with Dr. Thomas W. Whaley regarding this work is also appreciated.

Registry No.—**1**, 50-32-8; **1a**, 67194-47-2; **1b**, 67194-48-3; **1c**, 67194-49-4; **1d**, 67194-50-7; **2**, 42286-46-4; **3**, 60657-26-3; **6**, 66267-06-9; **7**, 57652-74-1; **8**, 67194-42-7; **9**, 57652-75-2; **10A**, 67194-43-8; **10B**, 67194-44-9; **11A**, 67194-45-0; **11B**, 67914-46-1; **12A**, 57652-73-0; **12B**, 57652-76-3; **13**, 24027-84-7; **17**, 3424-59-7; **18**, 58735-82-3; *N*-isopropylcyclohexylamine, 1195-42-2.

References and Notes

(1) Presented before the Division of Organic Chemistry at the 175th National Meeting of the American Chemical Society, Anaheim, California, March, 1978.
(2) Supported in part by Grant No. CA 16871 from the National Cancer Institute, DHEW.
(3) (a) L. F. Fieser and W. S. Johnson, *J. Am. Chem, Soc.*, **61**, 1647 (1939); (b) L. F. Fieser and W. S. Johnson, *ibid.*, **62**, 575 (1940).
(4) (a) L. F. Fieser and H. Heymann, *J. Am. Chem. Soc.*, **63**, 2333 (1941); (b) L. F. Fieser and M. A. Peters, *ibid.*, **54**, 4347 (1932).
(5) M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1970).
(6) R. D. Rieke and S. J. Uhm, *Synthesis*, **7**, 452 (1975).
(7) M. Bellassoued, R. Couffignal, and M. Gaudemar, *J. Organomet. Chem.*, **61**, 9 (1973).
(8) (a) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973); (b) M. W. Rathke, *ibid.*, **92**, 3222 (1970); (c) M. W. Rathke and A. Lindert, *ibid.*, **93**, 2318 (1971).
(9) P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973). It was originally intended to use methanesulfonic acid/P_2O_5 as described by Eaton et al., for these cyclizations; however, we have found that redistilled methanesulfonic acid without added P_2O_5 cyclized both the aldehydes and carboxylic acids in excellent yields under mild conditions.
(10) H.-J. Teuber and G. Steinmetz, *Chem. Ber.*, **98**, 666 (1965).
(11) R. G. Harvey, S. H. Goh, and C. Cortez, *J. Am. Chem. Soc.*, **97**, 3468 (1975).
(12) R. M. Moriarty, P. Dansette, and D. M. Jerina, *Tetrahedron Lett.*, **30**, 2557 (1975).
(13) D. J. McCaustland and J. F. Engel, *Tetrahedron Lett.*, **30**, 2549 (1975).
(14) G. A. Ropp, *J. Am. Chem. Soc.*, **72**, 2299 (1950).
(15) G. W. Buchanan and R. S. Ozubko, *Can. J. Chem.*, **53**, 1829 (1975).
(16) H. Yagi, G. M. Holder, P. J. Dansette, O. Hernandez, H. J. C. Yeh, R. A. LeMahieu, and D. M. Jerina, *J. Org. Chem.*, **41**, 977 (1976).
(17) L. F. Fieser and M. Fieser, *J. Am. Chem. Soc.*, **57**, 782 (1935).

Mechanism of Aryl Group Migration in the Formation of Stilbenes from 1,1-Bis(*p*-hydroxyaryl)ethane 2-*O*-Aryl Ethers

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The base-catalyzed displacement of the aryloxy substituent in 1,1-bis(*p*-hydroxyaryl)ethane 2-*O*-aryl ethers, via an aryl participation (A_1-3) reaction, and subsequent transformation to the corresponding stilbenes have been investigated. The relative migratory aptitudes of the phenolic nuclei were determined by rate studies and by the use of C-1 deuterium labeled substrates. The two methods gave similar results and showed that the A_1-3 reaction is enhanced when the migrating phenolic nucleus is substituted with electron-donating substituents. The rate-determining step in this reaction was found to be the intramolecular nucleophilic displacement of the aryloxy substituent by a cyclohexadienone carbanion.

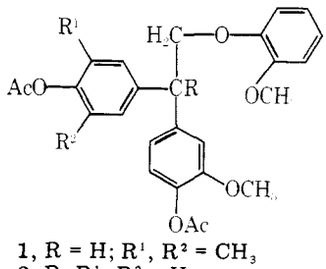
Recently, it was reported that the 1,1-bis(aryl)ethane 2-*O*-aryl ether **1** readily undergoes a base-catalyzed transformation to give, after reacetylation, stilbene **9**.[1] This transformation involves a [1,2] shift of an aryl group, and it was suggested that the mechanism may involve the displacement of the aryloxy substituent through an aryl participation (A_1-3) reaction (Scheme I). A priori, two possibilities for such a transformation can be formulated. As shown in Scheme I, the displacement can be brought about by an intramolecular nucleophilic attack by either carbanion **1b** or **1c** on the β-carbon atom, resulting in the formation of the spiro cyclohexadienone intermediate **8a** or **8b** which by rearrangement and elimination of a proton gives rise to stilbene **9a**.

This conversion of **1** → **9** by way of a spiro cyclohexadienone intermediate is based on well-established precedent, i.e., the alkaline solvolysis of 2-*p*-hydroxyphenylethyl bromide, which takes place by way of a spiro cyclohexadienone intermediate.[2,3] However, the transformation **1** → **9** involves a cyclohexadienone skeleton rearrangement, and the mechanism of this rearrangement with regard to the identity of the migrating group remains a point of considerable uncertainty and interest. Accordingly, in order to obtain more information about the reaction step in which the aryloxy substituent is split off, and to elucidate more fully the mechanism of this reaction, we have studied the effect of substituents on the migratory aptitude of phenolic nuclei in 1,1-bis(aryl)ethane 2-*O*-aryl ether compounds and have tried to correlate the resulting rate data with parameters characteristic for the electronic effect of the substituent. Some results of this study are now reported.

Results and Discussion

The 1,1-bis(aryl)ethane 2-*O*-aryl ether compounds **1–7** were synthesized in an average overall yield of 80–90% by reacting **19** or its deuterated analogue **20** with either phenol or one of three different ortho-substituted phenols in the presence of a small amount of hydrogen chloride,[4] followed by column chromatographic isolation and purification. The condensation products were subsequently used in the form of their crystalline acetate derivatives. Structural proof of new compounds was based on analytical and spectral data (NMR and MS).

Alkaline treatment (1 M NaOH, 170 °C, 2 h) of the 1,1-bis(aryl)ethane 2-*O*-aryl ethers **1–4**, followed by acetylation of the resulting reaction mixtures and gas chromatographic



1, R = H; R^1, R^2 = CH_3
2, R, R^1, R^2 = H
3, R, R^1 = H; R^2 = CH_3
4, R, R^1 = H; R^2 = OCH_3
5, R = ^2H; R^1, R^2 = CH_3
6, R = ^2H; R^1 = H; R^2 = CH_3
7, R = ^2H; R^1, R^2 = H

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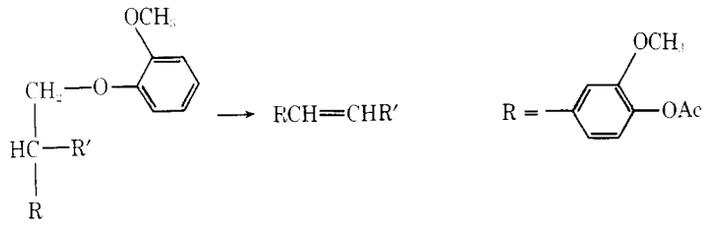
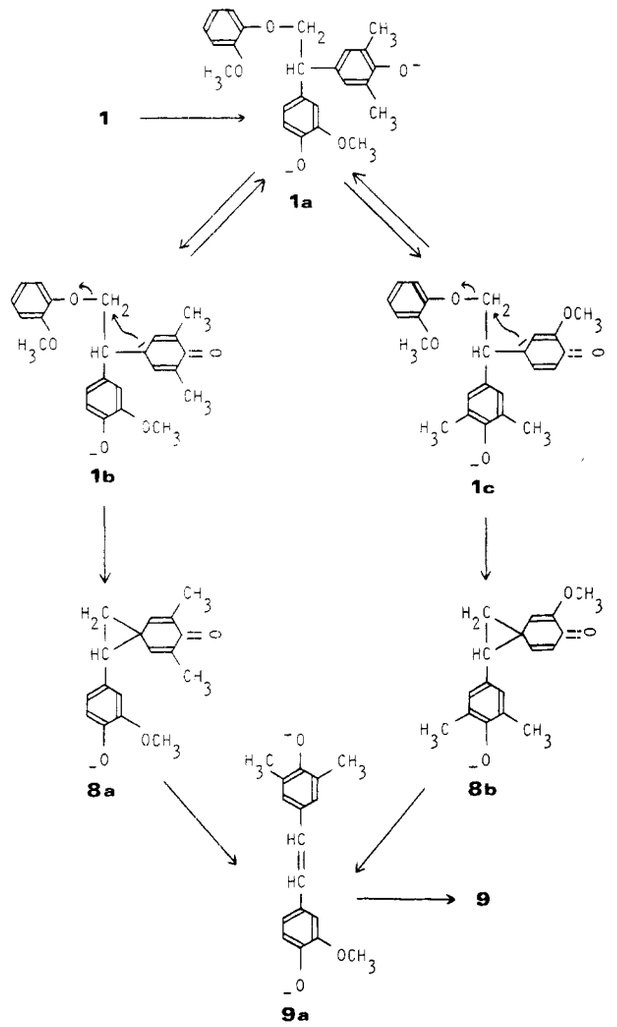
Table I. Stilbene Formation Data[a]



compd	registry no.	yields,[b] % starting material	yields,[b] % stilbene	registry no.	migrating group, extent of migration, % (% of total reaction) determined by rate studies R′	determined by rate studies R	determined by deuterium labeling[c] R′	determined by deuterium labeling[c] R	relative migration rate k_x/k_H	relative migration rate $\log k_x/k_H$
1	64702-05-2	31	69	67315-60-0	52 (75)	17 (25)			2.74	0.44
5	67315-54-2						50 (72)	19 (28)	2.50	
3	67315-55-3	51	49	67315-61-1	32 (65)	17 (35)			1.68	0.23
6	67315-56-4						32 (66)	17 (34)	1.60	
2	67315-57-5	64	36	67315-62-2	19 (53)	17 (47)			1.00	0.0
7	67315-58-6						20 (55)	16 (45)	1.00	
4	67315-59-7	66	34	54208-26-3	17 (50)	17 (50)			0.89	−0.05

[a] All reactions conducted in 1 M NaOH at 170 ± 1 °C for 2 h under atmosphere of N_2. [b] Determined by GLC. Accuracy ±1%. [c] Accuracy estimated to be ±3–5%.

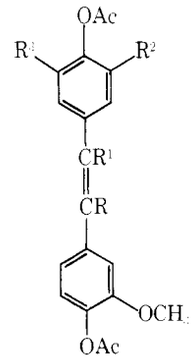
Scheme I



analysis, yielded the results summarized in Table I. For each compound, the yield of stilbene accounts for the total amount of starting compound consumed. Thus, no side reactions have taken place.

The rate study data listed in Table I were analyzed by the iterative dissection method, using the extent of reaction for the 1,1-bis(aryl)ethane compound containing two equivalent 4-hydroxy-3-methoxyphenyl moieties (**4**) to define the extent of migration of a single 4-hydroxy-3-methoxyphenyl nucleus, which was considered to be half (17%) that of the total amount (34%) of the symmetrical stilbene **12** formed under the reaction conditions. Assuming that this value is independent of the nature of the other phenolic moiety in the 1,1-bis(aryl)-ethane compound, the contribution of the latter moiety to the stilbene formation is obtained as the difference. The extents of migration of the two phenolic moieties are expressed as percent of the total reaction, and the migration rates of the substituted phenolic nuclei relative to that of the unsubstituted one, k_x/k_H, are obtained as the ratios of the corresponding extents of migration (Table I).

Identical treatment of the deuterated analogues **5–7** gave in each case a mixture of two deuterated stilbenes (**13–15**), the deuterium atom being located in the α position relative to the phenolic moiety which has not migrated. Catalytic hydrogenation of these stilbenes gave the corresponding deuterated 1,2-bis(aryl)ethanes **16–18**, the mass spectra of which revealed



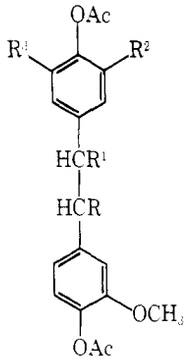
9, R, R^1 = H; R^2, R^3 = CH_3
10, R, R^1, R^2, R^3 = H
11, R, R^1, R^2 = H; R^3 = CH_3
12, R, R^1, R^2 = H; R^3 = OCH_3
13a, R = H; R^1 = ^2H; R^2, R^3 = CH_3
13b, R = ^2H; R^1 = H; R^2, R^3 = CH_3
14a, R, R^2, R^3 = H; R^1 = ^2H
14b, R^1, R^2, R^3 = H; R = ^2H
15a, R, R^2 = H; R^1 = ^2H; R^3 = CH_3
15b, R = ^2H; R^1, R^2 = H; R^3 = CH_3

Table II. Partial Mass Spectral Data for the Deuterated 1,2-Bis(aryl)ethanes[a]

mass, m/e	compound[b] 16	17	18
107		40	
108		36	
121			55
122			33
135	96		
136	47		
137	42	74	59
138	100	100	100

[a] Uncorrected for 1,2-bis(aryl)ethane-d_0, estimated at 2–3%. [b] Relative peak intensities uncorrected for C-13.

the deuterium atom location and content and, hence, the identity of the migrating phenolic moiety. Comparison of the relative intensities of the corresponding deuterated and undeuterated hydroxytropylium ion fragments[5] (Table II) gave the relative migration ratios shown in Table I.



16a, R = H; R^1 = ^{2}H; R^2, R^3 = CH_3
16b, R = ^{2}H; R^1 = H; R^2, R^3 = CH_3
17a, R = ^{2}H; R^1, R^2, R^3 = H
17b, R, R^2, R^3 = H; R^1 = ^{2}H
18a, R, R^2 = H; R^1 = ^{2}H; R^3 = CH_3
18b, R = ^{2}H; R^1, R^2 = H; R^3 = CH_3

As is evident from Table I, the two independent methods employed in this study for the elucidation of the identity of the migrating phenolic moiety gave essentially the same results. Evidently, other factors being equal, the rate of cleavage of the C–O bond (Scheme I) and subsequent formation of stilbene depend on the migratory aptitude of the phenolic nuclei, which the present study establishes is favored when the migrating phenolic nucleus is substituted with electron-donating substituents.

By treatment of the methyl and methoxyl groups as substituents on a phenolic nucleus, the empirical Hammett relationship was applied to the rate data. The Hammett plot of the log (k_x/k_H) values, calculated from the experimental results in Table I, vs. Brown's σ^+ substituent constants is shown in Figure 1. It can be seen that a straight line results with a slope of $\rho^+ = -3.3$. From the absolute value and the sign of the reaction constant it is evident that the reaction is facilitated by electron-donating substituents. The accelerating effect of electron-donating substituents X in the migrating aryl group as well as the magnitude of ρ^+ compare quite well to those observed in other anionotropic [1,2] aryl shifts.[6]

The overall effect of the electron-donating methyl substituents is to increase the basicity and nucleophilicity[7] of, for example, carbanion **1b** compared to that of the methoxyl-substituted carbanion **1c** (Scheme I), by increasing the electron density on the reaction center (inductive effect). Thus, the rates of formation of stilbene products are greater for compounds **1** and **3** than for compounds **2** and **4**. In harmony

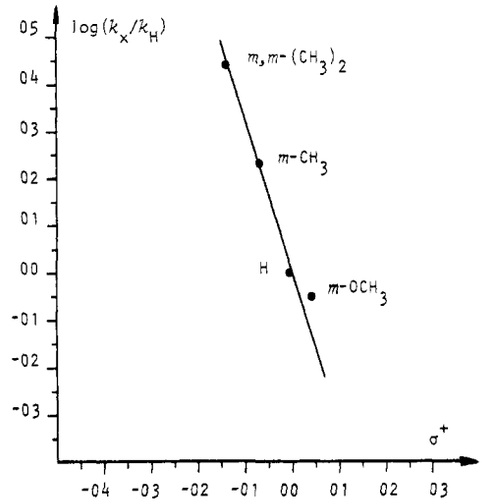
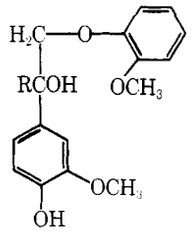


Figure 1. Hammett-Brown correlation of substituent effects on the migratory aptitude of phenolic nuclei.

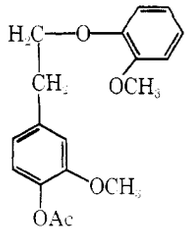
with this result and the general mechanism shown in Scheme I, the rates of migration of the methyl-substituted phenolic moieties are greater than that of the unsubstituted phenolic moiety (Table I). Conversely, a methoxyl substituent, due to its electron-withdrawing effect when situated meta to the reaction site, should retard the migration of a phenolic moiety. The data (Table I) indicate the expected migration retarding effect of a meta methoxyl substituent; however, the effect is considerably less than that which would be expected from the Hammett correlation (Figure 1). Probably, the electron-withdrawing effect of the methoxy substituent is more than compensated by the resonance effect of this substituent, an explanation which is compatible with the results of a wide variety of reactions involving a methoxyl group as a substituent on an aromatic nucleus.[8]

From a consideration of the overall reaction as depicted in Scheme I for the transformation 1 → **9**, it can be concluded that the key step of this reaction is the intramolecular nucleophilic displacement of the aryloxy substituent by the cyclohexadienone carbanion (**1b** or **1c**). This participation of the migrating group in the transition state of the rate-determining step explains the substantial effect of substituents X on the reaction rate. Owing to the facile electron redistribution, the unstable spiro cyclohexadienone intermediate[2,3] (**8a** or **8b**) is rapidly rearranged to the stilbene product **9a**. Overall then, this reaction is probably a concerted process with the [1,2] aryl shift occuring essentially simultaneously with the cleavage of the C–O ether bond.

When compound **21** was treated with alkali in a similar manner, no reaction was observed. This negative result shows that the aryl participation reaction is restricted to compounds containing at least two phenolic moieties linked to the β-carbon atom relative to the aryl ether linkage. The ability of a second aryl group β to a leaving group to facilitate the dissociation of the C_α–Z bond[9] is probably a major contributory factor to the substrate activation effect of a second aryl group



19, R = H
20, R = ^{2}H



21

at C_β observed for the 1,1-bis(aryl)ethane 2-*O*-aryl ether compounds and lends support to our earlier conclusion that the rate-determining step in this reaction (Scheme I) involves cleavage of the C–O ether bond.

The unreactivity of compound **21** compared to 2-*p*-hydroxyphenylethyl bromide[2,3] can be accounted for by the fact that an aryloxy group is a considerably poorer leaving group than bromine, as much as two or three orders of magnitude poorer in reactions such as nucleophilic substitution at sp^3-hybridized carbon and alkene-forming eliminations.[10,11] In addition, the unreactivity of **21** indicates that the limited alkaline cleavage (about 30%) of the alkyl–O ether bond observed[12] with compound **19** is due to a neighboring group participation reaction involving the ionized benzylic hydroxyl group rather than the phenolic moiety as the nucleophilically attacking species. Hence, the alkaline cleavage of the C–O ether bond in **19** proceeds via an epoxide (cf. also the behavior of nonphenolic β-aryl ethers[12]) rather than via a spiro cyclohexadienone intermediate.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were obtained on a Perkin Elmer R-12 spectrometer (60 MHz) using $CDCl_3$ (internal Me_4Si) as the solvent. Chemical shifts are reported on the τ scale. Mass spectra were recorded on a Finnigan quadrupole instrument at 40 eV using the direct inlet system. Gas chromatographic analysis was performed on a Perkin Elmer F 17 instrument with a flame ionization detector. The column material was SE-30 (3%) on Chromosorb 750 (80/100 mesh). Peak areas were obtained with a Pye Unicam DP 88 computing integrator. Preparative separations were carried out by column chromatography using silica gel (Merck, 0.063–0.200 mm, 70–230 mesh, ASTM) as the adsorbent and light petroleum (60–71 °C)–ethyl acetate (4:1) as the solvent.

Materials. The following compounds were prepared as previously described: **19**[12] and **21**.[13] Compound **20** was prepared from the appropriate acetophenone as described for **19** by reduction with sodium tetradeuterioborate.

The NMR data along with the melting points of all new compounds are summarized in Table III.[14] Physical constants and spectral data for compounds **1**, **9**, and **12** were identical with those reported[1] previously for these compounds.

Preparation of 1,1-Bis(aryl)ethane 2-*O*-Aryl Ethers. General Procedure. The benzyl alcohol **19** or its deuterated analogue **20** (0.34 mmol), the appropriate phenol (5.0 mmol), and concentrated HCl (0.25 mL) were heated at 80 °C for 1 h with magnetic stirring.[4] The resulting condensation product was isolated by column chromatography on silica gel (125 g), acetylated with pyridine–acetic anhydride (1:1), and crystallized from diethyl ether. Recrystallization from diethyl ether yielded the 1,1-bis(aryl)ethane 2-*O*-aryl ethers **1**–**7** in 80–90% overall yield.

2. Anal. Calcd for $C_{26}H_{26}O_7$: C, 69.33; H, 5.78; O, 24.89. Found: C, 69.75; H, 5.65; O, 24.45. MS *m/e* (rel intensity) 450 (1, M^+), 327 (4), 313 (7), 285 (69), 271 (33), 243 (100), 229 (81), 199 (53), 137 (37).

3. Anal. Calcd for $C_{27}H_{28}O_7$: C, 69.83; H, 6.03; O, 24.14. Found: C, 69.84; H, 6.03; O, 23.98. MS *m/e* (rel intensity) 464 (3, M^+), 341 (5), 299 (63), 285 (15), 257 (100), 243 (48).

4. Anal. Calcd for $C_{27}H_{28}O_8$: C, 67.50; H, 5.83; O, 26.67. Found: C, 67.97; H, 6.07; O, 26.03. MS *m/e* (rel intensity) 480 (5, M^+), 396 (1), 357 (7), 343 (2), 315 (73), 301 (19), 273 (100), 259 (68).

5. MS *m/e* (rel intensity) 479 (1, M^+), 356 (3), 342 (1), 314 (47), 300 (13), 272 (100), 258 (50).

6. MS *m/e* (rel intensity) 465 (2, M^+), 342 (5), 328 (1), 300 (59), 286 (14), 258 (100), 244 (52), 137 (23).

7. MS *m/e* (rel intensity) 451 (3, M^+), 328 (5), 314 (7), 286 (80), 272 (34), 244 (100), 230 (73), 200 (25), 137 (24).

Rate Studies. Solutions of the 1,1-bis(aryl)ethane 2-*O*-aryl ethers 1–4 (0.07 mmol) in 1.0 M aqueous NaOH (10 mL) and ethylene glycol monomethyl ether (1 mL) were heated under N_2 atmosphere in a stainless steel bomb (25 mL capacity) at 170 ± 1 °C for 2 h. The reaction solution was then diluted with H_2O (15 mL), neutralized with 10% phosphoric acid, and extracted with $CHCl_3$ (4 × 10 mL), and the combined organic layers were concentrated under reduced pressure, and the residue was acetylated with pyridine–acetic anhydride (1:1). The resulting mixture of acetylated reaction products was analyzed by GLC.

Isolation of Reaction Products. The 1,1-bis(aryl)ethane 2-*O*-aryl ethers 1–7 (0.2 mmol) were reacted as described above. The acetylated reaction products were then separated by column chromatography on silica gel (125 g). The stilbene products were recrystallized from acetone.

10. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52; O, 24.54. Found: C, 69.99; H, 5.59; O, 24.54. MS *m/e* (rel intensity) 326 (1, M^+), 284 (21), 242 (100), 199 (19), 181 (75), 153 (38).

11. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.60; H, 5.88; O, 23.52. Found: C, 70.42; H, 5.97; O, 23.50. MS *m/e* (rel intensity) 340 (13, M^+), 298 (35), 256 (100), 195 (27), 181 (10), 152 (12).

13. MS *m/e* (rel intensity) 355 (1, M^+), 313 (9), 271 (100), 210 (19), 182 (18), 166 (23).

14. MS *m/e* (rel intensity) 327 (5, M^+), 285 (25), 243 (100), 210 (4), 200 (5), 182 (16), 154 (9).

15. MS *m/e* (rel intensity) 341 (5, M^+), 299 (21), 257 (100), 196 (14), 173 (33), 113 (25), 99 (59).

Reduction of the Deuterated Stilbenes 13–15. The deuterated stilbenes **13–15** (20 mg) were dissolved in ethyl acetate (25 mL) and hydrogenated over 5% palladium/charcoal (100 mg) at atmospheric pressure and ambient temperature for 24 h. The reaction solution was filtered through Celite and the filtrate was concentrated under reduced pressure. The 1,2-bis(aryl)ethane products **16–18** were crystallized from diethyl ether and recrystallized from acetone–light petroleum.

Method of Deuterium Analysis. The deuterated 1,2-bis(aryl)-ethanes **16–18** were analyzed for deuterium content and location by mass spectrometric analysis of samples of the crystalline compounds. Consistent fragmentation patterns are produced which permit accurate localization and measurement of deuterium. The deuterium location and content were determined by monitoring the relative abundance of the deuterated and undeuterated hydroxytropylium ion fragments. Two sets of ions were monitored for each compound (Table II) corresponding to the hydroxytropylium ions originating from the two different aryl groups. The migration ratios of the aryl groups can be easily deduced from direct comparison of the relative peak intensities of the unlabeled and labeled ion fragments after correction due to the natural abundance (1.1%) of carbon-13.

Let P = the relative intensity of the unlabeled ion fragment, $P + 1$ = the relative intensity of the corresponding labeled ion fragment, and $(P + 1)_{corr}$ = the relative intensity of the labeled ion fragment corrected for the contribution of carbon-13. The P and $P + 1$ values are given in Table II.

$$\% \text{ aryl group migration} = \frac{P}{P + (P + 1)_{corr}} \times 100$$

The illustrative calculation for compound **17** is shown below:

$$m/e\ 107 \qquad P = 40$$

$$m/e\ 108 \qquad P + 1 = 36 \text{ and } (P + 1)_{corr} = 36 - (40 \times 0.077) = 32.92$$

$$\% \text{ } p\text{-hydroxyphenyl group migration} = \frac{40}{72.92} \times 100 = 55\%$$

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Registry No.—**13a,** 67315-63-3; **13b,** 67315-64-4; **14a,** 67315-65-5; **14b,** 67315-66-6; **15a,** 67315-67-7; **15b,** 67315-68-8; **16a,** 67315-69-9; **16b,** 67315-70-2; **17a,** 67315-71-3; **17b,** 67315-72-4; **18a,** 67315-73-5; **18b,** 67315-74-6; **19,** 7382-68-5; **20,** 67315-75-7; **21,** 29340-52-1; phenol, 108-95-2; 2,6-dimethylphenol, 576-26-1; *o*-methylphenol, 95-48-7; *o*-methoxyphenol, 90-05-1.

Supplementary Material Available: Table III containing melting point and NMR data (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) J. Gierer and I. Pettersson, *Can. J. Chem.*, **55,** 593 (1977).
(2) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79,** 756 (1957).
(3) R. Baird and S. Winstein, *J. Am. Chem. Soc.*, **79,** 4238 (1957).
(4) H. Nimz, *Holzforschung*, **23,** 84 (1969).
(5) J. M. S. Talt, T. W. Shannon, and A. G. Harrison, *J. Am. Chem. Soc.*, **84,** 4 (1962).
(6) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1962, Chapter 15.
(7) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1962, p 354.
(8) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, Chapter 9.

(9) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, J. Am. Chem. Soc., 74, 1113 (1952).
(10) D. R. Marshall, P. J. Thomas, and C. J. M. Stirling, J. Chem. Soc., Perkin Trans. 2, 1898 (1977).
(11) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, Chapter 10.
(12) J. Gierer and I. Norén, Acta. Chem. Scand., 16, 1713 (1962).
(13) G. Gellerstedt and J. Gierer, Acta. Chem. Scand., 24, 1645 (1970).
(14) See paragraph at the end of the paper regarding supplementary material.

Mechanism and Catalysis for *o*-Hydroxyacetophenone Phenylhydrazone Formation[1]

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Acetophenone phenylhydrazone formation, like that of meta-/para-substituted benzaldehydes, occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamines from this substrate is subject to general acid–base catalysis by carboxylic acid–carboxylate buffers. 2′-Hydroxyacetophenone phenylhydrazone formation also occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamine from this substrate is subject to specific acid catalysis, but is not subject to detectable general acid–base catalysis by carboxylic acid–carboxylate buffers. It is proposed that this lack of general acid–base catalysis is due to internal hydrogen bond formation between the acidic hydrogen of the *o*-hydroxy substituent and the carbonyl group. The same was observed for carbinolamine formation from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones (substituent = nitro, cyano, chloro, and methyl). Rate constants for the hydrated proton catalysis and for the pH-independent reaction are well correlated by a dual Hammett substituent parameter treatment.

The rates of reaction of *o*-hydroxybenzaldehyde and the corresponding para isomer with a variety of nitrogen nucleophiles, including hydroxylamine, semicarbazide, *p*-toluidine, and phenylhydrazine, have been reported to exhibit ortho/para ratios considerably greater than unity.[2-5] This has been attributed to greater stabilization of the para- than the ortho-substituted benzaldehydes by substituents which donate electrons by resonance.[5]

A detailed study of the kinetics of phenylhydrazone formation from acetophenone and 2′-hydroxy-5′-substituted acetophenones was undertaken in order to examine the effect of ortho substituents capable of forming hydrogen bonds with the carbonyl oxygen of the acetophenone on reactivity toward nucleophiles.

Experimental Section

Materials. Acetophenone, 2′-hydroxyacetophenone, phenylhydrazine hydrochloride, and the carboxylic acids employed were obtained commercially and were either redistilled or recrystallized before use. *p*-Methyl-, *p*-chloro-, *p*-cyano-, and *p*-nitrophenyl acetates were prepared by the procedure of Bender and Nakamura.[6] 2′-Hydroxy-5′-methylacetophenone,[7] 2′-hydroxy-5′-chloroacetophenone,[8] 2′-hydroxy-5′-cyanoacetophenone,[8] and 2′-hydroxy-5′-nitroacetophenone[9] were prepared from the esters indicated above by procedures described in the literature. The acetophenone phenylhydrazones were prepared by the procedure of Vogel.[7]

p-Cyanophenyl acetate: mp 57–58 °C; NMR (60 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 7.47 (q, 4 H); IR (KBr) 2200, 1760, 1196, 840 cm^{-1}. Anal. Calcd: C, 67.08; H, 4.37; N, 8.65. Found: C, 66.40; H, 4.39; N, 8.58. 2′-Hydroxy-5′-cyanoacetophenone: mp 105–106 °C; NMR (60 MHz, $CDCl_3$) δ 2.68 (s, 3 H), 7.08 (d, 1 H), 7.75 (q, 1 H), 8.12 (d, 1 H), 12.7 (s, 1 H); IR (KBr) 2220, 1648, 1480, 1210, 840 cm^{-1}. Anal. Calcd: C, 67.08; H, 4.37; N, 8.70. Found: C, 66.77; H, 4.36; N, 8.75. 2′-Hydroxy-5′-chloroacetophenone phenylhydrazone: 174–175 °C; NMR (60 MHz, $(CD_3)_2SO$) δ 2.40 (s, 3 H), 6.60–7.80 (m, 8 H), 9.67 (s, 1 H), 12.8 (s, 1 H); IR (KBr) 3300, 1625 cm^{-1}. Anal. Calcd: C, 64.52; H, 4.99; N, 10.75. Found: C, 64.06; H, 5.28; N, 10.80. 2′-Hydroxy-5′-cyanoacetophenone phenylhydrazone: 192–193 °C; NMR (60 MHz, $(CD_3)_2SO$) δ 2.40 (s, 3 H), 6.60–7.80 (m, 8 H), 7.90 (d, 1 H), 9.60 (s, 1 H); IR 3325, 2225, 1615 cm^{-1}. Anal. Calcd: C, 71.87; H, 5.21; N, 16.72. Found: C, 71.08; H, 5.28; N, 16.53.

Kinetic measurements were carried out spectrophotometrically in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the phenylhydrazone of acetophenone at 332 nm, of 2′-hydroxyacetophenone at 337 nm, of 2′-hydroxy-5′-methylacetophenone at 340 nm, of 2′-hydroxy-5′-chloroacetophenone at 342 nm, and of 2′-hydroxy-5′-nitroacetophenone at 345 nm up to pH 8 and at 450 nm in basic solution. The initial concentration of the acetophenones was 3.3×10^{-5} M, and in all cases a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from slopes of plots of log $(OD_\infty - OD_t)$ against time in the usual manner.

As a result of the strong UV light absorption of phenylhydrazine, it was difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines. Similar difficulties have been noted in attempts to determine equilibrium constants for the formation of other phenylhydrazine carbinolamines.[10,11] With each of the acetophenones studied, the reaction is first-order in phenylhydrazine over the concentration range of 0.020 to 0.20 M, at pH 7. Consequently, all kinetic studies have been made employing phenylhydrazine concentrations lower than 0.20 M. Second-order rate constants could therefore be determined directly by dividing first-order rate constants by the concentration of phenylhydrazine free base. Catalytic third-order rate constants were evaluated from the slopes of plots of second-order rate constants against the concentration of catalyst.

Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculation of the concentration of phenylhydrazine free base and of undissociated carboxylic acid was made employing the Henderson–Hasselbalch equation and values of pK_a from ref 12.

pK_a Determination. The pK_a values of the 2′-hydroxy-5′-substituted acetophenones were measured in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 using a Zeiss PMQ II spectrophotometer. The effect of pH on the absorption of light was measured at the appropriate wavelength (Table I). The values of K_a were determined employing the equation $(E^- - E_t)/(E_t - E^o) = (H^+)/K_a$, where E^- is the absorption of the phenoxide, E^o is the absorption of the phenol,

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