The Physical Organic Chemistry of Benzisoxazoles. I. The Mechanism of the Base-Catalyzed Decomposition of Benzisoxazoles

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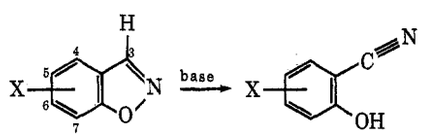
The mechanism of reaction of 5-, 6-, and 7-substituted benzisoxazoles with hydroxide or amines has been established as a concerted E2 elimination yielding *o*-cyanophenolate anions. With hydroxide in ethanol–water mixtures, these reactions have been shown to have a ΔH° in the range of -35 to -39 kcal/mol. The effects of salts and temperature on rates are considered, and the significance of the benzisoxazole system as a new kind of leaving group is discussed.

As has been extensively documented hitherto,[1] isoxazole derivatives bearing a 3 substituent which can act as an electron-deficient leaving group decompose rapidly and irreversibly to form an α-cyano ketone or its enol. Although this characteristic reaction has provided solutions for a number of synthetic problems,[2] its possible mechanistic significance has received small attention.[3] In this paper we present experimental evidence which defines the mechanism of base-catalyzed isomerizations of simple benzisoxazoles to *o*-cyanophenols.



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We were led to carry out a thorough investigation of this mechanism through the hope that the 3-benzisoxazolyl moiety may prove to be a useful leaving group for a variety of physical organic studies. Most attempts to vary the reactivity of a portion of a chemical system encounter the fundamental difficulty that secondary effects resulting from reactivity-increasing structural changes render quantitative interpretations ambiguous; a classical example is the curvature (or linearity) of a Brønsted plot which results from the inclusion of acids of differing structural types.

$$YL \longrightarrow Y^{+} + L^{-}$$

It would be useful to have a class of anionic leaving groups, L, which provide a substantial range of reactivities, but which have minimal steric or unpredictable electronic interaction with the reacting bonds of the group Y. In the summary section, we consider reasons for believing the 3-benzisoxazolyl grouping to be a good approximation to an ideal, noninteracting leaving group.

Before conclusions of this sort can be offered, the mechanism must be firmly established as a simple, intermediateless E2 elimination process.

(1) A. Quilico in "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Wiley, New York, N. Y., 1962, pp 159–176; K. H. Wünsch and A. J. Boulton, *Advan. Heterocycl. Chem.*, **8**, 290 (1967); R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **74**, 2226 (1952); W. Borsche, *Justus Liebigs Ann. Chem.*, **390**, 1 (1912).

(2) G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964); R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron, Suppl. 8*, 321 (1966); D. S. Kemp in "Peptides: Chemistry and Biochemistry," B. Weinstein and S. Lande, Ed., Marcel Dekker, New York, N. Y., 1970, pp 33–34.

(3) For mechanistic discussion of these reactions, see P. Piriono, A. Scartabelli, and E. Lombardi, *Rend. Ist. Lomb. Sci. Lett.*, **87**, 229 (1954), and ref 4 and 5.

(4) D. S. Kemp, *Tetrahedron*, **23**, 2001 (1967).

(5) D. S. Kemp and K. Paul, *J. Amer. Chem. Soc.*, **92**, 2553 (1970).

Experimental Section[6]

Materials.—Trimethylamine hydrochloride (Eastman) was recrystallized twice from absolute ethanol and dried under vacuum, mp 279.0–280.0° dec (lit.[7] mp 277–280°). Methyldiethanolamine (Aldrich) was distilled through a spinning band column and the middle fraction was collected, bp 89.0° (0.35 mm). Baker reagent grade KCl, Eastman Spectrograde acetonitrile, and Columbia Organic deuterium oxide (99.5%) were used without further purification. Baker reagent grade KOH was dissolved in boiled, distilled water, and the solution was standardized using potassium hydrogen phthalate. Hydroxylammonium *O*-sulfonate was freshly prepared by the procedure of Matsuguma and Audrieth[8] and was used only if iodometric titration revealed better than 89% purity.

4-Chloro- and 5-methoxysalicylaldehydes were prepared from the corresponding phenols by means of the Duff reaction;[9] 4-methoxysalicylaldehyde was prepared by methylation of 2,4-dihydroxybenzaldehyde,[10] while 4-nitrosalicylaldehyde was prepared from 2-acetoxy-4-nitrotoluene.[11] The properties of these substances corresponded to those reported in literature.

General Benzisoxazole Synthesis.—A modification of the procedure of Kemp and Woodward[12] was followed. In a 125-ml erlenmeyer flask, 2 g of the salicylaldehyde was dissolved in ethanol (*ca.* 10 ml) such that the solution was saturated at 25°. To this stirred solution was added 2 g (*ca.* 1.5 equiv) of hydroxylammonium *O*-sulfonate. After several minutes, 50 ml of dichloromethane was added, the mixture was cooled in ice, and a solution of 3 g of sodium bicarbonate in 25 ml of water was added. If a chloro- or nitrobenzisoxazole was prepared, this suspension was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with three 10-ml portions of dichloromethane, returned to the reaction flask, and stirred for 30 min with 50 ml of dichloromethane. The extraction was then repeated. If a methyl- or methoxybenzisoxazole was prepared, the solution was allowed to stir for 30 min before the initial extraction and an additional 90 min before the final extraction. The dichloromethane solutions were pooled, dried, and evaporated under vacuum. The resulting benzisoxazoles (Table I) were found to be free of parent aldehyde as judged by ir and tlc.

Crystalline benzisoxazoles were recrystallized to constant melting point, dried under vacuum, and stored in a desiccator at 3° in foil-wrapped vials. Benzisoxazoles which are liquid at

(6) Details concerning experiments with benzisoxazoles and carboxybenzisoxazoles may be respectively found in the following theses: Martha T. Link, Ph.D. Thesis, M. I. T., Cambridge, Mass., 1968; Kenneth G. Paul, Ph.D. Thesis, M. I. T., Cambridge, Mass., 1969. Synthetic details for benzisoxazoles and salicylonitriles will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2294.

(7) I. Heilbron, A. H. Cook, H. M. Bunsbury, and D. H. Hey, "Dictionary of Organic Chemistry," Vol. 5, Oxford University Press, London, 1965, p 3156.

(8) "Inorganic Synthesis," Vol. 5, McGraw-Hill, New York, N. Y., 1957, p 122.

(9) V. G. Yakovlev, *Zh. Obshch. Khim.*, **20**, 361 (1950).

(10) G. Zemplen, L. Farkas, and T. Sattler, *Acta Chem. Acad. Sci.*, **22**, 449 (1960); *cf. Chem. Abstr.*, **55**, 7406*h* (1961).

(11) J. R. Segesser and M. Calvin, *J. Amer. Chem. Soc.*, **64**, 825 (1942).

(12) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).

TABLE I

BENZISOXAZOLES PREPARED BY THE GENERAL PROCEDURE

Registry no.	Benzisoxazole	Yield, %	Recrystn solvent	Mp or bp (mm), °C	Uv max (water), nm (ε)
39835-05-7	6-Methoxy[a]	75	Ether	66 (0.1)	219 (9320)
				ca. 15	251 (7520)
					283 (5690)
					291 (5340)
39835-06-8	5-Methoxy[a]	78	Ether	71 (0.1)	236 (8380)
				ca. 5	306 (3490)
39835-07-9	6-Chloro[a]	90	EtOH	70.0–71.0	244 (9940)
					284 (2960)
39900-62-4	5-Chloro[a]	92	EtOH	65–67	236 (8940)
				(lit. 70)[b]	293 (3170)
39835-08-0	6-Nitro[a]	94	Acetonitrile	133.5–134.5	275 (15,000)

[a] Satisfactory combustion analytical data (±0.3%) for C, H, N, Cl were provided for these compounds and are reported in the microfilm edition (see footnote 6): Ed. [b] G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, **89**, 1009 (1959).

room temperature were distilled in a short-path still (1 mm) within 1 month of use.

Benzisoxazole was prepared by the method of Kemp and Woodward[12] and was distilled twice in a Hickman still before use.

[3-^{2}H]Benzisoxazole was prepared from [*formyl*-^{2}H]salicylaldehyde[13] by the above procedure. Mass spectroscopic analysis showed that the sample contained 97% monodeuterated material.

5-Nitrobenzisoxazole was prepared in 90% yield by nitration of benzisoxazole following the procedure of Lindemann and Thiele.[14] The product was recrystallized from acetonitrile three times and dried under vacuum for 12 hr, mp 127.0–128.0° (lit. mp 126.5–127.5°).[14]

[3-^{2}H]-5-Nitrobenzisoxazole was prepared analogously, mp 126.5–127.5°; nmr analysis showed the sample to contain >95% deuterium in the 3 position.

5,7-Dinitrobenzisoxazole.—A solution of 5-nitrobenzisoxazole (1.0 g, 6.1 mmol) in 8 ml of sulfuric acid was cooled to 0° and treated with 1.5 g of nitric acid. After 30 min of stirring at 25°, the solution was stirred for 10–15 hr at 50–60°. When starting material could no longer be detected in the reaction mixture by tlc, the mixture was poured on ice, and the product was collected and washed with ice water. The crude product (1.1 g, 86%) was recrystallized twice from acetonitrile, then was dissolved in dichloromethane. The resulting solution was extracted three times with 30 ml of cold, commercial pH 4.0 buffer and twice with water; the solution was dried and evaporated; and the residue was dried for 6 hr under vacuum at 25°, mp 122.0–123.0°. *Anal.* Calcd for $C_7H_3N_3O_5$: C, 40.20; H, 1.45; N, 20.10. Found: C, 40.40; H, 1.48; N, 20.30. It had λ_{max} (water, pH 3) 255 nm (ε 14,200), 305 (4080). [3-^{2}H]-5,7-Dinitrobenzisoxazole was prepared analogously; nmr analysis showed the sample to contain >95% deuterium in the 3 position.

General Procedure for the Preparation of Salicylonitriles.[15]—A solution of 0.5 g of benzisoxazole in 5–8 ml of ethanol and 5 ml of water was mixed with 15 ml of 2 *N* NaOH solution and allowed to stand for 10 min, at which time HCl was added to bring the pH to 1, and the solution was extracted with three 10-ml portions of dichloromethane which were pooled, dried, and evaporated. The residue was recrystallized (water, water–ethanol, or acetonitrile), dried under vacuum for 6 hr, and stored in foil-wrapped vials in a desiccator. In the case of the 3,5-dinitrosalicylonitrile, acidification was carried out immediately after addition of base. All melting points were in good agreement with literature values.

Test of the Products of Benzisoxazole Decompositions.—All nitriles could be isolated from the hydroxide- or amine-catalyzed reactions in at least 90% yield. Salicylonitriles which had been kept in 0.1 *N* sodium hydroxide solution for more than 1500 half-lives of the corresponding benzisoxazole decomposition were recovered by acidification and found to show no extraneous infrared absorption; moreover, decomposition of benzisoxazole tritiated in the 5 or 7 positions by triethylamine or diethanolamine buffers in the presence of salicylamide carrier yielded salicylamide with no detectable tritium content; the product therefore contains less than 0.3% salicylamide. All benzisoxazole decompositions carried out at uv concentrations gave products whose spectra were superimposable with those of the corresponding nitrile (Table II).

(13) D. S. Kemp, *J. Org. Chem.*, **36**, 202 (1971).

(14) H. Lindemann and H. Thiele, *Justus Liebigs Ann. Chem.*, **449**, 76 (1926).

(15) For additional data, see ref 6.

TABLE II

ULTRAVIOLET SPECTRA OF SALICYLONITRILES

Registry no.	Nitrile	Uv max (water), nm (ε) pH 2	Uv max (water), nm (ε) pH 10
611-20-1	Salicylonitrile	232 (8300)	241 (7130)
		295 (4040)	325 (5980)
39835-09-1	5-Nitro	219 (18,900)	327 (8160)
		223 (18,700)	380 (15,800)
		306 (10,900)	
25844-84-2	3,5-Dinitro	226 (19,900) (30% H_2SO_4)	326 (10,800)
		255 (14,500)	359 (15,200)
		328 (5700)	
39835-11-5	4-Methoxy	250 (16,400)	252 (10,200)
		291 (5260)	313 (7000)
39900-63-5	5-Methoxy	233 (8280)	241 (6680)
		319 (4670)	347 (5880)
30818-28-1	4-Chloro	240 (13,600)	246 (8720)
		299 (4760)	327 (6770)
13589-72-5	5-Chloro	232 (10,100)	251 (9500)
		308 (3950)	339 (5650)
39835-14-8	4-Nitro	214 (12,700)	234 (17,000)
		237 (7010)	264 (10,300)
		271 (8840)	404 (2870)
		342 (3140)	

Kinetic Measurements.—Absorbance measurements were made with a Zeiss PMQ II spectrophotometer fitted with a constant-temperature cell block through which water was circulated by means of a Haake Model F constant temperature circulator. Control experiments using a Beckman thermometer indicated that the water temperature was maintained within ±0.05°. Rates were followed at the longest wavelength absorption maximum of the cyanophenol. All substances of the study were found to obey Beer's law at the wavelengths employed. Buffer solutions were prepared by weighing out the appropriate amount of the amine or amine hydrochloride. In the former case standard HCl solution, and in the latter, standard KOH solution were added to give the desired buffer ratio, and boiled, distilled water was added to bring the solution to the mark. The concentration of amine in the buffer was determined by titration with 1.00 *M* HCl using a Radiometer titration assembly (pH meter 25, ABU 16 buret, and SBR 2C Titrigraph). The latter values were used in all calculations. For a given run, appropriate volumes of buffer stock solutions were measured by buret into 100 ml volumetric flasks containing sufficient KCl to bring the final ionic strength to 0.100, and the flasks were filled to within 3–4 ml of the mark and equilibrated at 30°. If necessary (pH >9) the solutions were each adjusted to the pH observed for the 0.010 *M* buffer by the addition of 0.5 *M* KOH solution. All precise pH measurements were performed using a Radiometer Model 4 pH meter equipped with a thermostated 30° cell bath and Radiometer G202C glass and K401 calomel electrodes. The meter was standardized before each measurement with a Fisher pH 6.98 phosphate buffer, and before each series of measurements with Fisher pH 4.01 and 9.90 buffers.

For a kinetic run, 1–2 μl of an acetonitrile solution of benzisoxazole was introduced by syringe into a cuvette containing thermally equilibrated buffer. (For the 6-nitrobenzisoxazole, the substrate was introduced into an upper layer formed from one or two microdrops of acetonitrile, and the solution was then stirred.) Identical A_∞ measurements were obtained after 10 half-lives or by terminating the reaction after 3 half-lives by the addition of one quarter pellet of KOH. Pseudo-first-order rate constants were obtained as the slope of a graph of $\ln (A_\infty - A_0/A_\infty - A_t)$ as a function of time; a minimum of eight measurements were used. Hydroxide catalytic constants were obtained from the zero intercepts of graphs of k_{obsd} as a function of amine concentration, using hydroxide concentrations calculated from pH and the data of Harned and Owen.[16]

(16) H. S. Harned and R. B. Owen, "The Physical Chemistry of Electrolyte Solutions," Reinhold, New York, N. Y., 1943, pp 638, 752.

Determination of pK_a Values of Salicylonitriles.—Spectrometric measurements in amine buffer solutions brought to ionic strength 0.1 with KCl were used for pK_a determinations. Measurements were taken at a wavelength at which un-ionized phenol showed no absorption, usually the long-wavelength maximum of phenolate. Tertiary amine buffers whose pK_a values were close to those of the phenol were chosen.[6]

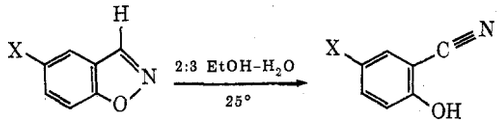
Calorimetric Measurements.—Crude measurements of $\Delta H°$ of reaction of benzisoxazoles and cyanophenols with sodium hydroxide were carried out as described by Daniels,[17] using 3 × 11 in. dewar flasks equipped with stirrer and Beckman thermometers. Reactions were carried out in 2:3 (v/v) ethanol–water, and the apparatus was calibrated by neutralizing NaOH with HCl solutions. For the experiments involving benzisoxazole or cyanophenol, roughly 10 mmol of substrate was contained in 100 ml of solvent and treated with 100 ml of 0.2 *M* NaOH solution; temperature increases lay in the range of 1.5° for benzisoxazole and 0.5° for the phenol. In the nitro series, the quantity of benzisoxazole was reduced by 7–8-fold.

Decompositions of Benzisoxazoles in the Presence of Exchangeable Tritium.—Three different tritium concentrations were employed in these experiments—0.025, 1.3, and 19 μCi/mmol of exchangeable hydrogen. (A fourth experiment utilized the catalytic efficacy of tetrabutylammonium acetate in dry or nearly dry acetone for benzisoxazole decompositions;[18] the exact tritium level for this experiment is not known, but must lie in the range of 50–70 μCi/mmol of exchangeable hydrogen.) No tritium incorporation into unreacted benzisoxazole could be detected in any of these experiments. For example, 10 ml of acetonitrile containing 1.0 g of 5-nitrobenzisoxazole was combined with a solution of 0.48 g of aminotri(hydroxymethyl)methane (Tris) in 1.5 ml of 1 *M* HCl, 2 ml of methanol, and 0.5 ml of water containing 4.3 mCi of tritium. The reaction was quenched at 17 min by the addition of HCl; uv monitoring at 380 nm indicated that 40% decomposition had occurred. The benzisoxazole was recovered after lyophilization, solution in CH_2Cl_2, and repeated extractions with pH 7 buffer and water. The recovered product was recrystallized from ethanol and decomposed with excess sodium methoxide in methanol. The methanol was isolated by bulb-to-bulb distillation and transferred to a liquid scintillation vial containing dioxane-based counting solution. The resulting count was indistinguishable from that of background: background, 23.6 cpm; methanol sample, 24.5 cpm. A control experiment with [3-^{3}H]benzisoxazoles established this procedure as quantitatively reliable for measuring tritium in the benzisoxazole 3 positions. Similar experiments were carried out at lower initial tritium levels using aqueous methanolic methyldiethanolamine and 3,4-lutidine buffers, applied respectively to benzisoxazole and 5,7-dinitrobenzisoxazole.

Results

General Properties of the Base-Catalyzed Benzisoxazole Decomposition.—From the product studies outlined in the Experimental Section, we conclude that the base-catalyzed decompositions of 3-unsubstituted benzisoxazoles in water, pH 5–13, consist of clean, quantitative conversions to salicylonitriles or their anions.

Approximate calorimetric measurements of the heats of reaction of benzisoxazole, 5-nitrobenzisoxazole, and the corresponding salicylonitriles with sodium hydroxide in 2:3 ethanol–water mixtures yielded values for $\Delta H°$ reported in Table III. It may be noted that



X = H, $\Delta H°$ = −27 kcal/mol
X = NO_2, $\Delta H°$ = −28 kcal/mol

(17) F. Daniels, J. H. Mathews, J. W. Williams, P. Bender, and R. Alberty, "Experimental Physical Chemistry," McGraw-Hill, New York, N. Y., 1956, p 37.

(18) D. S. Kemp and D. D. Cox, unpublished observations.

TABLE III

HEATS OF REACTION OF BENZISOXAZOLES AND SALICYLONITRILES WITH SODIUM HYDROXIDE[a]

Compd	$\Delta H°$, kcal/mol
Benzisoxazole	−35.1 ± 2.0[b]
2-Hydroxybenzonitrile	−8.4 ± 0.3
5-Nitrobenzisoxazole	−39.0 ± 1.5
2-Hydroxy-5-nitrobenzonitrile	−11.4 ± 0.3

[a] Temperature 25°, 2:3 (v/v) ethanol–water. [b] Estimates of precision are standard deviations based on 3–5 measurements.

the values obtained for heats of neutralization of phenols lie in the range which has been observed for phenols of comparable acidity.[19]

An estimate of the pK_a value of the conjugate acid of benzisoxazole was needed to determine the role of this species in base-catalyzed decomposition of the heterocycle. The uv spectrum of benzisoxazole in 92% sulfuric acid shows maxima at 259 nm (ε 13,800) and 300 (3500), which are in excellent accord with those observed for the 2-ethylbenzisoxazolium cation in water at pH 1 [258 nm (ε 13,000) and 297 (2900)].[12] In sulfuric acid–water mixtures spectra were quantitatively represented as linear combinations of protonated and free benzisoxazole spectra, with isosbestic points at 244, 278, and 287 nm. Benzisoxazole is found to be half-protonated in 62% sulfuric acid and thus can be assigned a pK_a value of −4.7 under the assumption that the H_0 function defines acidity for this substance. From this result it is clear that the conjugate acids of benzisoxazoles are irrelevant to the chemistry observed at a pH greater than 5.

Kinetics of the Base-Catalyzed Decomposition of Benzisoxazoles.—As indicated in the Experimental Section, the salicylonitriles formed from benzisoxazole decomposition under basic conditions show intense ultraviolet absorption maxima in the range of 310–400 nm, and reactions can therefore be followed conveniently at *ca.* 10^{-4} *M* substrate concentration. Table IV presents catalytic constants for the reaction of eight

TABLE IV

CATALYTIC CONSTANTS FOR BENZISOXAZOLE DECOMPOSITIONS AND pK_a VALUES FOR SALICYLONITRILES[a]

Benzisoxazole	k_{OH^-}, M^{-1} sec^{-1}	pK_a of salicylonitrile
5-Methoxy	1.8×10^{-1}	7.4
Unsubstituted	3.3×10^{-1}	6.9
6-Methoxy	3.8×10^{-1}	6.6
5-Chloro	9.2×10^{-1}	6.4
6-Chloro	1.2	6.1
6-Nitro	5.3	5.2
5-Nitro	1.5×10	4.1
5,7-Dinitro	1.5×10^3	0.6

[a] Temperature 30.0°, water, μ 0.10 (KCl).

substituted benzisoxazoles with hydroxide ion, along with pK_a values for the nitrile products.

The proton transfer step for reactions of hydroxide ion and tertiary amines with 5-nitrobenzisoxazole and 5,7-dinitrobenzisoxazole is rate determining and irreversible, for the 3-^{2}H derivatives show kinetic isotope effects in the range of 4–6, and, when reactions were carried out in tritiated water, recovered starting ma-

(19) C. T. Mortimer, "Reaction Heats and Bond Strengths," Pergamon Press, Elmsford, N. Y., 1962, p 169.

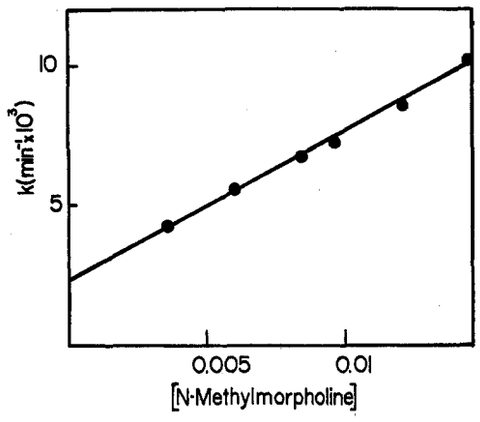


Figure 1.—Variation of pseudo-first-order rate constant for 5-nitrobenzisoxazole decomposition as a function of *N*-methylmorpholine concentration: 30°, water, μ 0.10, pH 8.00, buffer ratio 3:1 amine to amine salt.

terials showed no tritium incorporation. The conditions of the experiment allow one to conclude that, for benzisoxazole, conversion to salicylonitrile anion must occur at least 10^6 times faster than formation of tritiated starting material. For the nitro compounds the bound is at least 10^5, and at the highest tritium level, 10^7.

As shown in Figure 1, reactions conducted in amine buffers at high ratios of amine to amine salt concentrations show the linear dependence of pseudo-first-order rate constant on amine concentration expected for general catalysis. On the other hand, at low buffer ratios, more complex behavior is observed, typified by Figure 2.

A number of workers, for example Jencks and Gilchrist and more recently Salomaa and coworkers,[20] have noted that a change in cation from alkali metal to alkylammonium can result in rate changes which can mask or complicate the observation of general catalysis by amines. Such an effect might be expected to be important in the above cases, for, while the data points of Figure 1 correspond to a range of contributions of potassium ion to total cation of 99.7–85.0%, for Figure 2 the corresponding range is 90–40%. That the behavior of Figure 2 is indeed the result of a salt effect and not the consequence of mechanistic complexities follows from the observations of Table V.

From part A of Table V it is clear that anomalous behavior is observed only when potassium is the added cation; if tetramethylammonium chloride is used to maintain constant ionic strength, identical amine catalytic constants are observed at high and low buffer ratio. The first two entries of part B provide another example of the effect of mixing potassium and ammonium cations—neither the amine nor the hydroxide catalytic constant is invariant to a change in buffer ratio. The third entry establishes that this variance may be attributed to the cation; for it, as for the first entry, the buffer ratio is 2.6, but sufficient tetramethylammonium chloride has been added to simulate the salt environment characteristic of the second entry. The catalytic constants for the second and third entries are seen to be in reasonable agreement.

One can conclude that the base-catalyzed decompositions of benzisoxazoles exhibit general base catalysis, and that accurate catalytic constants can be obtained

(20) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 104 (1966); P. Salomaa, A. Kankaanpera, and M. Lahti, *ibid.*, **93**, 2085 (1971).

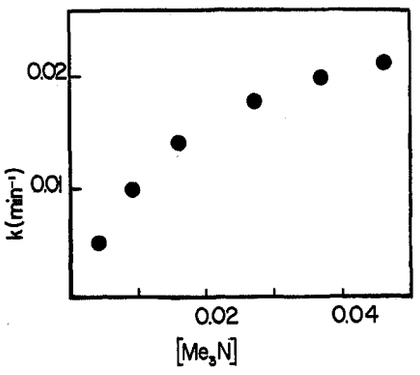


Figure 2.—Variation of pseudo-first-order rate constant for benzisoxazole decomposition as a function of trimethylamine concentration: water, 30°, μ 0.10, pH 9.36, buffer ratio 1:2.5 amine to amine salt.

TABLE V

EFFECTS OF CATION ON CATALYTIC CONSTANTS[a]

A. Effect of Salt on the Reaction of Benzisoxazole with Trimethylamine

[Me₃N]/[Me₃N⁺H]	[Me₃N] range × 10³	Salt added[b]	k_{Me_3N}, M^{-1} sec^{-1}[c] × 10³
3.0	2–12	$Me_4N^+Cl^-$	8.0 ± 0.7
0.43	3–13	$Me_4N^+Cl^-$	7.6 ± 0.5
2.8	4–14	KCl	9.2 ± 0.9
0.4	4–50	KCl	Nonlinear plot (Figure 2)

B. Effect of Salt on the Reaction of 5-Nitrobenzisoxazole with Methyldiethanolamine

[R₃N]/[R₃N⁺H]	Salt added	k_{R_3N},[c] M^{-1} sec^{-1} × 10²	k_{OH^-}, M^{-1} sec^{-1}
2.6	KCl	3.80 ± 0.1	15.4
0.31	KCl	3.22 ± 0.1	19.5
2.6	KCl, Me_4N^+Cl[d]	3.28 ± 0.2	20.6

[a] Water, 30.0°, *ca.* 10^{-4} *M* substrate. [b] μ 0.1. [c] Error estimates are standard deviations obtained by a least-squares analysis. [d] $[R_3N]/([R_3NH^+] + [Me_4N^+]) = 0.31$.

from the conventional plots of pseudo-first-order rate constants as functions of buffer amine, provided that amine cations are used to maintain constant ionic strength, or provided that an alkali metal cation is allowed to dominate the cation composition.

Table VI[21,22] lists the effects of total ionic strength, solvent and kinetic isotope, and temperature on catalytic constants. Included in part A are data from Harned and Owen[21] which indicate that 0.5 *M* KCl is the concentration most favorable for the ionization of water. It is not unreasonable to expect, therefore, that the reaction of benzisoxazole with hydroxide, which results in charge dispersion at the transition state, would show a minimum in catalytic constant at this salt concentration, as is in fact observed.

Discussion

Given the evidence of a substantial kinetic isotope effect, general base catalysis, and the failure of benzisoxazoles to incorporate tritium from solvent in the presence of bases, one must regard the mechanism of reaction of bases with benzisoxazoles as a concerted elimination of the E2 type (eq 1) or as an E1cB elimi-

(21) Reference 16, p 578.

(22) P. Saloman, L. L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 1 (1964).

TABLE VI

IONIC STRENGTH, KINETIC AND SOLVENT ISOTOPE AND TEMPERATURE EFFECTS ON CATALYTIC CONSTANTS FOR BENZISOXAZOLE DECOMPOSITIONS[a]

A. Effect of KCl Concentration on the Reaction of 5-Nitrobenzisoxazole with Methyldiethanolamine

μ	k_{R_3N},[b] M^{-1} sec^{-1} × 10^2	k_{OH^-},[b] M^{-1} sec^{-1} × 10	$\frac{\gamma_{OH^-} - \gamma_{H^+}}{a_{H_2O}}$[c]
0.10	3.80 ± 0.13	1.53 ± 0.06	0.627
0.30	4.10 ± 0.25	1.41 ± 0.20	0.561
0.50	4.18 ± 0.10	1.36 ± 0.03	0.533
0.75	4.65 ± 0.18	1.45 ± 0.03	0.560
1.00	4.35 ± 0.10	1.55 ± 0.02	0.587

B. Kinetic Deuterium Isotope Effects for Reactions of 3-Deuteriobenzisoxazoles with Bases[a]

Base	k_H/k_D Benzisoxazole	5-Nitrobenzisoxazole	5,7-Dinitrobenzisoxazole
Hydroxide	4.59	4.36	6.08
Trimethylamine	4.16	4.75	
N-Methylmorpholine	3.85	4.72	5.94

C. Solvent Deuterium Isotope Effect for the Reaction of 5-Nitrobenzisoxazole with Methyldiethanolamine[c]

$$\frac{k_{OD^-}}{k_{OH^-}} = \frac{24.5 \pm 0.7}{15.3 \pm 0.7} = 1.60 \pm 0.11$$

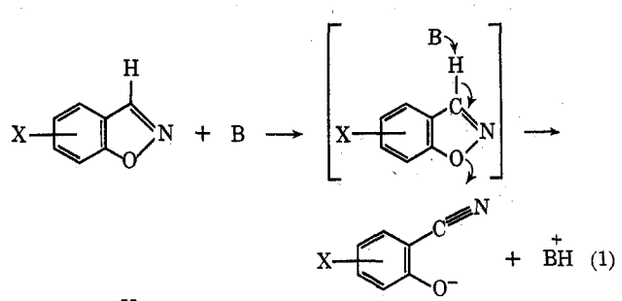
$$\frac{k_{R_3N(D_2O)}}{k_{R_3N(H_2O)}} = \frac{(3.35 \pm 0.1) \times 10^{-2}}{(3.90 \pm 0.13) \times 10^{-2}} = 0.86 \pm 0.08$$

D. Activation Parameters for the Reactions of Benzisoxazoles with Bases[d]

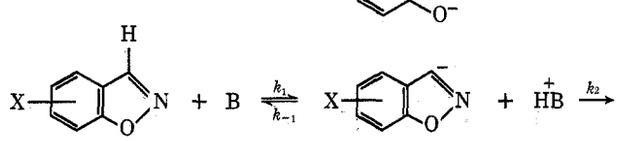
Substrate	Base	$\Delta H^{\neq}$, kcal/mol	$\Delta S^{\neq}$, cal/deg mol, 30°
Benzisoxazole	Hydroxide	14.6 ± 1.7	−12.8 ± 5.6
Benzisoxazole	Trimethylamine	18.7 ± 0.4	−6.2 ± 1.3
5-Nitrobenzisoxazole	Hydroxide	11.5 ± 1.7	−15.2 ± 5.6
5-Nitrobenzisoxazole	Methyldiethanolamine	14.5 ± 2.0	−17.5 ± 6.6

[a] Water, 30.0°. [b] Error estimates are standard deviations based on a least-squares analysis. [c] Solvent isotope effects were calculated assuming a ratio of ion products of H_2O and D_2O of 6.5 and a glass electrode correction pD = pH − 0.60: P. Saloman, L. L. Schlaeger, and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 1 (1964). [d] Activation parameters were calculated from an Arrhenius plot using catalytic constants measured at 20, 25, 30, and 35°. [e] Reference 21.

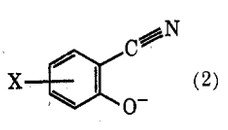
nation (eq 2) in which isomerization of an intermediary anion occurs much faster than reprotonation.



(1)



$k_2 \gg k_{-1}$



(2)

The E1cB class of elimination mechanism has been believed to have few examples and to require a resonance or inductively stabilized intermediary anion,[23] but it should also be recalled that both ylide and simple anionic intermediates which lack resonance stabilization have been encountered in the proton exchange reactions of five-ring heterocycles.[24] Moreover, Bordwell has recently drawn attention to the inconclusive evidence concerning the mechanisms of many elimination reactions and has affirmed that many reactions hitherto regarded as concerted E2 eliminations in fact belong to one of the several E1cB categories.[25]

There appear to be two independent, conclusive arguments which establish an elimination mechanism as E2. One, noted by Bordwell,[25] involves demonstration of both a sizable deuterium isotope effect for C–H cleavage and substantial dependence of rate on the nature of the leaving group. The other uses a measured rate of back exchange and Eigen's reprotonation rate data to exclude anionic intermediates as too unstable to contribute to the given elimination process. Both arguments can be applied definitively to the benzisoxazole isomerizations.

Both E2 and E1cB mechanisms predict that electron-withdrawing benzo substituents should accelerate the isomerization rate. However, not only should the effect be much smaller for the 3 anion of the E1cB mechanism, but the meta–para correlation expected for 5- and 6-substituted benzisoxazoles should be reversed from that expected for the incipient oxyanion of the E2 mechanism. The data of Table IV indicate that the rate of reaction of benzisoxazoles with hydroxide ion is strongly accelerated by electron-withdrawing substituents and that the effect is of the magnitude expected for development of partial negative charge on oxygen at the rate-determining transition state. (It may be noted that the effects of ionic strength on rate, the solvent isotope effects, and the activation parameters are all in accord with a process in which appreciable charge delocalization has occurred at the transition state.)

Data presented in Figure 3 permit comparison of the relative effectiveness of 5 and 6 substituents at stabilizing the transition state for benzisoxazole decomposition. Clearly, the assignment of σ_{meta} to 6 and σ^-_{para} to 5 substitutents gives a simple linear correlation with log k_{OH^-}, while the reverse assignment, σ_{meta} to 5 and σ_{para} to 6, gives an unsatisfactory correlation. This observation is best explained by a transition state in which substantial negative charge has appeared on oxygen.

It could, of course, be argued that the above conclusion is premature without an adequate model for

(23) D. J. McLennan, *Quart Rev., Chem. Soc.*, **21**, 491 (1967).

(24) R. A. Olofson, T. M. Landesberg, K. M. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966); R. Olofson and J. M. Landesberg, *ibid.*, **88**, 4263 (1966); R. A. Olofson, J. S. Michelman, and W. R. Thompson, *ibid.*, **86**, 1865 (1964); H. W. Wanzlich, *Angew. Chem.*, **74**, 127 (1962); R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, **26**, 685 (1970).

(25) F. G. Bordwell, *Accounts Chem. Res.*, **5**, 374 (1972), and references cited therein. Assignment of an E1cB mechanism to the benzisoxazole cleavages might seem especially appropriate in the light of Bordwell's view[25] that most HC=EY eliminations belong to this class. However, we do not regard Miller's observations[26] on the experimentally difficult and possibly atypical case, *cis*-1,2-dibromoethylene, as convincing evidence for a prototypic judgment.

(26) S. I. Miller and W. G. Lee, *J. Amer Chem. Soc.*, **81**, 6313 (1959); W. K. Kwok, W. G. Lee, and S. I. Miller, *ibid.*, **91**, 468 (1969).

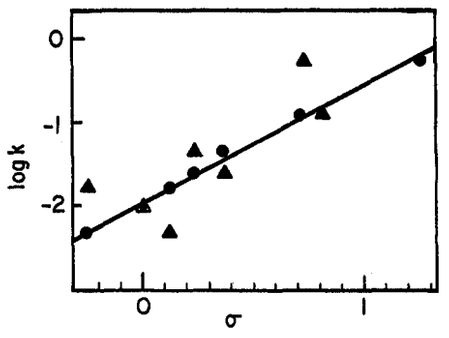
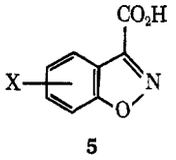


Figure 3.—Log k_{cat} for *N*-methylmorpholine-catalyzed decomposition of 5- and 6-monosubstituted benzisoxazoles as functions of Hammett values: ▲ points are plotted as functions of σ_{meta} for 5 substituents and σ_{para} for 6 substituents (test of charge localization at C-3); ● points are plotted as functions of σ^-_{para} for 5 substituents and σ^-_{meta} for 6 substituents (test of charge appearance at oxygen).

the positional effects of benzo substituents on the stability of charge at the 3 position of an intact benzisoxazole. Such a model is available in the form of pK_a values for 3-carboxybenzisoxazoles (**5**) prepared in

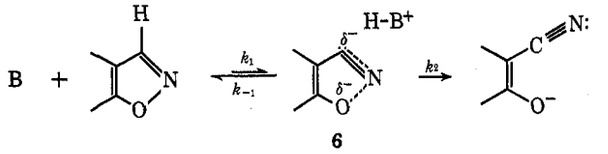


5

X = 5-nitro, 6-nitro, 6-chloro, 6-methoxy

connection with another study.[5,6] A Hammett plot of these pK_a values, using σ_{para}^- for the 6 substituents and σ_{meta} for the 5-nitro compound, gives a ρ value of 0.29, with a correlation coefficient of −0.997. Clearly a localized benzisoxazole 3 anion should be more stabilized by an electron-withdrawing substituent in the 6 position, and the correlations of Figure 3 do correctly test the two mechanistic cases. The plots of Figures 4 and 5 establish this point more directly. Figure 4 plots log k_{OH^-} as a function of the pK_a value of the salicylonitrile formed as product of the reaction. Figure 5 plots log k_{OH^-} as a function of the pK_a value of the corresponding benzisoxazole-3-carboxylic acid. For the first case, a linear correlation is observed, while, for the second, the points for the critical nitro substituents deviate widely from linearity. Clearly, the transition state for the benzisoxazole decompositions has little of the character of an inductively stabilized, localized 3 carbanion, and very much the character of a salicylonitrile anion.

Although the above arguments establish by isotope and substituent effects that both C–H and N–O bonds are extensively cleaved at the rate-determining transition state, one could still argue that an extensively delocalized 3 carbanion such as **6** is not excluded by these



6

findings. Evidence pertinent to this possibility is available from tritium exchange experiments.

The conditions of the exchange experiments with tertiary amines allow one to assert that, if an E1cB

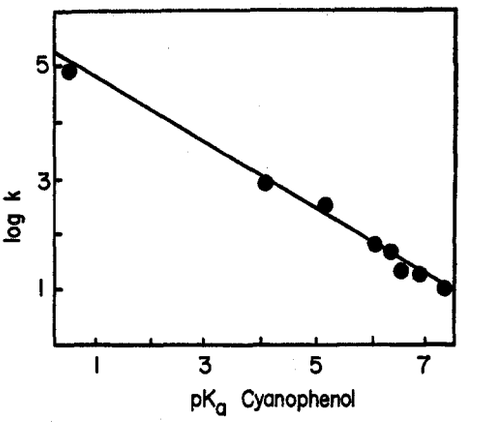


Figure 4.— Log k_{OH^-}, M^{-1} min^{-1}, for decomposition of benzisoxazoles as a function of salicylonitrile pK_a. Points from left to right correspond to 5,7-dinitro, 5-nitro, 6-nitro, 6-chloro, 5-chloro, 6-methoxy, H, 5-methoxy.

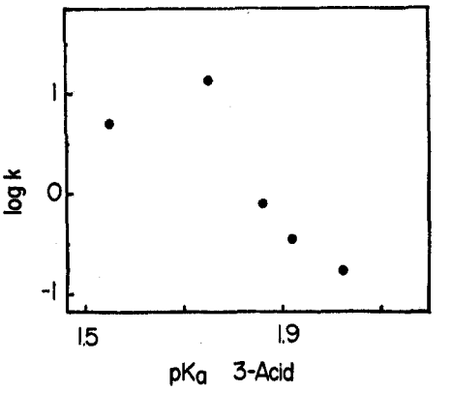


Figure 5.—Log k_{OH^-}, M^{-1} sec^{-1}, for decomposition of benzisoxazoles as a function of pK_a of benzisoxazole-3-carboxylic acid. Points from left to right correspond to 6-nitro, 5-nitro, 6-chloro, H, 6-methoxy.

mechanism is involved in benzisoxazole decompositions, for benzisoxazole in methyldiethanolamine buffer, k_{-1}/k_2 must be smaller than 10^{-6}; with 5-nitrobenzisoxazole in methyldiethanolamine buffer and with 5,7-dinitrobenzisoxazole in 3,4-lutidine buffer, the corresponding ratio must be less than 10^{-5}. Since no tritium incorporation was detected in any of these experiments, the magnitudes of these bounds are set by the experiment, and the limiting ratios may well be orders of magnitude smaller. If one assumes that a benzisoxazole 3 carbanion would react with methyldiethanolammonium ion at diffusion-controlled rates, a reasonable assumption for a localized carbanion in the light of Eigen's work[27] and recent observations concerning heterocyclic ylides,[28] then, since the concentration of ammonium ion was *ca.* 0.1 *M* in these experiments, one can estimate k_{-1} to lie in the range of 10^9–10^{10} sec^{-1}, whereupon k_2 is calculated as 10^{15}–10^{16} sec^{-1}, which is impossibly fast for a unimolecular decomposition.

Could the occurrence of tight ion pairing and resulting internal return drastically reduce the effectiveness of the tritium exchange probe as a test for intermediary anions? Cram has extensively investigated fluorenyl and indenyl systems which permit assessment of relative

(27) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(28) D. S. Kemp and J. T. O'Brien, *J. Amer. Chem. Soc.*, **92**, 2554 (1970).

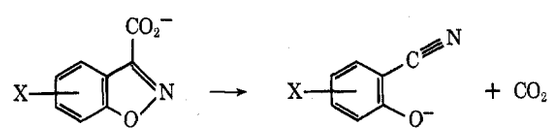
rates of internal isomerization and exchange *vs.* external exchange.[29] The results of Cram and coworkers can be briefly and qualitatively summarized. (1) In media of low dielectric constant and with tertiary amines as catalysts, isomerization can be as much as 300 times faster than external exchange. (2) In polar media, external exchange competes effectively with internal isomerization processes. (3) With primary amines as catalysts, exchange is always competitive with isomerization, presumably because the rate-determining step for exchange is reduced to a slight rotation of the cation component of a tight ion pair.

Although internal return processes seem unlikely in the polar media of our study, we carried out a final exchange experiment with 5-nitrobenzisoxazole and an acetonitrile–methanol–water solution of aminotris(hydroxymethyl)methane, a primary amine catalyst which is expected to maximize exchange within a tight ion pair. Using an order of magnitude higher tritium concentration than with the previously described experiments, we observed no exchange; under these conditions, k_{-1}/k_2 would have to be smaller than 10^{-7}.

In the light of the above evidence, we confidently conclude that the mechanism of base-catalyzed benzisoxazole decomposition is a concerted, intermediateless E2 elimination.

A further mechanistic point concerns the possible importance of subsidiary catalytic effects, such as acid catalysis or hydrogen bonding at the benzisoxazole oxygen.

Recently we gave a preliminary account of a related study[5,6] of the mechanism of decarboxylation of benzisoxazole-3-carboxylic acids in which it was shown that loss of carbon dioxide also occurs concertedly with N–O bond cleavage. The rate of the reaction in water was found to be proportional to the concentration of acid anion, and, remarkably, no general acidc atalysis



could be detected, even under conditions for which protonation of the cyanophenolate intermediate is thermodynamically favorable by a factor of 10^5.

From the similarity of mechanism and dependence of reactivity on substitution, it seems likely that the chemistry of proton transfer and decarboxylation of these two benzisoxazole systems are closely related, and one may therefore conclude that general acid catalysis is unlikely to play a role in accelerating the reactions of benzisoxazoles with bases.

Two points which are unrelated to the rate and mechanism problem arise from the data of the preceding section and seem worthy of comment. The pK_a value of -5 for the N-protonated conjugate acid of benzisoxazole contrasts with those of simple isoxazoles. Albert quotes values of 1.3 and 2.3 for the pK_a of protonated isoxazole and 5-methylisoxazole,[30] and, while benzo fusion is expected to result in an increase in acid strength, the change is usually only one to two pK_a units,[31] rather than the six or seven here observed. On the other hand, the very low basicity of benzisoxazole correlates well with its abnormal inertness toward alkylating agents,[32] and it might be noted that the conjugate acids of oximes have pK_a values near zero,[33] and an oxime with electronegative substituents, such as a benzisoxazole, should be materially less basic. It appears, therefore, that benzisoxazole in fact has the basicity expected by analogy with acylic relatives, and that the abnormality is the high basicity of simple isoxazoles.

The availability of an estimate of $\Delta H°$ for the isomerization of benzisoxazoles to salicylonitriles permits a reexamination of the question of the degree of resonance stabilization of isoxazoles. If one takes the value 48 kcal/mol for the normal O–N bond strength,[34] then, using standard values of the strengths of other bonds, one obtains an estimate of -30 kcal/mol for the heat of isomerization, which may be compared with the observed value of -27 kcal/mol. Strain in the isoxazole ring should not exceed 3–5 kcal/mol, and if included would render the estimated $\Delta H°$ more negative. Although there is appreciable uncertainty in these estimates, largely arising from the value for the O–N bond strength, it seems clear that benzisoxazole is roughly as resonance-stabilized as its isomer, salicylonitrile, and early estimates of a substantial resonance stabilization for isoxazoles are in error.[35]

Summary

The reaction of 3-unsubstituted benzisoxazoles with bases has been shown to be a quantitative, irreversible, highly exothermic process, proceeding by a concerted E2 mechanism. Rate depends on the concentration of base, and catalysis has been shown, by analogy with a related system, to be involved only in removing the 3 proton. The reaction is strongly accelerated by electron-withdrawing substituents, and is markedly sensitive to the strength of the base. Two other studies have shown that an identical mechanism applies to the decomposition of 2-alkylbenzisoxazolium salts[5] and to the decomposition of benzisoxazole-3-carboxylic acids.[4] Although final proof must await further mechanistic studies, we conjecture that clean E2 cleavage with marked sensitivity of rate to benzo substituents will be a characteristic feature of the decomposition of any benzisoxazole which bears a 3 substituent which can act as an electron-deficient leaving group.

Considered as an anionoid leaving group, the benzo-substituted 3-benzisoxazolyl function has several unique and desirable features. In all cases studied, the reactions appear to be clean and quantitative. The reactions can be easily monitored, for the uv properties of the system permit detection at very low substrate con-

(29) D. J. Cram, W. T. Ford, and L. Gosser, *J. Amer. Chem. Soc.*, **90**, 2598 (1968); W. T. Ford and D. J. Cram, *ibid.*, **90**, 2606 (1968); W. T. Ford and D. J. Cram, *ibid.*, **90**, 261 (1968); J. Almy and D. J. Cram, *ibid.*, **91**, 4459 (1969).

(30) A. Albert, "Heterocyclic Chemistry," 2nd ed, Oxford University Press, London, 1968, p 442. These values seem more reasonable than earlier values quoted by Quilico, ref 1, pp 41 and 53.

(31) Compare, for example, imidazole, $pK_a = 7.0$, with benzimidazole, $pK_a = 5.5$.

(32) E. P. Kohler and W. F. Bruce, *J. Amer. Chem. Soc.*, **53**, 644 (1931).

(33) E. M. Arnett in "Progress in Physical Organic Chemistry," S. Cohen, A. Streitweiser, Jr., and R. Taft, Ed., Interscience, New York, N. Y., 1963, p 282.

(34) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworths, London, 1958, p 278.

(35) See, for example, R. A. Barnes in "Heterocyclic Compounds," Vol. 5, R. A. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 453; also see G. Del Re, *Tetrahedron*, **10**, 81 (1960).

centrations. The direct correlation between reaction rate constant and salicylonitrile pK_a provides a built-in measure of the expected effects of substitution on reactivity. (In fact, if more refined thermodynamic measurements can establish that substituent effects on the benzisoxazole–salicylonitrile equilibrium constant are very small, then the salicylonitrile pK_a values must provide an exact measure of the effect of substituents on equilibria for the conversion of benzisoxazoles to salicylonitrile anions.) The predictability of the effect of benzo substitution on rate, together with the rigidity of the benzisoxazole function and the large separation of the 3 position and the reactivity-influencing benzo sites, implies that the leaving group properties of the benzisoxazole can be varied predictably and independently, with minimal idiosyncratic interaction with the region of reacting bonds adjacent to the 3 position. Because of this property, we feel that families of substituted benzisoxazoles offer much promise as experimental tools for the analysis of a variety of subtle mechanistic questions. In an initial study of this kind,[6,36] we have approached the problem of the existence of intrinsic curvature of Brønsted plots by determining the joint effects of base strength and ring substitution on the rates of proton transfer from benzisoxazoles. Other studies of solvent effects have been completed or are in process.[6,18] The ready availability of 3-acylbenzisoxazoles and their rapid cleavage by nucleophiles suggest an obvious application to acyl transfer chemistry which remains to be explored.

(36) D. S. Kemp and M. L. Casey, submitted to *J. Amer. Chem. Soc.*

Registry No.—Hydroxylammonium *O*-sulfate, 2950-43-8; 4-chlorosalicylaldehyde, 2420-26-0; 5-chlorosalicylaldehyde, 635-93-8; 5-methoxysalicylaldehyde, 672-13-9; 4-methoxysalicylaldehyde, 673-22-3; 4-nitrosalicylaldehyde, 2460-58-4; benzisoxazole, 271-95-4; 5-nitrobenzisoxazole, 39835-28-4; [3-^{2}H]-5-nitrobenzisoxazole, 39835-29-5; [*formyl*-^{2}H]-5-nitrosalicylaldehyde, 39835-30-8; 5,7-dinitrobenzisoxazole, 39835-31-9; trimethylamine, 75-50-3; methyldiethanolamine, 105-59-9.

Acknowledgment.—Support for this work was provided by the National Science Foundation, Grants GP 8329 and 33265x. Fellowship support from the National Institutes of Health (M. L. C.) and the National Science Foundation (K. G. P.) is gratefully acknowledged.

Chemistry of Diarylazoalkanes. IV. Effect of Substituents on the Thermal Decomposition of Symmetrically Disubstituted 1,1′-Diphenyl-1,1′-azoethanes[1,2]

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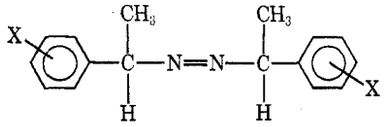
Received August 15, 1972

The effect of substituents upon the first-order thermal decomposition of symmetrically disubstituted 1,1′-diphenyl-1,1′-azoethanes was studied in *p*-cymene using a spectroscopic method. The observed effects can best be explained in terms of the relative importance of inductive and resonance effects (including hyperconjugation). Steric factors resulting from electrostatic repulsions are also involved in some cases. The importance of steric effects was especially evident in the increased rate of decomposition with an *o*-methoxy substituent on each phenyl group. The substituted α-phenylethyl radicals, formed by thermal decomposition of the respective azo compounds in *o*-dichlorobenzene, coupled to form disubstituted 2,3-diphenylbutanes. Minor amounts of substituted ethylbenzenes were also produced, probably by disproportionation. The corresponding substituted styrenes were not found and presumably were polymerized under the conditions of the reaction. Activation parameters were determined for most of the thermal decompositions.

Shelton and coworkers[2,3] investigated the effect of substituents upon the thermal decomposition of disubstituted azocumenes $[XC_6H_4(CH_3)_2CN{=}]_2$, X = H, *p*-CH_3, *p*-CH_3CH_2, *p*-$(CH_3)_2CH$, *p*-$(CH_3)_3C$, *p*-F, *p*-Br, *p*-Cl, and *m*-Cl, as part of their continuing study of the behavior of radical species.[4] The effects of the substituents upon the rates were small but significant, as also observed in the similar systems of the previous investigations.[5]

The availability in this laboratory of a modified synthetic mathod[6] suggested the possible preparation of a series of symmetricaly disubstituted 1,1′-diphenyl-1,1′-azoethanes (A) by oxidation with freshly made mercuric oxide of appropriately substituted hydrazines.



A, X = H, *o*-CH_3O, *p*-CH_3, *p*-CH_3CH_2, *p*-Cl, *p*-F, *p*-CH_3O, *m*-CH_3, *m*-CH_3O, *m*-Cl, *m*-F, *m*-CF_3

It was the purpose of this study to investigate the effects of the various substituted groups on the rate of decomposition and product distributions of these azo compounds. Some known derivatives are included in the series as a basis for comparison with prior studies.[5]

(1) Taken from the Ph.D. Thesis of C. K. Liang, Case Western Reserve University, 1969.

(2) Paper III of the series: P. Kovacic, R. R. Flynn, J. F. Gormish, A. H. Kappelman, and J. R. Shelton, *J. Org. Chem.*, **34**, 3312 (1969).

(3) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968).

(4) J. R. Shelton and C. W. Uzelmeier, *J. Amer. Chem. Soc.*, **88**, 5222 (1966).

(5) S. G. Cohen, S. J. Groazes, and D. B. Sparrow, *J. Amer. Chem. Soc.*, **72**, 3947 (1950); S. Solomon, C. H. Wang, and S. G. Cohen, *ibid.*, **79**, 4104 (1957).

(6) J. R. Shelton and C. K. Liang, *Synthesis*, (4), 204 (1971).