The Influence of Charge Delocalization on Aryl Migration in Cationic 1,2 Shifts

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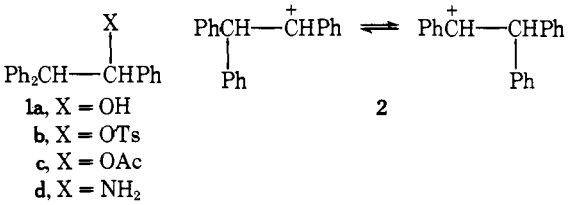
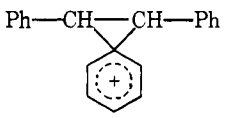
Abstract: We have previously suggested that more extensive charge delocalization (**7**) at the migration terminus of the carbocation intermediate (**5**) in the deamination of 1,2,2-tri(*p*-anisyl)ethylamine (**4**) was the cause of the *lesser p*-anisyl migration observed during deamination of **4** than the phenyl migration observed during deamination of 1,2,2-triphenylethylamine (**1d**). This hypothesis further predicted that 1-phenyl-2,2-di(*p*-anisyl)ethylamine (**8**) should deaminate with *more p*-anisyl migration than the phenyl migration noted for **1d**, and that 1-(*p*-anisyl)-2,2-diphenylethylamine (**9**) should deaminate with *less* phenyl migration than the *p*-anisyl migration noted for **4**. This prediction has been tested experimentally by synthesizing amines **8** and **9**, subjecting them to deamination with nitrous acid, and isolating the alcohol products resulting therefrom. Degradation of these alcohol products into mixtures of benzoic and *p*-anisic acids and determination of the compositions of these mixtures (as methyl esters) gas chromatographically allowed an estimate of the extents of aryl migration attending the deaminations of amines **8** and **9**. In qualitative accord with the above hypothesis, deamination of amine **8** was accompanied by 90.8% *p*-anisyl migration (as compared to 27% phenyl migration for **1d**), while amine **9** deaminated with only 0.9% phenyl migration (as compared to 16.7% *p*-anisyl migration for **4**). Additional ramifications of these observations are discussed.

Seeking evidence bearing on the existence of bridged, nonclassical carbocation intermediates, Bonner and Collins[2] a number of years ago initiated an extensive radiochemical investigation of the 1,2,2-triphenylethyl system. Their initial studies involved the dehydration of radioactive 1,2,2-triphenylethanol (**1a**), the formolysis, acetolysis, hydrolysis,



1a, X = OH
b, X = OTs
c, X = OAc
d, X = NH_2

2



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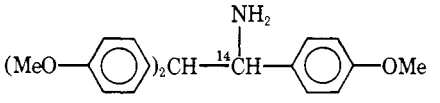
and reduction of its tosylate (**1b**), the label redistribution of the olefin corresponding to **1a**, the radioisomerization and acetoxy exchange in the acetate (**1c**) of **1a**, and the nitrous acid deamination of the corresponding primary amine, 1,2,2-triphenylethylamine (**1d**). The molecular rearrangements occurring during such processes were studied using ^{14}C labels both at C1, at the phenyl group on C1, and (in **1c**) at the acetoxy substituent on C1. The ability to calculate the ^{14}C-label redistribution during reactions of the C1 labeled series of compounds from the observed label redistribution in the C1-phenyl labeled series argued strongly that the sole cationic intermediates in these reactions consisted of equilibrating classical ions (**2**), and that the sought after nonclassical bridged phenonium ion **3** was here mechanistically excluded. Such solvolysis and deamination reactions in the 1,2,2-triphenylethyl system were subsequently studied in detail also from a stereochemical viewpoint,[3,4] confirming the intervention of and expanding behavioral knowledge about the equilibrating classical ions **2**. These conclusions contrasted sharply to those reached on the basis of similar solvolytic[5] and deamination[6,7] reactions in the 3-phenyl-2-butyl and related systems, where convincing stereochemical and radiochemical[7] evidence for the intervention of nonclassical phenonium ions has been presented. Probable reasons for the existence of two such separate mechanistic paths have been discussed.[8]

In a preliminary investigation to see if substituent effects were in accord with the equilibrating classical ion mechanism, Bonner and Putkey[9] more recently undertook a radiochemical study of the deamination of 1,2,2-tri(*p*-anisyl)ethylamine-*1*-^{14}C (**4**), assuming that the reaction intermedi-



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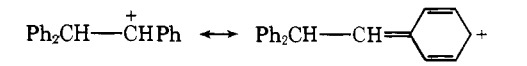
5 (An ≡ *p*-anisyl)

ates would again involve equilibrating tri(*p*-anisyl)ethyl carbocations (**5**), strictly analogous to the previously established equilibrating ions **2**. The generally and often markedly superior migratory aptitude of *p*-anisyl versus phenyl in carbocation reactions accompanied by competitive aryl 1,2 shifts[4,10] led us to anticipate that the extent of *p*-anisyl migration (as measured by label redistribution) should be noticeably greater on deamination of **4** than the 26–28% phenyl migration previously observed[2e,3a,b] during deamination of the unsubstituted analog **1d**. The deamination of **4**, however, was attended by only ca. 17% *p*-anisyl migration, a mere 62% of the extent of the phenyl migration accompanying the previous deaminations of **1d**. Although the *p*-anisyl/phenyl migration ratios for deamination reactions (ca. 1.2–2.0)[10] are generally much smaller than such ratios for solvolysis or other reactions (ca. 6–500),[10] the ratio of 0.62 found in this study[9] represented the first observation that phenyl in one system could migrate preferentially to *p*-anisyl in a closely related system. The following tentative explanation has been advanced[9] to rationalize this unexpected result.

If benzylic resonance hybrids such as **6** stabilize the



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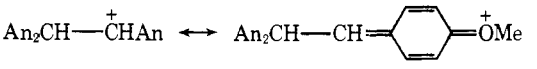

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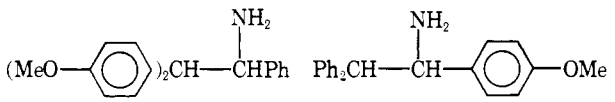
1,2,2-triphenylethyl carbocation **2** at a lower total energy than the nonclassical bridged ion **3**, such as to preclude the

intervention of **3** as a mechanistic intermediate in cationic reactions in this system, then a yet lower energy hybrid with canonical structures such as **7**, which permit an even greater charge delocalization at the migration terminus than is possible in **6**, must stabilize the 1,2,2-tri(*p*-anisyl)ethyl carbocation **5** to an even greater extent. Now, if the nucleophilicity of the group at the migration origin is important in determining migratory aptitude, it seems reasonable that the electrophilicity of the migration terminus should likewise be important. Thus, while the greater nucleophilicity of the *p*-anisyl at C2 in **7** versus the phenyl at C2 in **6** makes for a greater *p*-anisyl migratory tendency, the more delocalized positive charge at the migration terminus in **7** versus **6** would conversely argue for a less extensive aryl migration in **5** than in **2**, if the latter effect outweighed the former. Such an explanation finds some precedent in the work of Collins and coworkers,[11] who found that aryl/hydrogen migration ratios decreased in certain carbocation rearrangements as the charge at the migration terminus could become more delocalized.

It has been suggested[9] that the above hypothesis might be critically tested by observing the aryl migration occurring during deaminations of 1-phenyl-2,2-di(*p*-anisyl)ethylamine (**8**) and 1-(*p*-anisyl)-2,2-diphenylethylamine (**9**). If the



8 **9**

hypothesis is correct, the deamination of **8**, with its superior migrating *p*-anisyl groups at C2 and its less extensively charged delocalized migration terminus at C1, should be attended by *more p*-anisyl migration than the 26–28% phenyl migration noted for amine **1d**. Conversely, the deamination of **9**, with its inferior migrating phenyl groups at C2 and its more extensively charged delocalized migration terminus at C1, should be accompanied by *less* phenyl migration than the 17% *p*-anisyl migration found during deamination of amine **4**. The experimental test of these predictions is the subject of the present research.

Procedures and Results

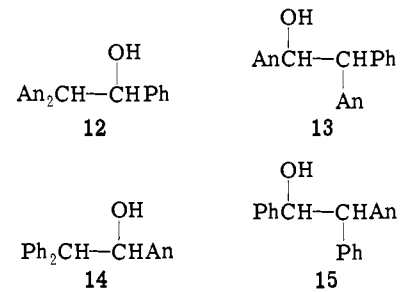
1-Phenyl-2,2-di(*p*-anisyl)ethylamine (**8**) was prepared by the following sequence of reactions. Di(*p*-anisyl)acetonitrile[9,12] was hydrolyzed to di(*p*-anisyl)acetic acid and the latter was converted to its acid chloride by means of oxalyl chloride.[13] Reaction of the acid chloride with diphenylcadmium produced phenyl di(*p*-anisyl)methyl ketone (**10**) as a

10 **11**

crude oil which we could not crystallize. Alternatively, the crude oil containing **10** could be prepared directly by the action of phenylmagnesium bromide on di(*p*-anisyl)acetonitrile, followed by acid hydrolysis. The crude ketone **10** was characterized by conversion to its oxime, whereby two stereomers, mp 173–174° and 151–152°, were isolated. Each isomer was readily convertible into the amine **8**, mp 81–84°, by reduction with dissolving sodium in ethanol. The amine **8** was also obtainable directly from the ketone **10** by the Leuckart reductive amination reaction using ammonium formate.[14]

1-(*p*-Anisyl)-2,2-diphenylethylamine (**9**) was synthesized by roughly comparable reaction sequences. *p*-Anisyl benzhydryl ketone (**11**), mp 127.5–128.5°, was prepared either by means of the action of di(*p*-anisyl)cadmium on diphenylacetyl chloride or by the direct acylation of anisole with diphenylacetic acid in the presence of chloroacetic anhydride.[15] Similar Leuckart reductive amination of the ketone **11** readily yielded the desired amine **9**, mp 98–99°.

Our next objective was to synthesize for comparison purposes the normal and rearranged alcohol products which would be anticipated from the deaminations of amines **8** and **9**. Amine **8** could yield the unrearranged alcohol, 1-phenyl-2,2-di(*p*-anisyl)ethanol (**12**), as well as the rearranged alcohol, 2-phenyl-1,2-di(*p*-anisyl)ethanol (**13**), while amine **9** would yield 1-(*p*-anisyl)-2,2-diphenylethanol (**14**) as the unrearranged alcohol and 2-(*p*-anisyl)-1,2-diphenylethanol (**15**) as the rearranged product. Lithium aluminum hydride reduction of the ketone **10** readily yielded the alcohol **12**, mp 142–144°, while sodium borohydride reduction of **11** afforded **14**, mp 156–160°. The alcohol **15**, mp 127–129°, was also prepared by the sodium borohydride reduction of the corresponding ketone, 2-(*p*-anisyl)-1,2-diphenylethanone, which was synthesized in turn by the action of phenylmagnesium bromide on the known[16] α-(*p*-anisyl)-α-phenylacetonitrile. The thin layer chromatographic behavior of the normal and rearranged alcohol products **14** and **15** was then investigated. The two alcohols showed identical R_f values, and when their mixture was chromatographed only one spot developed which showed no tendency toward splitting. Because the alcohol products **12** and **13** were closely related structurally to **14** and **15**, it was assumed that there should likewise be little or no difference in the R_f values of **12** and **13**, and that most probably all four alcohols would display essentially indistinguishable chromatographic characteristics. In the deamination (below) of both amines **8** and **9**, then, the isolation of only one preparative thin layer chromatographic band (R_f ca. 0.4 (benzene)) was required, on the assumption that this band would contain all of the desired alcohol deamination products.



12 **13**

14 **15**

Amines **8** and **9** as their hydrochlorides in acidified aqueous solution were individually deaminated at 5° by the dropwise addition of 10% aqueous sodium nitrite, conditions comparible to those previously employed[2e,3a,9] for the deaminations of amines **1d** and **4**. The crude deamination products were subjected to preparative thin layer chromatography, and the fractions containing the alcohol mixtures were isolated. The crude alcohol mixtures, comprising ca. 55–60% of the total deamination products, were degraded directly as described below, with no attempt made to isolate the individual constituents. In the case of the deamination of amine **9**, a major (ca. 25%) by-product crystallized, mp 160–163°. Its infrared and NMR spectra and elemental analysis suggested it to be 1-nitro-1-(*p*-anisyl)-2,2-diphenylethane, formed presumably by competitive nitrite ion attack on the unrearranged 1-(*p*-anisyl)-2,2-diphenylethyl carbocation intermediate involved. No attempt was made to isolate other nonalcoholic by-products from the deaminations.

To establish the compositions of the alcohol mixtures obtained from and thus the aryl migration accompanying the deaminations of amines **8** and **9**, the alcohol products were next degraded into two fragments. This was accomplished by first oxidizing the alcohol mixtures to the corresponding ketones with chromic anhydride–pyridine reagent,[17] then

cleaving the ketones into diarylmethane fragments and carboxylic acid fragments by means of sodium ethylate. The latter procedure has been shown to be attended by no molecular rearrangement when applied to the cleavage of phenyl benzhydryl ketone-^{14}C.[9] The carboxylic acid products were then separated and converted to their methyl esters, whereupon the methyl ester mixtures were examined for their compositions by analytical gas chromatography. Note that the unrearranged alcohol **12** would yield An_2CH_2 and PhCOOH on cleavage, while the rearranged alcohol **13** would produce $PhCH_2An$ and AnCOOH. Thus, the quantity of methyl *p*-anisate in the final ester mixture from the degradation of the alcohol products obtained on deamination of **8** provides a direct measure of the *p*-anisyl migration attending this deamination. Similarly, the normal alcohol product **14** would degrade to Ph_2CH_2 and AnCOOH, while the rearranged alcohol **15** would give $PhCH_2An$ and PhCOOH. Here, the fraction of methyl benzoate in the final ester mixture likewise indicates the percent phenyl migration attending the deamination of amine **9**. The average aryl migrations observed during the deaminations of **8** and **9** are shown in Table I, along with a comparison of the aryl migrations observed in earlier studies of deaminations in the 1,2,2-triarylethylamine system.

Table I. Aryl Migrations on Deaminations of 1,2,2-Triarylethylamines

Amine		Net migration		
No.	Structure	Group	%	Ref
4	An_2CH-$CH(NH_2)An$	An	16.7	8
8	An_2CH-$CH(NH_2)Ph$	An	90.8[a]	This study
9	Ph_2CH-$CH(NH_2)An$	Ph	0.9[a,b]	This study
1d	Ph_2CH-$CH(NH_2)Ph$	Ph	27[b]	2e

[a] Average from 5 to 10 gas chromatographic analyses. [b] Average from several deamination experiments.

Discussion

In previous experiments involving 1,2,2-triphenylethyl compounds[2,3] and 1,2,2-tri(*p*-anisyl)ethylamine,[9] the use of a radioactive ^{14}C label at C1 or the C1 aryl group was necessary to provide a means of differentiating between products derived from the structurally equivalent unrearranged and rearranged equilibrating classical carbocations such as **2** and **5**. Such is not necessarily the case in the present rearrangements, however, since the initial rearranged ions (**17** from amine **8** and **21** from **9**) are structurally nonequivalent to the unrearranged ion precursors (**16** and **20**, respectively), and each ion type thus yields in turn structurally distinct alcohol products (**12**, **13** and **14**, **15**, respectively). A potential complication arises, however, in connection with the rearranged ions **17** and **21**, namely, nonequivalent "back migration". While back migrations in ions **2** or **5** again yield structurally equivalent species, back migrations with ions **17** and **21** produce structurally nonequivalent ions. Thus, **17** affords either **16** or **18** depending on whether *p*-anisyl or phenyl back migrates from C1 to C2, and **21** can likewise give either **20** or **22**. Similarly, the further rearranged ion **18** may also back migrate to the structurally nonequivalent pair **17** and **19**, and **22** likewise to **21** and **23**. Thus, the ratios of the alcohol products **13**/**12** from amine **8** and **15**/**14** from **9** actually reflect the total extent to which the multiple equilibria of eq 1 and 2 have reached completion prior to quenching via product formation, and not merely the *initial* aryl migration equilibria. We originally hoped to estimate the extents to which the initial ions **16** and **20** had achieved the full equilibrations implied in eq 1 and 2 by using a ^{14}C label (indicated by C*) at C1 in amines **8** and **9** as in previous studies. Thus, the label distribution among the PhCOOH, AnCOOH, An_2CH_2, and $PhCH_2An$ products from the alcohols resulting from ions **16** through **19** in eq 1, for example, should provide a measure of the relative importance of each ion in the overall equilibria prior to quenching. The same reasoning applies to the ionic intermediates in eq 2. Although our above syntheses were developed as pilot procedures for the incorporation of the desired ^{14}C label into the C1 positions of amines **8** and **9**, our initial deamination results suggested that such a refinement would be superfluous.

$$An_2CH\text{—}\overset{+}{C}\text{*}HPh \underset{}{\overset{An\sim}{\rightleftharpoons}} An\overset{+}{C}H\text{—}C\text{*}HPh \overset{Ph\sim}{\rightleftharpoons}$$

16 **17**

$$AnCH\text{—}\overset{+}{C}\text{*}HAn \overset{An\sim}{\rightleftharpoons} PhCH\text{—}C\text{*}HAn_2 \quad (1)$$

18 **19**

$$Ph_2CH\text{—}\overset{+}{C}\text{*}HAn \overset{Ph\sim}{\rightleftharpoons} PhCH\text{—}C\text{*}HAn \overset{An\sim}{\rightleftharpoons}$$

20 **21**

$$PhCH\text{—}\overset{+}{C}\text{*}HPh \overset{Ph\sim}{\rightleftharpoons} An\overset{+}{C}H\text{—}C\text{*}HPh_2 \quad (2)$$

22 **23**

As seen in Table I, the deamination of amine **9** was accompanied by an average of less than 1% net phenyl migration. This low value makes it apparent that intermediate **20** is the dominant cationic species in this deamination, and that the rearranged ions **21**, **22**, and **23** are of only negligible importance. This is presumably a consequence of the fact that the initial phenyl migration (**20** → **21**) in eq 2 is a highly unfavorable process thermodynamically, proceeding from a more stable carbocation with its charge highly delocalized by an adjacent *p*-anisyl group to a less stable cation whose charge is delocalized only less effectively by an adjacent phenyl group. In any case, the obviously low amount of initial phenyl migration and the experimental errors in determining the small relative amounts of the alcohols arising from ions **21**, **22**, and **23** argue strongly against the need or practicality of the originally planned radioactive labeling experiments.

The deamination of amine **8** (Table I), on the other hand, was accompanied by over 90% net *p*-anisyl migration. In view of this large value, one might question the extent to which the back migration ions **18** and **19** of eq 1 might be involved as intermediates in this deamination. It would appear, however, that progress beyond the first intermediate **17** should again be extremely unlikely for several reasons. First, the transition **17** → **18** involves a phenyl migration to a *p*-anisyl stabilized migration terminus, a process seen above in the deamination of amine **9** to be unfavorable (although here ions **17** and **18** have equal energies). Second, when one considers that for such phenyl migration to occur there must be a prior 120° rotation about the C1-C2 bond of **17**, and further that bond rotation, migration, and product formation may compete at comparable rates,[3c] the probability of the phenyl migration from **17** to **18** appears diminished even more. Last, the known generally superior migratory aptitude of *p*-anisyl over phenyl might argue that back migration from ion **17** may well involve reversion to **16** rather than **18**, even though **18** is thermodynamically more stable. In any case, all of these factors suggest that the probability of the equilibria of eq 1 proceeding significantly beyond intermediate **17** is quite low and that therefore radioactive labeling at the C1 position of amine **8** would likewise be unnecessary and unjustified.

Regardless of the exact extent to which the subsequent back migrations shown in eq 1 and 2 actually occur, it is clear that our original qualitative predictions[9] regarding the extents of aryl migration to be expected on deamination of amines **8** and **9** are dramatically borne out. That is, amine **8**, as predicted, shows significantly more *p*-anisyl migration (90.8%) than the phenyl migration (26–28%) previously noted on deamination of **1d**. Likewise as predicted, amine **9** deaminates with significantly less phenyl migration (0.9%) than the *p*-anisyl migration (16.7%) previously found for amine **4**.

The previously postulated[9] effect of charge delocalization at the C1 migration terminus on the migratory capability of aryl groups at C2 further shows up consistently when the net aryl migrations during deaminations of amines **4** versus **8** and **9** versus **1d** are compared. Thus, the initial carbocation **7** from amine **4** has greater possibility for charge delocalization at the migration terminus than does the original cation **16** from amine **8**. Since the C1 migration terminus in ion **16** is therefore more electrophilic than that in **7**, it follows that amine **8** deaminates with significantly more *p*-anisyl migration (90.8%) than does amine **4** (16.7%). For the same reason, phenyl migration to the more charge delocalized migration terminus of initial ion **20** from amine **9** is significantly less (0.9%) than the phenyl migration (27%) to the less charge delocalized migration terminus of carbocation **6** from amine **1d**.

Examination of Table I also reveals several interesting ratios which permit some tentative conclusions. The *p*-anisyl/phenyl migration ratio obtained during deaminations of amines **4** and **9** is 18.6 (i.e., 16.7/0.9), while the ratio prevailing during deaminations of amines **8** and **1d** is only 3.4 (i.e., 90.8/27). In other words, the deaminations involving amines having *p*-anisyl at the migration terminus show a greater discrimination between different migrating groups than do deaminations of amines with phenyl at the migration terminus. We thus conclude qualitatively that the greater the charge delocalization at the migration terminus (i.e., the greater the stability of the initially formed carbocation), the greater will be the ability of the migration terminus to discriminate between two aryl groups of different migratory aptitude. If one considers the migrating aryl groups in such cationic intermediates as "intramolecular nucleophiles", this conclusion is clearly in accord with the generalization noted by Streitwieser[18] in 1956, namely, that "the less stable a carbonium ion is relative to its reaction with one nucleophilic substance, the less sensitive its reactivity will be to the nucleophilicities of other reactants."

Finally, it is also possible to assess qualitatively the sensitivity of the migrating groups themselves toward differences in charge distribution at the migration terminus. Thus, the ratio of *p*-anisyl migration values observed during deaminations of amines **8** and **4** is 5.4 (i.e., 90.8/16.7), while the ratio of phenyl migration values for amines **1d** and **9** is 30.0 (i.e., 27/0.9). In other words, the migrating phenyl group is clearly more sensitive to differences in charge distribution at the migration terminus than is the migrating *p*-anisyl group. By this comparison, we conclude qualitatively that the greater the intrinsic migratory aptitude of a group (i.e., the greater its nucleophilicity), the less sensitive it will be to differences in charge delocalization at the migration terminus.

Experimental Section

Di(*p*-anisyl)acetonitrile, mp 153–156°, was prepared in 30–50% overall yield according to literature procedures.[9,12] It was used in the reactions below without further purification.

Phenyl Di(*p*-anisyl)methyl Ketone (10). Procedure 1. A mixture of the above crude nitrile (30 g) and sodium hydroxide (30 g) in ethanol (205 ml) and water (110 ml) was heated under reflux for 43 hr and then distilled until the distillation temperature reached 100°. The residue was cooled, diluted with water (200 ml), and extracted with ether (200 ml; discard). The aqueous layer was poured onto ice and treated with excess hydrochloric acid and the resulting gummy solid was extracted into benzene (600 ml). The extract was clarified with Norit, dried over $MgSO_4$, concentrated to 100 ml at reduced pressure, and diluted with hexane. Cooling to 0° afforded 30.4 g (94%) of colorless di(*p*-anisyl)acetic acid, mp 110–111.5°, in agreement with the literature.[19] The acid was converted to its sodium salt by dissolving in dilute ethanol, neutralizing to the phenolphthalein end point with aqueous sodium hydroxide, and evaporating the solution to dryness. The dry sodium salt (32 g) was added in small portions over 30–40 min with magnetic stirring to an ice-cold solution of oxalyl chloride (20 g) in dry, thiophene-free benzene. The mixture was warmed to room temperature, refluxed for 45 min, then boiled for 30 min without condenser to remove excess oxalyl chloride. Benzene (20 ml) was added, the solution was filtered and stripped of solvent at 70° under vacuum, and the residue was dissolved in dry ether. The solution was treated with Norit and $MgSO_4$, concentrated, diluted with hexane, and cooled. The resulting 27.2 g (84%) of di(*p*-anisyl)acetyl chloride had mp 61.5–63° in agreement with the literature.[20] The above is an adaptation of the procedure of Adams and Ulich.[13] A small amount of colorless solid, mp 115–117°, was isolated from the mother liquors of the above acid chloride. Its infrared spectrum (bands at 5.46 and 5.70 μm), positive ferric hydroxamate test, and analytical data indicated it to be di(*p*-anisyl)acetic anhydride.

Anal. Calcd for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74; mol wt, 527. Found: C, 73.01; H, 5.87; mol wt, 507.

Phenylmagnesium bromide was prepared from bromobenzene (59.8 g) and magnesium (8.43 g) in dry ether (225 ml) and the solution was treated with dried cadmium chloride (34.9 g).[2a] The mixture was stirred for 30 min, heated under reflux for 30 min, then distilled until the vapors reached 85–90°. Dry, thiophene-free benzene (200 ml) was added to the residue, followed by rapid addition with stirring of the above acid chloride (27.2 g) in dry benzene (50 ml). The mixture was heated on the steam bath for 10 min, cooled, treated with ice and sufficient dilute sulfuric acid to acidify, and then stirred for 30 min. The organic layer was separated, washed successively with water, dilute sodium hydroxide, and water, dried over $MgSO_4$, filtered, and stripped of solvent to yield 36.3 g of viscous yellow oil. The oil failed to crystalize on prolonged standing. Its infrared spectrum and thin layer chromatographic examination suggested it to be at least 80% the desired phenyl di(*p*-anisyl)methyl ketone, which has been reported as having mp 57–58° [21] or 91–92°.[22] The material was characterized as its oxime (below) and used in subsequent reactions in the crude state.

Procedure 2. Phenylmagnesium bromide (0.07 mol) in dry ether (50 ml) was treated with di(*p*-anisyl)acetonitrile (5 g; 0.02 mol) dissolved in warm dry benzene (90 ml), and the mixture was heated under reflux for 22 hr, flushing the apparatus several times with nitrogen. The mixture was then treated slowly with 6 *N* sulfuric acid (50 ml), stirred under reflux for 2 hr, and cooled, and the phases were separated. The aqueous layer was extracted with benzene and ether, the extracts were combined with the organic phase, and the mixture was washed with water, dried over $MgSO_4$, filtered through Norit, and stripped of solvent to yield about 6 g of amber oil. This partially solidified on standing. It was partially dissolved in ether and filtered to yield 0.6 g of unreacted nitrile, mp 145–151°. The filtrate was stripped of solvent to yield an oil whose infrared spectrum and thin layer chromatogram indicated it to be an impure mixture of the desired ketone. This was used in subsequent reactions without further purification.

Phenyl Di(*p*-anisyl)methyl Ketoximes. A mixture of the crude ketone oil from procedure 1 above (2.5 g), hydroxylamine hydrochloride (1.12 g), pyridine (2.5 ml), and ethanol (12 ml) was heated under reflux for 8 hr and then cooled to 0° and refrigerated. A greyish solid, "oxime A" (0.78 g), formed, mp 163.5–165.6°. The mother liquors were chilled further yielding additional crystals of "oxime B" (0.85 g), mp 148–150°. The crude yield of oximes was thus 1.63 g (62%). Each product was recrystallized from aqueous acetone, when oxime A had mp 173–174° and oxime B 151–152°. The oximes had identical infrared spectra (mull) in the 2.5–9.0 μm region, but differed significantly in the fingerprint region, and each

readily reduced Tollens' reagent. The literature[21] records mp 164–165° for this oxime, apparently a mixture of the present oxime isomers. No attempt was made to determine the geometrical configurations of the present two stereoisomers.

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; H, 4.03. Found (oxime A): C, 75.82; H, 6.09; N, 3.99. Found (oxime B): C, 76.25; H, 6.12; N, 3.97.

1-Phenyl-2,2-di(*p*-anisyl)ethylamine (8). The above oxime A (1.5 g) and absolute ethanol (30 ml) were heated under reflux and small pieces (50–100 mg) of sodium (3.2 g; under dry toluene) were added over a 40-min period. Additional ethanol (10 ml) was added, refluxing was continued for another 15 min to dissolve all sodium, and water (150 ml) was added, whereupon the mixture was rotary evaporated at 70° under vacuum to remove ethanol. The residue was cooled and extracted with ether, and the extract was washed with water, dried, and decolorized, then concentrated on the steam bath and diluted with hexane. Slightly discolored crystals of the desired amine resulted, mp 78–82°. Exactly the same procedure was applied to oxime B, resulting again in the same amine, mp 78–82°, mixture melting point with above product 78–82°. The two products were combined, dissolved in ether, and extracted into 1 *N* hydrochloric acid. The aqueous layer was extracted with benzene and ether until colorless, then cooled in ice and made alkaline with sodium hydroxide solution. The gummy white amine product was extracted into ether and hexane was added, ultimately yielding a sample with mp 81–84°, unchanged by two further recrystallizations. The purified amine was relatively stable for several weeks, but rapidly discolored when in solution.

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.10; H, 6.84; N, 4.19.

Alternatively, a mixture of 90% formic acid (8.2 ml) and ammonium carbonate (10.0 g) was heated to 180° (distilling ca. 1 ml of water), then cooled to 170° and treated with the ketone oil obtained by procedure 2 above. The mixture was maintained at 175–185° for 10 hr, cooled, stirred with water (150 ml) and hydrochloric acid (25 ml), heated under reflux for 2 hr, then filtered. The filtrate was clarified with Norit and made basic with sodium hydroxide solution, causing precipitation of the desired amine. The filter cake was subjected several times to similar additional acid hydrolysis, until no more amine precipitated on adding base to the final filtrate. The crude amine was extracted from the basic solution with ether, and the ether extract was dried, filtered, and saturated with dry hydrogen chloride. A total of 2.2 g (34%) of the precipitated amine hydrochloride was isolated. A sample was purified to colorless needles by dissolving in water, extracting with ether, clarifying with Norit, adding hydrochloric acid, and allowing the solution to evaporate slowly. The above is an adaption of the procedure of Ingersoll and coworkers.[14]

Anal. Calcd for $C_{22}H_{24}NO_2Cl$: C, 71.43; H, 6.54; N, 3.79. Found: C, 71.24; H, 6.58; N, 3.72.

***p*-Anisyl Benzhydryl Ketone (11). Procedure 1.** *p*-Anisylmagnesium bromide was prepared from magnesium (6.1 g) and *p*-bromoanisole (31.5 ml) in ether (200 ml) and then treated with anhydrous cadmium chloride (22.0 g) while stirring at 0°. The mixture was then stirred at 0° for 15 min and at room temperature for 10 min, then was heated while stirring to drive off most of the ether. Benzene (150 ml) was added, distillation was continued until the vapors reached 68°, and the mixture was cooled. A solution of diphenylacetyl chloride (25.4 g) in benzene (60 ml) was added dropwise with stirring and cooling and the mixture was stirred at room temperature for 60 min, then under gentle reflux for 30 min. The mixture was cooled, treated with excess dilute hydrochloric acid, and filtered. The benzene layer was washed with water, 5% sodium hydroxide, and water, dried ($MgSO_4$), treated with Norit, and stripped of solvent. The refrigerated residue yielded a semisolid mass. Repeated recrystallization from ethanol yielded 8.8 g (26%) of material having mp 125–128°. A portion of this was purified to mp 127.5–128.5°.

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.58, 83.67; H, 5.96, 6.10.

Procedure 2. A sealed Carius tube containing diphenylacetic acid (8.4 g), chloroacetic anhydride (13.9 g), and anisole (4.35 ml) was heated at 170° for 65 hr, cooled, and opened, and its tarry contents were extracted into ether. The solution was extracted with sodium bicarbonate solution until neutral, dried, treated with Norit, filtered, and stripped of solvent. The dark, oily product (13 g) could not be crystallized, but thin layer chromatography indicated that it contained a large quantity of the desired ketone. It was used in the preparation below without further purification. This procedure is an adaptation of that of Unger.[15]

1-(*p*-Anisyl)-2,2-diphenylethylamine (9). The above oil (11 g) from procedure 2 was converted to the desired amine using formic acid and ammonium carbonate, exactly as described in the preparation of amine **8** above. The 3.0 g (29%) of crude amine obtained had mp 92–96°. The crude amine was dissolved in ether and converted to its hydrochloride using anhydrous hydrogen chloride as above. An aqueous solution of the hydrochloride was treated with base, and the precipitated free amine was filtered and air dried, mp 98–99°.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.16; H, 7.03; N, 4.62.

1-Phenyl-2,2-di(*p*-anisyl)ethanol (12). This alcohol was prepared by reduction of the ketone **10** with lithium aluminum hydride. Its recrystallization from a mixture of acetone and hexane gave a product having mp 142–144°, in agreement with the literature.[23]

1-(*p*-Anisyl)-2,2-diphenylethanol (14). This alcohol was prepared by the sodium borohydride reduction of *p*-anisyl benzhydryl ketone. Its recrystallization from ethyl acetate gave a product having mp 156–160°, in agreement with the reported value of 160°.[24]

2-(*p*-Anisyl)-1,2-diphenylethanol (15). A mixture of benzaldehyde (53 g) and *p*-toluenesulfonyl chloride (95 g) was cooled to ca. 0° and treated under stirring with a solution of potassium cyanide (33 g) in water (100 ml) at such a rate as to maintain the temperature below 7°. The mixture was stirred an additional 60 min at 7° and then filtered. The filter cake was dissolved in 250 ml of a 2:2:1 mixture of ethanol: acetone: ether and the solution was filtered and poured onto 150 g of ice. The resulting oily α-cyanobenzyl tosylate crystallized on chilling for several days, 61 g (wet). It was used directly without purification. The moist product (18.5 g) and anisole (50 g) were mixed and cooled to 5°, then treated under stirring with small portions of aluminum chloride (totaling 16 g), maintaining a temperature of 5–10°. After addition, the mixture was warmed to 95° and stirred at 95° for 6 hr, cooled, and poured onto ice (100 g) and hydrochloric acid (25 ml). The mixture was extracted with benzene and the extracts were washed with water, saturated sodium bicarbonate solution, and water and then were steam distilled. The pot residue was extracted with benzene, and the extract was dried (Na_2SO_4), filtered, and stripped of solvent, affording a dark oil which solidified. Recrystallization from ethanol gave a sample of α-(*p*-anisyl)-α-phenylacetonitrile mp 126–129°, in fair agreement with the literature.[16] The crude nitrile product was converted into 2-(*p*-anisyl)-1,2-diphenylethanone by reaction with phenylmagnesium bromide, in exactly the manner described above under procedure 2 for preparing phenyl di(*p*-anisyl)methyl ketone. The crude ketone could not be crystallized and was reduced directly. A solution of the crude product (0.90 g) in ethanol (20 ml) was treated with sodium borohydride (0.2 g) and 5% methanolic potassium hydroxide (1 ml) in 1:1 methanol:ethanol (40 ml). After 20 hr, water was added and the precipitated alcohol **15** was collected and recrystallized from ethyl acetate, mp 127–129°.

Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.42; H, 6.65.

Deamination of Amines 8 and 9 and Isolation of Their Alcohol Deamination Products. The amine hydrochloride (1.00 g) was dissolved in hot water or (in the case of **9**) the amine was dissolved in water (100 ml) containing concentrated HCl (1 ml). The solution was extracted with ether (15 ml; discard), cooled to 5°, and treated with acetic acid (1 ml), whereupon a solution of sodium nitrite (2.2 g) in water (22 ml) was added dropwise with stirring and cooling, causing precipitation of a yellow solid. The mixture stood at room temperature for 60 min, then was made basic with KOH and extracted with ether. The extracts were dried, filtered, and stripped of solvent to yield ca. 0.8 g of crude deamination product, which was subjected to preparative thin layer chromatography on 8 × 8 in. plates coated with silica gel HF 1 mm thick, using benzene as eluent. Two major areas were recovered, affording fraction 1, R_f 0.4–1.0, 0.23 g and fraction 2, R_f 0.01–0.4, 0.47 g. Fraction 2 contained the desired alcohol products, and was rechromatographed using 4:1 benzene:ether. The band having R_f 0.4–0.8 was removed and 0.39 g of alcohol product was recovered from it, 56% of the total fractions. This material was degraded as described below.

Table II. Esters from the Deamination of 1-Phenyl-2,2-di(*p*-anisyl)ethylamine (8) Experiment

Injection	Methyl benzoate, %	Methyl *p*-anisate, %[a]
1	7.5[b]	92.5[b]
2	12.1	87.9
3	9.1	90.9
4	8.8	91.2
5	8.7	91.3
Av	9.24	90.76 ± 1.71

[a] Equivalent to net *p*-anisyl migration. [b] By cut-and-weigh technique.

Table III. Esters from the Deamination of 1-(*p*-Anisyl)-2,2-diphenylethylamine (9) Experiments

No.	Injection	Methyl *p*-anisate, %	Methyl benzoate, %[a]
1	1	98.7[b]	1.3[b]
	2	97.5	2.5
	3	99.3	0.7
	4	98.3	1.7
	5	99.4	0.6
	6	99.3	0.7
	7	98.3	1.7
	Av	98.69	1.31 ± 0.70
2	1	99.52[c]	0.48[c]
	2	99.57	0.43
	3	99.54	0.46
	4	99.54	0.46
	5	99.52	0.48
	6	99.51	0.49
	7	99.62	0.38
	8	99.60	0.40
	9	99.56	0.44
	10	99.56	0.44
	Av	99.55	0.45 ± 0.04

[a] Equivalent to net phenyl migration. [b] Cut-and-weigh technique. [c] By (peak height)(half-peak width) technique.

Fraction 1 from the deamination of amine **9** partially crystallized on standing. Recrystallization from ethanol gave ca. 0.17 g of product, mp 160–163°, whose infrared and NMR spectra and elemental analysis suggested it to be 1-nitro-1-(*p*-anisyl)-2,2-diphenylethane.

Anal. Calcd for $C_{21}H_{19}O_3N$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.55; H, 5.92; N, 4.00.

Degradation of the Alcohol Deamination Products. The rechromatographed fractions 2 from the deaminations above containing the alcohol product mixtures (0.5 g) in dry pyridine (5 ml) were each added with swirling to slurries of chromic oxide (0.5 g) in dry pyridine (5 ml). The mixtures stood overnight, were poured into water (150 ml), and were extracted with benzene and ether. The extracts were filtered through Celite, washed with water, dried, filtered, and stripped of solvent to yield ca. 0.4 g of mixed ketones, shown by thin layer chromatography to be free of residual unoxidized alcohols.

Sodium (5.5 g) was dissolved in absolute ethanol (70 ml) under nitrogen, and a solution of the above ketone product (0.4 g) in absolute ethanol (20 ml) was added. The mixture was refluxed for 5 hr and diluted with water (90 ml), and the ethanol was distilled. The aqueous residue was cooled, extracted with ether (discard), and acidified with HCl, precipitating the benzoic and anisic acid products. These were extracted into ether and the extract was washed with water, dried, filtered, and freed of solvent. The residual acids (0.21 g) were dissolved in methanol (25 ml) containing H_2SO_4 (0.5 ml), and the solution was refluxed for 2 hr and diluted with water (20 ml). The mixture was extracted with ether and the extracts were washed with saturated $NaHCO_3$ solution and water, dried, and filtered. Solvent removal left 0.19 g of mixed methyl esters which were purified by quick short-path distillation then analyzed by gas chromatography as described below.

Cleavage of *p*-Anisyl Benzhydryl Ketone. To see if the above ketone **11** prepared by procedure 2 was homogeneous, a sample of the crude product was subjected to cleavage with sodium ethoxide in the manner described above. The acid fragment was converted to its methyl ester as above and analyzed by gas chromatography. The product proved to be pure methyl *p*-anisate, free of any methyl *o*-anisate which would have resulted had *o*-anisyl benzhydryl ketone been present in the crude ketone product.

Determination of the Extents of Aryl Migration. The mixtures of methyl esters obtained by the above degradations of the alcohol products resulting from the deaminations of amines **8** and **9** were analyzed gas chromatographically using a ⅜ in. × 9 ft column packed with 10% QF-1 phase on 60–80 Chromosorb W, installed in an Aerograph A-90-P gas chromatograph using a thermal conductivity detector. Base-line resolution of the methyl benzoate and *p*-anisate peaks was achieved operating isothermally at 220° with a helium flow rate of ca. 50 ml/min. Peak area integration was accomplished either by cutting out the gc recorder traces and weighing them, or by the (peak height)(half-peak width) measurement technique. The former method gave a slightly larger methyl *p*-anisate:methyl benzoate ratio because of tailing effects, but only slight corrections were necessary. Table II shows the relative peak areas (%) for the two esters in a number of consecutive GC analyses of the ester mixture obtained from amine **8**, and Table III shows similar data for the esters from the separate deaminations of amine **9**.

Internal Checks. A mixture containing 0.510 mmol of methyl benzoate and 0.402 mmol of methyl *p*-anisate was subjected to gas chromatographic separation under the above conditions, and the relative peak area per mole for each component was compared and found identical within experimental error. This indicates that the gas chromatographic technique employed was providing a uniform molar response for each ester component.

To see if the alcohol products from the above deaminations had the same response to the overall degradation scheme employed, an equimolar mixture containing 0.2198 g of **14** and 0.2199 g of **15** was subjected to the above degradation involving initial oxidation to the ketone and subsequent cleavage with sodium ethylate. The acidic products were esterified and analyzed gas chromatographically as usual, whereupon it was found that the methyl *p*-anisate was produced in slightly higher yield than was the methyl benzoate. By the cut-and-weigh integration technique, the methyl benzoate:methyl *p*-anisate ratio was 0.895 ± 0.025 (average from 9 GC injections), while the ratio was 0.945 ± 0.037 using the (peak height)(half-peak width) integration. Assuming that approximately these same ratios would be obtained on a similar control degradation of an equimolar mixture of alcohols **12** and **13**, these ratios have then been used to correct the methyl benzoate average analytical figures in Tables II and III.

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Nitroxide Radical Induced Nuclear Magnetic Resonance Contact Shift Studies.[1] Potential Utility of Specific Downfield ^1H Contact Shifts Induced by Hydrogen Bonding with Di-*tert*-butyl Nitroxide Radical

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Abstract: Utility of a nitroxide radical as a paramagnetic shift reagent in proton NMR spectroscopy is reported. DTBN (di-*tert*-butyl nitroxide radical) induces *upfield* contact shifts for the X–H proton in proton donor molecules and *downfield* shifts for C–H protons other than the X–H proton. This *downfield* contact shift, which is concerned in this study, is proved to be characteristic of protic molecules and shows conformational dependence. The proton lying on the zigzag path from the hydroxyl or NH group exhibits preferential DTBN induced downfield shift, obeying the "W letter rule". The origin of this contact shift is also discussed in terms of stereospecific electron spin transmission through the intervening bonds from the X–H proton donor group hydrogen bonded with DTBN. Potential utility of this downfield contact shift for structural elucidation around the proton donor group in organic and biologically important molecules is discussed. It is also revealed that the methyl protons in close spacial contact with N–H or O–H proton donor group exhibit substantial DTBN induced *downfield pseudocontact shift*, which is discussed in terms of anisotropy of the *g* value and the mode of hydrogen bond complex.

We wish to report here a novel downfield ^1H NMR contact shift induced by hydrogen bonding with a nitroxide radical, which is quite characteristic of protic molecules and shows geometrical or conformational dependence. This downfield contact shift is shown to provide potential utility as a sensitive tool for structural elucidation around the proton donor group and the mode of hydrogen bonding.

Our recent studies[2,3] on NMR contact shifts have shown that the nitroxide radical di-*tert*-butyl nitroxide, or DTBN, can be used to probe chemical phenomena associated with molecular interactions such as hydrogen bond[2] and charge transfer[3] interactions involving the free radical. In some of our early reports, we described[2a-f] that the X–H···DTBN hydrogen bond induces a strong *upfield* contact shift, characteristic of negative spin density, for the X–H proton, providing fruitful information on the intrinsic nature of this interaction. In the present study we are concerned with the specific DTBN induced *downfield* shift for the C–H proton other than the X–H proton in various proton donor molecules. We have measured here DTBN-induced proton contact shifts for various organic molecules with proton donor groups, such as aliphatic and aromatic alcohols, amines, and carboxylic acids and for some biologically important molecules.

Experimental Section

Materials. DTBN radical was prepared after the method of Briere and Rassat (see ref 2). Other chemicals used in the present study except for deuterated cyclohexanol derivative were commercially available and used without further purification. A deuterated cyclohexanol derivative such as *trans*-4-*tert*-butylcyclohexanol-d_4 was provided by Dr. T. Suzuki. Adamantanol was also supplied by Professor M. Kawanishi.

Proton NMR Measurement. Most of the proton NMR signals in the presence of DTBN radical exhibit substantial broadening. It is therefore preferable to use high-field NMR in order to avoid overlapping of the broadened signals. Proton NMR spectra were obtained with a Varian Associates HR-220 at 220 MHz at room temperature. DTBN was added drop by drop and linear plots of the DTBN-induced shifts vs. the concentration of added DTBN were obtained. Cyclohexane was used as an internal reference, since it was most insensitive to the DTBN-induced shift.

Results and Discussion

A. DTBN-Induced Downfield Shifts. Figure 1a shows the DTBN-induced spectral perturbation for diethylamine in CCl_4 solution. Addition of DTBN radical to the CCl_4 solution of the proton donor molecules caused a large *upfield* shift for the hydroxyl or amine proton, accompanied by strong line broadening, as reported previously.[2] Most of the other C–H protons in aliphatic alcohol or amine, however, experienced substantial *downfield* shifts, attenuating in magnitude along the aliphatic chain. Figure 1b shows the DTBN-induced downfield shifts for isopropyl alcohol, as an example. In Table I are presented the DTBN-induced downfield proton shifts for some proton donor molecules. These downfield shifts are proportional to the concentration of added DTBN radical and characteristic of the proton donating group (such as -OH, -COOH, $-NH_2$ and >N-H), although the X–H proton signals themselves showed remarkable broadening and upfield shift. On the other hand, when these X–H groups are replaced by the ones incapable of hydrogen bonding with DTBN radical (i.e., OCH_3, $COOCH_3$, $COCH_3$, $N(CH_3)_2$, $>NCH_3$, NO_2, etc.) or when a strong proton acceptor such as DMSO (dimethyl sulfoxide) is used as a solvent, the proton signals no longer exhibited the downfield shift, but rather experience a slightly upfield shift, implying that the C–H proton serves as a weak proton donor in the C–H···DTBN hydrogen bond.[2c] For example, the ring protons of pyrrole showed DTBN-induced down-