The Role of Solvent Hydrogens in the Dehydro Diels–Alder Reaction

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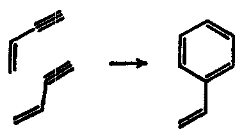
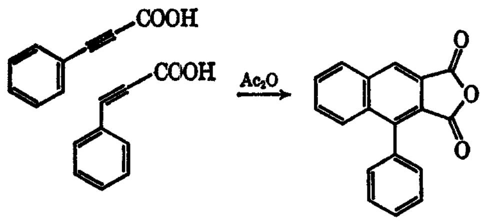
The hydrogen transfers associated with the dimerization of phenylpropiolic acid, a dehydro Diels–Alder reaction, proceed by an intermolecular rather than an intramolecular pathway.

The Diels–Alder reaction involving enynes, typified by the dimerization of vinylacetylene to styrene[1] (eq 1),



(1)

represents a surprisingly general variant of the Diels–Alder reaction.[2] The oldest and best studied example of this reaction is the high-yield dimerization of phenylpropiolic acid to 1-phenylnaphthalene-2,3-dicarboxylic acid anhydride (eq 2) on refluxing a solution of the acid



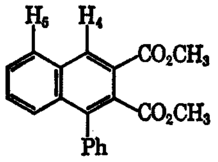
(2)

I II

in acetic anhydride. This dimerization was discovered by Michael and Bucher[3] in 1895 and the product (II) was correctly formulated[4–8] and the generality[9] of the reaction, employing simple functional derivatives of I, demonstrated in the succeeding years.

The ability of this dimerization to proceed undisturbed in the presence of a wide variety of functional groups[9–12] on the aromatic rings has been of considerable value in the synthesis of lignan derivatives.[13,14] Arylpropiolic acids other than phenyl have been demonstrated to undergo the isomerization.[15,16]

The fact that such peculiar intermediates must be proposed if one rationalizes this as an ordinary Diels–Alder reaction has prompted us to synthesize 2-deuteriophenylpropiolic acid (I-d_1) and examine its fate in this dimerization reaction. Refluxing a solution of I-d_1 in acetic anhydride containing a large molar excess of acetic acid produces an approximately 1:1 mixture of II-d_1 and II-d_2 (Table I). Decreasing the amount of acetic acid in the reaction mixture leads to an increased II-d_2:II-d_1 ratio. Cyclization of deuterium-free I with a mixture of acetic anhydride and acetic acid-d_1 results in substantial if not complete formation of II-d_1. Examination of the nmr spectrum of the dimethyl ester of II (III) enables one to locate the deuterium on the naphthalene ring in the deuterated derivatives of II. The nmr spectrum of III shows a singlet of area 1 H at δ 8.62 assignable to H_4 and a multiplet of area 1 H at δ 8.0 assignable to H_5. In the spectrum of the III-d_1/III-d_2 mixture from cyclization of I-d_1 in acetic anhydride–acetic acid the signal at δ 8.62 still corresponds to one hydrogen but the multiplet at δ 8.0 has been reduced in area by one-half. The nmr spectrum of III-d_1 (64% d_1, 36% d_0) from cyclizing I in the presence of acetic acid-d_1 had the multiplet at δ 8.0 unchanged in area but now the singlet at δ 8.62 corresponded to only 0.3 hydrogen.



III

Discussion

Our labelling results, although rather crude, require that the fates of the protons involved in this rearrangement are as in Figure 1.[17]

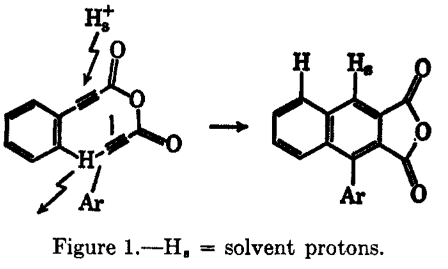


Figure 1.—H_s = solvent protons.

Moreover, the nmr experiments require that no skeletal isomerization leading to net movement of the side chains about the aromatic rings can be occurring during the course of the cyclization. This is also

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[1] H. B. Dykstra, *J. Amer. Chem. Soc.*, **56**, 1625 (1934).

[2] See the numerous examples by A. S. Onishchenko, "Diene Synthesis," L. Mandel, Trans., Daniel Davey and Co., Inc., New York, N. Y., 1964, pp 249–254 ff and pp 635–637.

[3] A. Michael and J. E. Bucher, *Chem. Ber.*, **28**, 2511 (1895).

[4] A. Michael and J. E. Bucher, *Amer. Chem. J.*, **20**, 89 (1898).

[5] A. Michael and J. E. Bucher, *Chem. Ber.*, **41**, 70 (1908).

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[7] H. Stobbe, *Chem. Ber.*, **39**, 1908 (1906).

[8] H. Stobbe, *ibid.*, **41**, 70 (1908).

[9] J. E. Bucher, *J. Amer. Chem. Soc.*, **32**, 212 (1910).

[10] R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935).

[11] R. D. Haworth and W. Kelley, *ibid.*, 745 (1936).

[12] F. G. Baddar, L. S. El-Assal, and N. A. Doss, *ibid.*, 1027 (1959), and previous papers.

[13] D. Brown and R. Stevenson, *J. Org. Chem.*, **30**, 1759 (1965).

[14] L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelley, E. Trod, and T. M. McGuire, *Tetrahedron*, **22**, 1797 (1966).

[15] B. L. West, *J. Amer. Chem. Soc.*, **42**, 1656 (1920)

[16] L. I. Vereshchagin, S. P. Korshunov, S. L. Aleksandrova, and R. L. Bolshedvorskaya, *Zhur. Org. Khim*, **1**, 960 (1965).

[17] One must qualify this statement by pointing out that we generally detect between 2 and 4% more II-d_1 than should be there in the acetic anhydride–acetic acid cyclization of I-d_2. Whether this is the result of some intramolecular hydrogen transfer to C-4 of II, a small isotope effect associated with rate-limiting deprotonation of a reversibly formed intermediate or experimental instrumental vagaries we are not prepared to say. Our gross conclusions are unchanged, however.

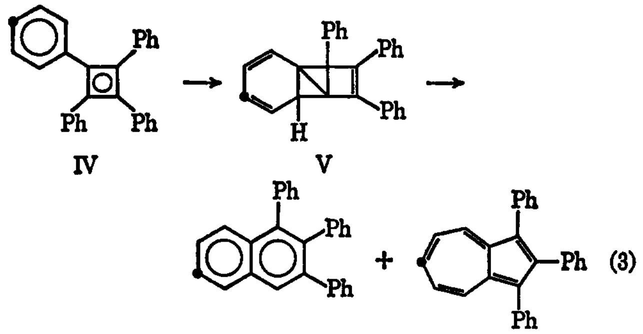
TABLE I

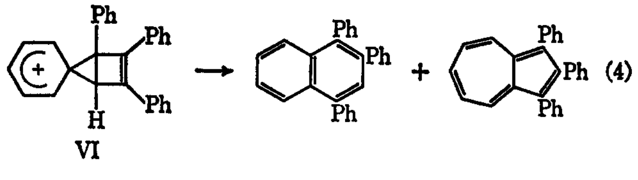
Expt	Phenylpropiolic acid	Solvent mixture	Reflux time, hr	Yield of II, %	Isotope analysis of II		
					d_0	d_1	d_2
1	d_0	Ac_2O	3.5	66			
2[a]	d_0	Ac_2O DOAc	3.5	82	76	64	0
3[b]	d_1	Ac_2O	3.5	68	1	43	56
4[c]	d_1	Ac_2O HOAc	26	22	2	44	52

[a] The molar ratio of acetic acid-d_1:phenylpropiolic acid was 15:1 which would be decreased through the reaction to a value of approximately 10:1. [b] No acetic acid was added. The relatively high retention of two deuterium atoms is due to substantial contribution of the liberated o-hydrogens to the proton pool. [c] The molar ratio of acetic acid:phenylpropiolic acid d_1 was 80:1. The phenylpropiolic acid was 95.6% d_1, 2.2% d_0, 2.2% d_2, these values being ±0.5%. The quoted isotope composition is of the crude product, mp 263–265°. The product also had 2% d_3. Repetition of this experiment using a 65 equiv excess of 1:1 acetic acid acetic anhydride and refluxing 4 hr afforded a 28% yield of II. Isotope analysis indicated the composition 1.5% d_0, 47.2% d_1, 51.2% d_2.

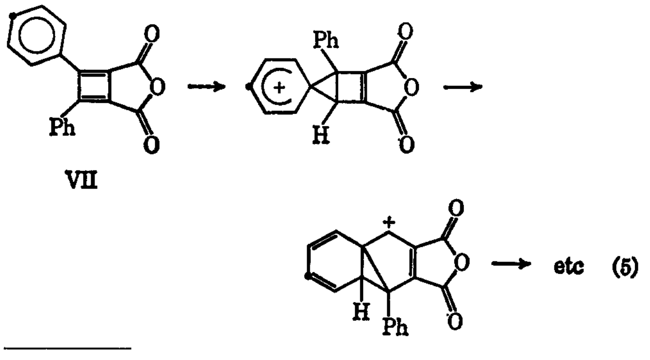
required by the many studies of the cyclization of substituted phenylpropiolic acids.[9–14]

There are a number of reactions similar to the above in their over-all result (formation of trisubstituted naphthalenes) that have been suggested to proceed by way of cyclobutadiene intermediates. Buchi and coworkers[18] have suggested that the irradiation of tolane proceeds *via* IV and V (eq 3), while Breslow and Battiste[19] have suggested that the dehydration of diphenylcyclopropyldiphenylcarbinol proceeds *via* VI (eq 4). Several masked derivatives of VI have been suggested as intermediates in similar reactions.[20,21]

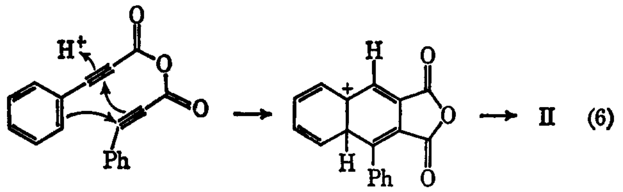




Although one can fit the phenylpropiolic acid dimerization to a scheme of this sort that involves initial cyclobutadiene formation (VII, eq 5) and in a manner that generates the correct arrangement of groups on the naphthalene ring, the process involves choosing only a narrow set of reactions from a relatively large number of equally plausible looking possibilities that would be expected to give at least some positional or structural isomers of II.



The simplest mechanism for the dimerization of I consistent with the known facts would seem to be acid-catalyzed cyclization as in eq 6. A concerted cyclization of the type in eq 6 is not without precedent[22] and catalysis by acid is at least consistent with qualitative observations to this effect.



Experimental Section[23]

2-Deuteriobenzyldimethylamine.—The general procedure of Jones, Zinn, and Hauser[24] was employed. A solution of 13.5 g (0.1 mol) of benzyldimethylamine and n-butyllithium (0.2 mol, 78 ml of a 2.6 M solution in heptane) in 300 ml of ether was allowed to stand at room temperature (26°) for 3 days. With stirring 18 ml of deuterium oxide (99.5% deuterium) was added and stirring was continued over 1 hr. The mixture was filtered and the filtrate was dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation afforded 7.5 g (55% yield) of 2-deuteriobenzyldimethylamine, bp 78° (25 mm). By mass spectrometry the material was ~95% d_1. Interference by the prominent P − 1 peak, even at low voltage, prevented more accurate assessment of the isotopic purity so that the amine was carried through to phenylpropiolic acid-d_1 which was assayed by mass spectrometry.

2-Deuteriobenzoic Acid.—Oxidation of 2-deuteriobenzyldimethylamine by the procedure of Jones and Hauser[25] gave 2-deuteriobenzoic acid in 90% yield. Examination of its nmr spectrum confirmed the position of deuterium, the low-field multiplet assigned to the two o-hydrogens having a relative area of one. This acid was converted into its acid chloride in 96% yield by reaction with thionyl chloride.

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[18] G. Buchi, C. W. Perry, and E. W. Robb, *J. Org. Chem.*, **27**, 4106 (1962).

[19] R. Breslow and M. Battiste, *J. Amer. Chem. Soc.*, **82**, 3626 (1960).

[20] H. H. Freedman, *J. Org. Chem.*, **27**, 2298 (1962).

[21] R. Breslow and J. Dowd, *J. Amer. Chem. Soc.*, **85**, 2729 (1963).

[22] H. W. Whitlock and P. E. Sandvick, *J. Amer. Chem. Soc.*, **88**, 4525 (1966).

[23] Isotope analyses were carried out at low voltages on either a CEC-103C mass spectrometer fited with an all-glass heated inlet system held at 250–300° or on an MS-902 mass spectrometer *via* its direct access probe. Results obtained on both machines were consistent with one another, as were the calculated and experimentally determined P + 1 and P + 2 values of the compounds in question. Results at 70 V ionizing voltage varied in the manner expected for loss of hydrogen from the parent ions.

[24] F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

[25] F. N. Jones and C. R. Hauser, *ibid.*, **26**, 2979 (1961).

Diethyl 2-deuteriobenzoylmalonate, bp 128–130° (0.2 mm), was prepared by the ethoxymagnesium malonic ester procedure of Hauser.[26]

Diethyl 2-Deuteriobenzoylmalonate Enol *p*-Bromobenzenesulfonate.—A modification of the procedure of Fleming and Harley-Mason[27] was used. To a stirred suspension of 6 g (0.11 mol) of sodium methoxide in 50 ml of dry tetrahydrofuran was added dropwise a solution of 24 g (0.1 mol) of diethyl 2-deuteriobenzoylmalonate in 35 ml of tetrahydrofuran. After stirring at 25° for 3 hr the mixture was cooled to −78° and a solution of 34 g (0.14 mol) of *p*-bromobenzensulfonyl chloride in 100 ml of tetrahydrofuran was added. The reaction mixture was allowed to warm to room temperature and to stand at room temperature 2 days. The reaction mixture was concentrated and poured into water, and the aqueous layer was extracted with ether. The ether extracts were washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated to afford, after one recrystallization from ethanol, 29 g (60% yield) of the enol bromobenzenesulfonate, mp 91–93° (lit.[27] mp 91–91.5°).

2-Deuteriophenylpropiolic Acid.—The procedure of Fleming and Harley-Mason[27] was employed. 2-Deuteriophenylpropiolic acid was isolated in 50% yield. Isotopic analysis was carried out at 9–12 V, nominal, using either the parent ion region of the acid, m/e 144, or (better) the parent ion of phenylacetylene produced from the acid in the heated inlet. In a typical preparation of 2-deuteriobenzyldimethylamine, the phenylpropiolic acid had the composition 1.5% d_0, 1.5% d_2, 97% d_1.

1-Phenylnaphthalene-2,3-dicarboxylic Acid Anhydride.—The procedure of Michael and Bucher[3] as generalized by Baddar, *et al.*,[28] was used. Typically, a solution of 1.26 g of phenylpropiolic acid in 60 ml of acetic anhydride was heated under reflux for 3.5 hr. Evaporation of the solvent *in vacuo* and washing of the precipitate with ether gave a 66% yield of the anhydride, mp 264–265°. Decreasing the concentration of phenylpropiolic acid, and diluting the acetic anhydride with acetic acid decreased the yield under these reflux conditions. When a solution of 100 mg of phenylpropiolic acid (d_1) in a mixture of 4.5 ml of acetic anhydride and 1 ml of acetic acid was refluxed 16 hr, the yield of 1-phenylnaphthalene-2,3-dicarboxylic anhydride was 26%. Substantial amounts of recovered phenylpropiolic acid were detected in those reactions that were incomplete.[29] In experiments using a solvent mixture of acetic anhydride and acetic acid-d_1, the solvent was prepared by addition of the requisite amount of deuterium oxide to acetic anhydride, followed by brief refluxing. Results of the various experiments using labeled and unlabeled phenylpropiolic acid and labeled and unlabeled acetic acid-containing acetic anhydride as solvent are in Table I.

Registry No.—I, 637-44-5.

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[26] (a) H. G. Walker and C. R. Hauser, *J. Amer. Chem.*, **68**, 1386 (1946). (b) *Org. Syn.*, **30**, 70, (1950).

[27] I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 4771 (1963).

[28] F. G. Baddar and L. S. El-Assal, *ibid.*, 1267 (1948).

[29] The recovered phenylpropiolic acid was of undiluted isotope composition by mass spectrum.

The Transmission of Electronic Effects. Proton Magnetic Resonance Chemical Shifts for Benzyl Halides in Several Solvents[1a]

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Proton magnetic resonance (pmr) shifts are reported for substituted benzyl fluorides, chlorides, and bromides in several solvents. At finite concentrations, molecules of the same or different compounds interact specifically. Thus the apparent association constant for benzyl chloride and *p*-nitrobenzyl chloride in carbon tetrachloride at *ca.* 37° is $K = 0.27\ M^{-1}$. Obviously, comparisons of substituent effects should be made with chemical shifts at infinite dilution (ν^0). Even so, each ν^0 of the benzyl halides still reflects specific interactions with the solvent peculiar to itself. Attempted correlations of ν^0 of the benzyl halides according to Hammett or Yukawa–Tsuno relations are poor. A literature survey of *ca.* 100 Hammett correlations of pmr data indicates that the majority of them have unsatisfactory correlation coefficients, *e.g.*, <0.90–0.95. The ρ values appear to have no pattern. However, the use of a polar solvent with certain families, *e.g.*, DMSO for phenols and amines, gives large ρ values and excellent correlations; presumably enhanced electronic effects typical of chemical reactions dominate possible anisotropy effects on ν^0. In general, ρ's cannot be used in the way that reactivity ρ's are used, namely as indices of transmission efficiency in aryl systems Ar–T–H.

It is generally agreed that proton magnetic resonances (pmr) chemical shifts at any point in a molecule are in some sense related to the rest of the molecule and its environment. By examining this relation, a number of workers have attempted to reduce its complexity. Contributions from π-electron density, resonance, electric field, magnetic field, van der Waals forces, and ring currents have all appeared to be important at least for some systems or some substituents.[2] On this basis, it has sometimes appeared that the factors that affect substituent chemical shifts (SCS) are understood. In our own survey of the transmission of electronic effects from a substituent (R) to a proton in *ca.* 30 aryl systems, *e.g.*, R–C_6H_4T–H, we too seemed to uncover an underlying regularity that appeared to apply to some systems.[3] In this study we examine the transmission of electronic effects in the benzyl halides in some depth and find that such regularities are often more apparent than real.

As a family, the benzyl halides are of considerable interest.[4] Pmr studies of related families are available and comparison with the toluenes, say, is possible. Our work was completed about the time that a paper on both the ^{1}H and ^{19}F nmr spectra of benzyl fluorides appeared.[5] A graphical comparison of the pmr chemical shifts for the ten substituted benzyl fluorides common to Béguin's work and ours, indicated significant discrepancies for seven of the compounds. After coping with this problem, we could approach the initial issue, namely, substituent effects on chemical shifts.

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[1] (a) This work was supported by the National Science Foundation, Grant GP 5740. (b) Postdoctoral fellow, 1966–1967. (c) Author to whom inquiries should be addressed.

[2] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, Chapter 4.

[3] S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

[4] R. R. Fraser, Gurudata, C. Reyes-Zamora, and R. B. Swingle, *Can. J. Chem.*, **46**, 1595 (1968).

[5] C. Béguin, *Bull. Chim. Soc. Fr.*, 4214 (1967).