the instrument conditions used and for natural abundance ^{13}C contributions to the integrated NMR peaks.

Entry 2 shows our repetition of the experiment reported by Wynberg and Wolf.[3] We find that scrambling of the label does indeed occur under these conditions, although "randomization" was far from complete in our experiment, which employed the smallest amounts of $AlCl_3$ and H_2O reported by Wynberg and Wolf.[3] With the same molar ratio of biphenyl/$AlCl_3/H_2O$ under more dilute conditions (entry 3), no scrambling of the label was observed at all.

In dilute solutions of [1-^{13}C]biphenyl in benzene, it is possible to achieve complete equilibration of the label, as long as a relatively high concentration of $AlCl_3$ is maintained (entry 4); however, there appears to be a threshold concentration of $AlCl_3$ below which the reaction ceases (compare entries 4 and 5).[14]

Further experiments showed that $AlBr_3/H_2O$ in benzene is an extremely effective catalyst for scrambling the label in [1-^{13}C]biphenyl. With a biphenyl/$AlBr_3/H_2O$ molar ratio of 3:10:1, essentially complete equilibration of the label is achieved within 30 min at reflux (entry 6). As with $AlCl_3$, however, there appears to be a threshold concentration of $AlBr_3$ below which the reaction ceases (compare entries 6 and 7).[14] At sufficiently high concentrations of this catalyst, on the other hand, $AlBr_3/H_2O$ (*ca.* 10:1) randomizes the label in [1-^{13}C]biphenyl even at room temperature (entry 8)!

Entry 9 in Table 1 provides a time-resolved view of the biphenyl degenerate isomerization through the first several half-lives. From this experiment, it is clear that the label begins to appear first in the *ortho* position, then in the *meta* position, and finally in the *para* position, *i.e.*, the migration is stepwise, one position at a time.

Discussion and Theoretical Calculations

In addition to corroborating the report by Wynberg and Wolf[3] that unsubstituted biphenyl suffers degenerate isomerization on treatment with $AlCl_3/H_2O$ in refluxing benzene, our results reveal for the first time that the phenyl migration takes place *via* stepwise 1,2-shifts. In the original ^{14}C-labeling experiments, Wynberg and Wolf determined only the percentage of label remaining in the *ipso* position after degenerate isomerization but were not able to measure *ortho*/*meta*/*para* ratios.

By varying the catalyst and concentrations, we have furthermore found conditions under which the biphenyl degenerate isomerization can be made to proceed even at room temperature. This latter discovery is particularly striking in light of the early work by Olah and Meyer on $AlCl_3/H_2O$-catalyzed rearrangements of substituted biphenyls, which require many hours to reach equilibrium at temperatures of 140 °C or more.[5a,b]

Scheme 2 shows the reaction mechanism for acid-catalyzed degenerate isomerization of biphenyl that we consider most reasonable; this picture amplifies on the original suggestions of Olah and Meyer[5a] and Wynberg and Wolf.[3] Similar mechanisms have been generally accepted to explain the acid-catalyzed migration of alkyl and halogen substituents around aromatic rings.[4]

Protonation of the labeled *ipso* carbon atom is envisaged as the first step of the mechanism. Though intuitively offensive at first sight, this *ipso* protonation is actually quite reasonable on energetic grounds (see further discussion below). A 1,2-shift of the phenyl substituent in **2**, *via* the novel phenonium ion **3**, would generate a new *ipso*-protonated biphenyl (**4**), which could then either rearomatize to [2-^{13}C]biphenyl (**5**) or proceed on to the other labeled biphenyls, *via* phenonium ion **6**. The fact that we see the ^{13}C label growing sequentially, first in the *ortho* position, then in the *meta* position, and finally in the *para* position, indicates that rearomatization of the *ipso*-protonated biphenyls by proton loss must be faster than continued phenyl migration, *i.e.*, the activation energy for phenonium ion formation from *ipso*-protonated biphenyl must be higher than that for deprotonation under our reaction conditions; phenyl migration around the protonate ring does not fully equilibrate the ions prior to rearomatization.

A priori, one would expect biphenyl to be protonated preferentially in the *ortho* and *para* positions so that the resulting cation could be stabilized by conjugation with the second phenyl group. The *ortho*/*para*-directing properties of a phenyl substituent in electrophilic aromatic substitution reactions are certainly well-established,[15a] and to our knowledge, *ipso* substitution reactions on biphenyls have not been reported. In

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[13] By analogy with the tetralin → naphthalene conversion: Braude, E. A.; Jackman, L. M.; Linstead, R. P. *J. Chem. Soc.* **1954**, 3564.

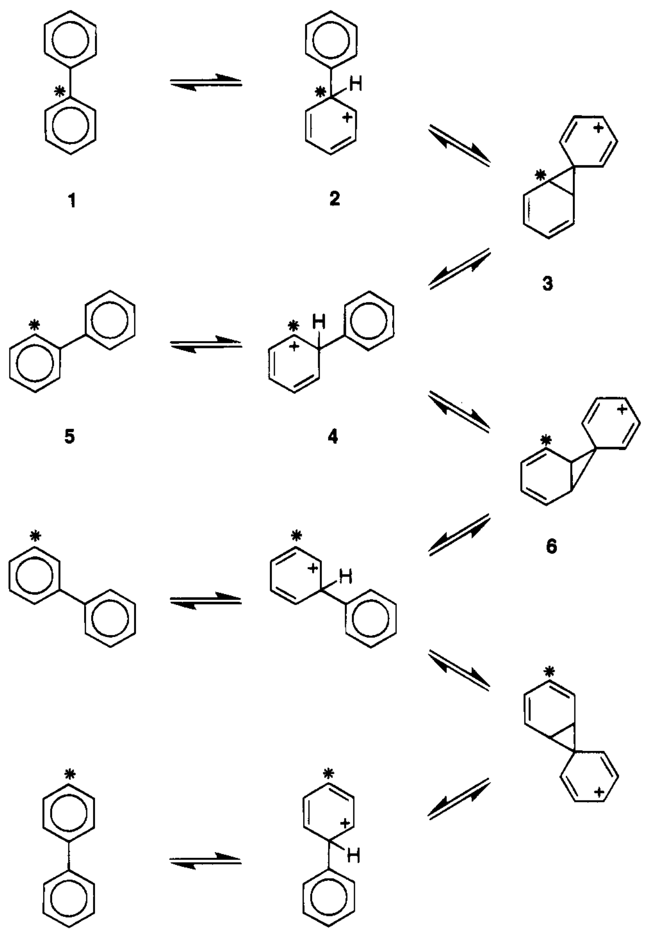
[14] The impotence of AlX_3 when used in low concentrations has been noted for many years in a variety of circumstances. Possible explanations include consumption of the first portion of the "catalyst" by inhibitors in the reaction medium and/or a higher than first-order dependence of the reaction rate on [AlX_3]. See, for example: (a) Roberts, R. A.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry*; Marcel-Dekker: New York, 1984; p 141. (b) Roberts, J. D.; McMahon, R. E.; Hine, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4237–4244.

Table 1. Acid-Catalyzed Degenerate Isomerizations of Labeled Biphenyl

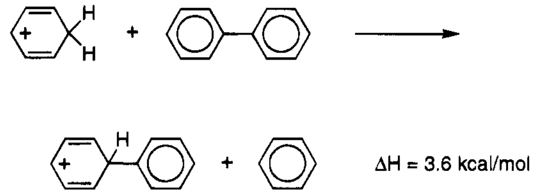
entry	biphenyl (mmol)	AlX_3 (mmol)	H_2O (mmol)	benzene (mL)	temp	time	label distribution[a] (*ipso*/*ortho*/*meta*/*para*)
1[b]	3.25	0.37–0.75 ($AlCl_3$)	0.28–0.56	10	reflux	12 h	"randomized"
2	0.32	0.037 ($AlCl_3$)	0.028	1	reflux	12 h	61:34:5:0
3	0.32	0.037 ($AlCl_3$)	0.028	5	reflux	12 h	100:0:0:0
4	0.13	0.90 ($AlCl_3$)	0.044	5	reflux	2 h	18:34:32:16
5	0.13	0.45 ($AlCl_3$)	0.022	5	reflux	2 h	100:0:0:0
6	0.13	0.45 ($AlBr_3$)	0.044	5	reflux	30 min	18:37:33:12
7	0.13	0.22 ($AlBr_3$)	0.022	5	reflux	2 h	100:0:0:0
8	0.13	0.90 ($AlBr_3$)	0.088	5	25 °C	2.5 h	17:36:31:16
9	0.39	1.12 ($AlBr_3$)	0.112	8	reflux	5 min	77:21:2:0
						15 min	52:41:6:1
						25 min	40:44:13:3
						40 min	17:38:31:14

[a] Accuracy of the values for distribution of the label is estimated at ±3. [b] Reference 3.

Scheme 2



harmony with these generalizations, semiempirical molecular orbital calculations at the AM1 level of theory predict that *ipso* protonation of biphenyl should be disfavored relative to protonation in the *ortho* and *para* positions by *ca.* 13 kcal/mol.[16] However, as a guide to whether the *ipso* protonation of biphenyl is reasonable, such internal comparisons are misleading. More relevant is the recognition that *ipso* protonation of biphenyl should be energetically comparable to the protonation of unsubstituted benzene, perturbed only by the inductive effect of a phenyl substituent. This qualitative supposition is supported by AM1 calculations,[16] which predict that *ipso* protonation of biphenyl ought to be only 3.6 kcal/mol less favorable than protonation of benzene (eq 1).



(1)

The fact that electrophilic reagents other than a proton never seem to attack biphenyl at the *ipso* carbon atom is primarily a manifestation of the greatly enhanced reactivity of the *ortho* and *para* positions and not the consequence of some greatly diminished reactivity of the *ipso* position. Protonation likewise occurs preferentially at the *ortho* and *para* positions in biphenyl,[15b] but the biphenyl degenerate isomerization results demonstrate that even *ipso* protonation can occur at a reasonable rate under conditions of reversible protonation.

Conclusions

Degenerate isomerization of biphenyl initiated (presumably) by protonation at the site of the aryl–aryl bond is a surprisingly easy process. The conditions required resemble those used in many Friedel–Crafts reactions, which are commonly conducted with $AlCl_3$ at relatively high concentration, often in 2-fold molar excess or more, and at elevated temperatures.[17] Skeletal rearrangements of the sort typified here by the acid-catalyzed degenerate isomerization of biphenyl may well play an important role in the high-temperature, acid-catalyzed reactions of larger molecular systems, including such complex materials as coal and the heavier aromatic products of petroleum hydrotreating and hydrocracking.[18]

Experimental Section

Methyl [7-^{13}C]Benzoate. To a solution of [7-^{13}C]benzoic acid (2.0 g, 16 mmol, 99% ^{13}C) in 7 mL of absolute methanol was added 0.18 mL (0.32 g) of concentrated sulfuric acid, and

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(15) (a) Reference 4a, pp 49, 401, and 402. (b) Reference 4a, pp 90–91.

(16) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *97*, 3902–3909. AM1 ΔH_f (kcal/mol): *para*-protonated biphenyl, 221.38; *ortho*-protonated biphenyl, 222.75; *meta*-protonated biphenyl, 229.06; and *ipso*-protonated biphenyl, 235.10. Calculations performed with the Spartan program, release 3.0.2 (Wavefunction, Inc., Irvine, CA) installed on a Silicon Graphics workstation. All structures have critical points of order zero.

(17) For a few typical examples, see: *Organic Syntheses*; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, pp 6, 24, 109, *inter alia.*

(18) (a) Sullivan, R. F.; Mieczyslaw, M.; Boduszynski, M.; Fetzer, J. C. *Energy Fuels* **1989**, *3*, 603 and references cited therein. (b) Olah, G. A.; Bruce, M. R.; Edelson, E. H.; Husain, A. *Fuel* **1984**, *63*, 1130–1137. (c) Olah, G. A.; Bruce, M. R.; Edelson, E. H.; Husain, A. *Fuel* **1984**, *63*, 1432–1435. (d) Olah, G. A.; Husain, A. *Fuel* **1984**, *63*, 1427–1431.

the solution was brought to reflux. After 4 h, the methanol was removed by distillation, and the residue was poured into water. The aqueous mixture was extracted several times with benzene, and the combined extracts were dried over anhydrous sodium sulfate. Removal of the benzene by distillation gave the crude product, which was distilled to give 1.9 g (86%) of methyl [7-^{13}C]benzoate (bp 110 °C/2 mmHg).[19]

1-Phenyl[1-^{13}C]cyclohexene. To an ice bath-cooled solution of the pentane 1,5-di-Grignard reagent, prepared according to the published procedure[11] from 1,5-dibromopentane (9.3 g, 40 mmol) and magnesium turnings (2 g, 0.08 g atom) in 50 mL of anhydrous ether, was added a solution of methyl [7-^{13}C]benzoate (1.9 g, 13.9 mmol) in 15 mL of anhydrous ether with vigorous stirring. Stirring was continued while the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then heated at reflux for 1 h, cooled back to room temperature, and quenched with saturated aqueous ammonium chloride. The ether layer was removed, and the aqueous layer was extracted several times with additional ether. The ether layers were combined, dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The crude 1-phenyl [1-^{13}C]cyclohexanol thereby obtained was not purified but was heated at 140 °C for 4 h with a crystal of iodine. The resulting material was cooled to room temperature and dissolved in ether. The ethereal solution was washed first with aqueous sodium thiosulfate and then with water, dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The crude product, which still contained a small amount of starting alcohol, was chromatographed on alumina, using petroleum ether as the eluant to give 1.2 g (55% overall yield from methyl benzoate) of 1-phenyl[1-^{13}C]cyclohexene.[19]

[1-^{13}C]Biphenyl (1). To a solution of 1-phenyl[1-^{13}C]cyclohexene (1.2 g, 7.6 mmol) in 20 mL of benzene was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 3.3 g, 16.9 mmol), and the mixture was heated at reflux for 45 min. A second portion of DDQ (3.3 g, 16.9 mmol) and an additional 10 mL of benzene were then added, and heating at reflux was continued for a further 3 h. The reaction mixture was then cooled to room temperature, concentrated under reduced pressure, and chromatographed on alumina using petroleum ether as the eluant to give 0.7 g (64%) of [1-^{13}C]biphenyl (**1**).[19]

Degenerate Isomerizations (Representative Procedure: Table 1, Entry 6). To 3.0 mL of benzene were added $AlBr_3$ (120 mg, 0.45 mmol) and water (0.8 μL, 0.044 mmol), and the mixture was heated to reflux. A solution of [1-^{13}C]biphenyl (**1**, 20 mg, 0.13 mmol) in 2.0 mL of benzene was then added *via* syringe. The reaction mixture was maintained at reflux for 30 min and then quenched by the addition of 1.0 N aqueous HCl. Biphenyl was recovered from the mixture by extraction with benzene, which was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and analyzed by ^{13}C NMR spectroscopy.

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(19) All labeled compounds were identified by comparing their physical and spectroscopic properties with those of unlabeled material.