Kinetics of Cyclization of o-Halobenzophenone Oximes to 3-Phenyl-1,2-benzisoxazole[1]

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In these base-ctalyzed cyclizations, the order of halogen mobility is somewhat unusual, F > Br > Cl. The rates, enthalpies and entropies of activation for fluoro-oxime Ia with respect to chloro-oxime Ib bear a relationship normal for aromatic nucleophilic substitutions. It is bromo-oxime Ic which is unusually reactive, owing to exalted ΔS^{*} probably of steric origin. Rates of cyclization of iodo-oxime Id were erratic and could not be measured satisfactorily.

The alkali-induced cyclization of o-halobenzophenone oximes (I) to 3-phenyl-1,2-benzisoxazole (II) has long been known.[2-6] Our interest was

Ia, X = F; Ic, X = Br　　　　　II
b, X = Cl; d, X = I
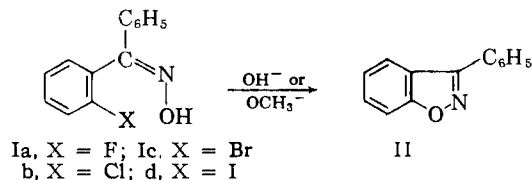
attracted by indications, from preparative experience, of an unusual order of halogen mobility: I > Br $\sim$ F > Cl.[7] The usual sequence in aromatic nucleophilic displacements effected by oxygen-anion reagents is: F >> Cl $\sim$ Br > I.[8-10] We felt that exact kinetic data would be useful.

The fact that only one stereoisomer of Ib or Ic has ever been isolated under any conditions, in spite of diligent efforts to find a second, attracted much interest in times past. That the isolable oxime had a *syn* relationship of –OH to halogenated ring, as shown in structural formula I, was indicated by the ease of cyclization to II and by the fact that Beckmann rearrangements of both Ib and Ic afforded o-halobenzanilides. Meisenheimer and Meis[5] pointed out that, strictly speaking, these observations do not preclude rearrangement of the *anti* to the *syn* isomer prior to cyclization or Beckmann rearrangement, but considered this improbable because Ib or Ic recovered from an interrupted cyclization was the same as introduced. Moreover, the conditions (PCl₅ in ether) used for the Beckmann rearrangements are not conducive to *syn* $\rightleftarrows$ *anti* isomerization.[11]

We have confirmed that Beckmann rearrangements of Ib and Ic give o-halobenzanilides, and have found that Ia and Id do the same. It thus appears that all four oximes possess the configuration with –OH *syn* to $-C_6H_4X$.[12]

(1) We are pleased to acknowledge financial support by the National Science Foundation.

(2) W. R. Cathcart and V. Meyer, Ber., **25**, 1498, 3291 (1892).

(3) P. J. Montagne and S. A. Koopal, Rec. trav. chim., **29**, 136 (1910).

(4) S. A. Koopal, ibid., **34**, 115 (1915).

(5) M. Meisenheimer and H. Meis, Ber., **57**, 289 (1924).

(6) W. Borsche and W. Scriba, Ann., **540**, 83 (1939).

(7) An early hunch² that fluoro-oxime Ia would cyclize very slowly was refuted by Borsche and Scriba⁶ who found that Ia and Ic gave similar yields of II under comparable conditions.

(8) (a) J. F. Bunnett and R. E. Zahler, Chem. Revs., **49**, 273 (1951); (b) J. F. Bunnett, Quart. Revs., **12**, 1 (1958).

(9) C. W. L. Bevan, J. Chem. Soc., 2340 (1951).

(10) A. L. Beckwith, J. Miller and G. D. Leahy, ibid., 3552 (1952).

(11) L. G. Donaruma and W. Z. Heldt, Organic Reactions, **11**, 1 (1960).

(12) Other o-substituted benzophenones also give predominantly the

Kinetics

All our work dealt with reactions in methanol solution induced by sodium methoxide. Rates were followed photometrically by measurements at 290 mμ on acid-quenched aliquots of the reaction solutions; II absorbs strongly at this wave length (ϵ 7400), but the oximes do not (nor do the parent ketones). The oximes were always present in minor amount ($ca. 5 \times 10^{-4} M$), so that pseudo-first-order kinetics were observed. One run with Ic was followed by titration of bromide ion, and the resulting rate coefficient was in agreement with those determined photometrically.

Rate coefficients for cyclization of Ia, Ib and Ic are displayed in Table I.

TABLE I

RATES OF CYCLIZATION OF o-HALOBENZOPHENONE OXIMES (I) TO 3-PHENYL-1,2-BENZISOXAZOLE (II), INDUCED BY SODIUM METHOXIDE IN METHANOL

Halogen	Temp., °C.	[NaOCH₃],[a] M	Reacn. at last point, %	$10^5 k_\psi$ sec.⁻¹
F	49.8	1.12	52	2.50
	59.7	1.06	76	8.35
	79.9	0.26	94	72.6
		.51	93	92.8
		.77	86	94.3
		.87	82	92.4
		1.03	87	95.6[b]
Cl	100.5	1.04	75	3.44
	110.0	0.049	71	4.23
		.097	68	6.11
		.243	77	8.07
		.49	80	9.16
		.73	80	9.46
		.97	85	9.40[c]
	126.7	.98	86	58.5
Br	79.9	1.03	62	2.94
	100.5	1.04	94	42.9
	110.0	0.049	80	51.2
		.097	91	79.8
		.243	94	97.8
		.49	88	111.5
		.73	86; 90	116; 115
		.97	90	114[c]
	89.9	1.01	63	11.0[d]

[a] Corrected for solvent expansion. [b] 95.0 × 10⁻⁵ sec.⁻¹ was taken as the best value for computing activation parameters. [c] "Best value." [d] Analysis by titration of bromide ion; the rate coefficient interpolated from the photometric data for 89.9° is 12.3 × 10⁻⁵ sec.⁻¹.

oxime with the o-substituted phenyl group *syn* to the oxime –OH. A convincing interpretation of why such oximes should be thermodynamically favored has been given by P. A. S. Smith and E. P. Antoniades, Tetrahedron, **9**, 210 (1960). For similar reasons the same isomers would be favored when configuration was kinetically controlled.
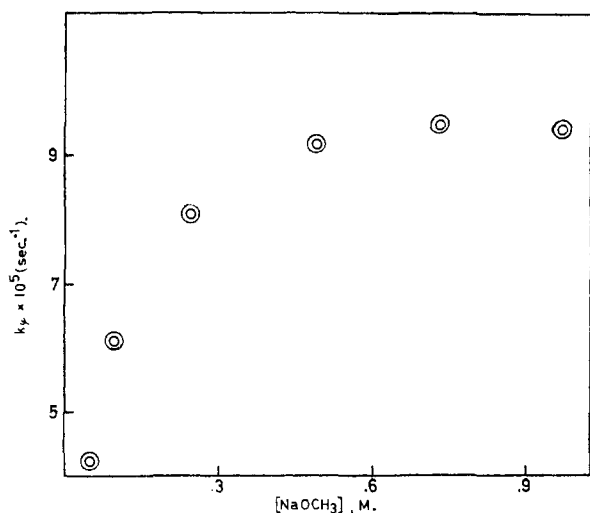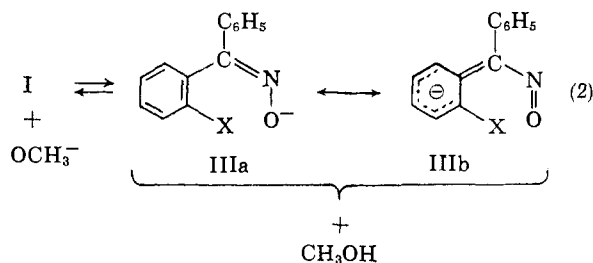
Fig. 1.—Rate of cyclization of chloro-oxime Ib as a function of sodium methoxide concentration.

Earlier workers had observed that the rate of ring closure was strongly dependent on base concentration; indeed, some[2,6] preferred to prepare Ic under mildly alkaline conditions even though it cyclizes rapidly in more concentrated alkali. We therefore studied the dependence of rate on sodium methoxide concentration. The result in the case of Ib is shown in Fig. 1; similar plots for Ia and Ic can be constructed from data in Table I.

The curvature in this plot is attributed to the equilibrium reaction

$$
\begin{array}{c}
\text{I} \\
+ \\
\text{OCH}_3^-
\end{array}
\rightleftharpoons
\underbrace{
\text{IIIa} \longleftrightarrow \text{IIIb}
}
\quad (2)
$$

$$
+ \\
\text{CH}_3\text{OH}
$$

Substantially complete conversion of the oxime to its anion III evidently is not achieved until [NaOCH₃] is about 1 M.[13] The measured rate co-

(13) A kinetic expression taking account of reaction 2 is easily derived (neglecting dependence of rate and equilibrium constants on [NaOCH₃])

$$k_\psi = k \left(\frac{K[\text{NaOCH}_3]}{1 + K[\text{NaOCH}_3]} \right)$$

where k_ψ is the measured pseudo-first-order rate coefficient, k the rate coefficient for the transformation of III to II, and K the equilibrium constant for reaction 2 in the forward direction. Using k_ψ values at 0.097 M NaOCH₃, and letting k_ψ values at 0.97 M represent k, one computes K to be 19 for Ib and 24 for Ic. The difference between these values is not considered to be significant. The agreement of k_ψ values computed for various [NaOCH₃] by this expression with measured k_ψ's was only approximate. Thus, the calculated k_ψ values for Ib at 110° were: 0.049 M, 4.55; 0.097 M, 6.13; 0.243 M, 7.75; 0.49 M, 8.50; 0.73 M, 8.78 (all in sec.⁻¹ × 10⁵); these should be compared with the experimental values in Table I. The aberration is in the direction of k_ψ (calcd.) being too low at higher [NaOCH₃], and is presumably due to dependence of k and/or K on [NaOCH₃].

The above K should be equal to K_A/K_M, where K_A is the oxime acid dissociation constant and K_M the methanol autoprotolysis constant. Literature K_A values[14a,b] for various oximes are about 5 × 10⁻¹² in water, corrected to 5 × 10⁻¹⁷ by the rule-of-thumb[14c] that pK_a's for neutral acids increase by about 5 on change from water to

efficients (k_ψ) at *ca.* 1 M NaOCH₃ are considered to represent unimolecular transformation of the oxime anions to II, and are used for rate comparisons.

No consistent rate measurements could be made on cyclization of iodo-oxime Id. The absorbance of quenched aliquots from any reaction solution did not increase regularly with time. The results, such as they were, suggested the superposition of some erratic factor on an underlying cyclization somewhat slower than that of fluoro-oxime Ia (at 79.9°). Catalysis by traces of metal ions adventitiously present in some ampoules was suspected, but the complication was not suppressed by addition of ethylenediaminetetraacetic acid in small amounts. The possibility that the disturbance was a radical reaction was not eliminated.

Rate coefficients at 100.5°, enthalpies and entropies of activation are set forth in Table II.

TABLE II

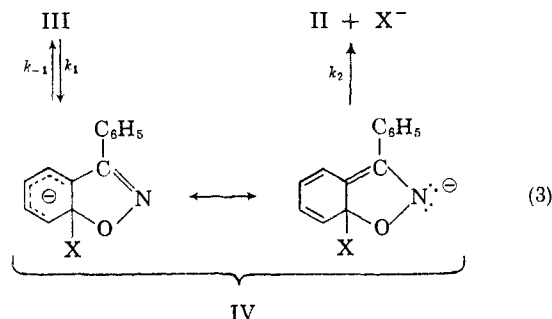KINETICS OF CYCLIZATION OF Ia, Ib AND Ic TO II[a]

Oxime, X =	$10^5 k_\psi$, sec.⁻¹ at 100.5°	ΔH^*, kcal.	ΔS^*, cal./deg.
Ia, F	812[b]	27	+3
b, Cl	3.44	31	+4
c, Br	42.9	31	+9

[a] Based on data from Table I for reactions in *ca.* 1 M NaOCH₃. [b] Extrapolated from lower temperatures.

Discussion

The possibility that cyclization occurs *via* an elimination–addition (benzyne) mechanism[15] is disfavored because alkoxide ions in alcoholic solvents have been found incapable of generating arynes from aryl halides.[16]

A normal intermediate complex mechanism[8] (eq. 3) seems probable, with $k_2 \gg k_{-1}$ so that k_1 is

$$
\begin{array}{ccc}
\text{III} & & \text{II} + \text{X}^- \\
k_{-1}\Big\updownarrow k_1 & & \Big\uparrow k_2 \\
\underbrace{
\text{(structure IVa)} \longleftrightarrow \text{(structure IVb)}
} & & (3)
\end{array}
$$

$$\text{IV}$$

virtually identical to the experimental k. The reaction is activated only by the oxime group which, though negatively charged on oxygen in the starting oxime anion, can nevertheless accommodate negative charge on nitrogen in the transition state, which presumably approaches inter-

ethanol solvent. K_M is 2 × 10⁻¹⁷ (25°)[14c]; K is then reckoned to be 2.5, in satisfactory agreement with the above experimental value of about 20 in view of all the approximations involved.

(14) (a) O. L. Brady and N. M. Chokshi, *J. Chem. Soc.*, 947 (1929); (b) C. V. King and A. P. Marion, *J. Am. Chem. Soc.*, 66, 977 (1944); (c) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 256–260.

(15) J. F. Bunnett, *J. Chem. Education*, 38, 278 (1961); J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, 83, 1691 (1961).

(16) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, 23, 904 (1958); F. Scardiglia and J. D. Roberts, *ibid.*, 23, 629 (1958).

mediate IV in structure. This is not expected to be a strong activating group, and indeed the enthalpies of activation are much higher than those for reactions of alkoxide ions with nitroaryl halides. For example, ΔH^* of 31 kcal. for Ib may be compared with 17 kcal. and 19 kcal., respectively, for reactions of methoxide with 2,4-dinitrochlorobenzene[10] and of ethoxide with p-chloronitrobenzene.[9] That the oximes cyclize to II at conveniently accessible temperatures is a consequence of the very favorable entropies of activation, common for intramolecular cyclization processes.[17]

The order of halogen mobility is F > Br > Cl, in harmony with indications from preparative work.[2-6] The relative mobilities of F and Cl, which are in the ratio 236:1, are similar to those in reactions of alkoxide ions with mono- and dinitrohalobenzenes. The latter lie in the range of 200:1 to 2000:1.[9,10,18] The difference in ΔH^* of cyclization between Ia and Ib is also normal. These correspondences with typical aromatic nucleophilic substitutions substantiate the mechanism postulated (eq. 3).

The relative mobility of bromine is unusual, however. Customarily,[8-10] bromine is displaced about as fast as chlorine and with nearly the same activation parameters. The present results are "normal" insofar as ΔH^* relationships are concerned; the exceptionally high mobility of bromine stems from an exalted entropy of activation.

We think this entropy effect is of steric origin. Possibly the condition of mesomerism, IIIa ↔ IIIb, is sterically inhibited (lessening the contribution of IIIb) when X is Br but not so much when X is Cl or F. Since the effect of this mesomerism is to disperse negative charge, the bromo-oxime anion should have a higher localization of charge on oxygen and therefore greater solvation. The transition state geometry is presumably rather independent of the identity of the halogen, and consequently differences in solvation of steric origin should vanish in the activation process. The more heavily solvated oxime anion, the bromo anion, should therefore release more solvent with resulting greater gain in entropy.

If steric acceleration is correctly diagnosed here, it is a mild case, far different from the colossal effect observed earlier in the Smiles rearrangement of 2-hydroxy-2'-nitrodiphenyl sulfones on introduction of 6-substituents.[19]

Experimental

Chloro-oxime Ib was made by heating o-chlorobenzophenone with hydroxylamine in 1 M ethanolic sodium hydroxide at reflux for 2 hours.[4] Oximes Ia, Ic and Id were prepared by heating ketone and hydroxylamine at reflux in 1 M ethanolic hydrogen chloride for 2 days.[20] The oximes were recrystallized from petroleum ether. Melting points were: Ia, 121°; Ib, 130°; Ic, 125°; Id, 151°; these correspond to literature values.[2,5,20,21]

3-Phenyl-1,2-benzisoxazole (II), m.p. 83°, was prepared by refluxing Ib with 1 M sodium hydroxide in ethanol for 2 days.[3]

Beckmann rearrangement of the oximes was brought about by treatment with phosphorus pentachloride in ether.[11] Melting points of the amides obtained were: from 1a, 99°; from 1b, 116°; from 1c, 119°; from 1d, 143°; all were crystallized from ethanol. These correspond to literature values for the o-halobenzanilides[6,20] except for o-fluorobenzanilide which has not previously been described. o-Fluoro-, o-bromo- and o-iodobenzanilides were obtained independently from condensation of the appropriate o-halobenzoyl chlorides with aniline, and agreed in melting point and infrared spectrum with the relevant Beckmann rearrangement products. o-Fluorobenzanilide, m.p. 99°, is a new compound.

Anal. Calcd. for $C_{13}H_{10}FNO$: C, 72.54; H, 4.68. Found:[22] C, 72.57; H, 4.70.

Reagent grade methanol was re-dried by the magnesium metal method. Sodium methoxide solutions were prepared by dissolving clean sodium metal in methanol and standardized against potassium hydrogen phthalate.

Kinetic Procedure.—Reaction solutions were prepared by dissolving a weighed amount of the oxime in methanol, adding a measured amount of standard methanolic sodium methoxide, and diluting to a volume of 100 cc. The total oxime concentration (molecule plus anion) was about 5 × 10^{-4} M in all cases. Aliquots (5 cc.) of this solution were placed in ampoules which were flushed with nitrogen and sealed. The ampoules for a run (usually twelve) were wrapped in copper sinkers and all placed in the thermostat at once. They were withdrawn at recorded times (the first after 10 minutes), cooled under tap water, opened, and their contents transferred to 25-cc. volumetric flasks which were made up to the mark with ca. 0.5 M acetic acid in methanol. Absorbances (A_t) were read with a Beckmann DU spectrophotometer at 290 mμ.

For most runs two "infinity" ampoules were taken from the thermostat after at least eight half-lives, and "infinity" absorbances (A_∞) were obtained with the same quenching and analysis procedure. Plots of log ($A_\infty - A_t$) versus time were satisfactorily linear to 80 or 90% of reaction in most cases; the slopes were multiplied by −2.30 to get k_ψ values.

Thermostat temperatures varied about ±0.2° above 100° and ±0.1° below; they were checked against National Bureau of Standards-certified thermometers.

Detail on a typical run is presented in Table III.

TABLE III
KINETICS OF CYCLIZATION OF Ib TO II; A TYPICAL RUN

Initial concentrations: Ib, 5.65 × 10^{-4} M; NaOCH$_3$, 0.825 M at room temperature, or 0.73 M at reaction temperature, 110°

Time, min.	A_t (290 mμ)	$A_\infty - A_t$	$1 + \log (A_\infty - A_t)$
10	0.114	0.709	0.850
40	.227	.596	.775
70	.325	.498	.697
100	.399	.424	.628
130	.468	.355	.550
160	.532	.291	.464
190	.580	.243	.386
220	.598	.225	.352
250	.632	.191	.281
280	.663	.160	.204
∞	.825		
∞	.815		
∞	.825		

A_∞ was taken as 0.823. The plot of log ($A_\infty - A_t$) vs. time was strictly linear through 130 min. and slightly scattered (but not curved) beyond, with slope −4.11 × 10^{-3} sec.$^{-1}$; k_ψ is then 9.46 × 10^{-3} sec.$^{-1}$.

The enthalpy and entropy of activation, ΔH^* and ΔS^*, were calculated from standard expressions.[23]

(17) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 250–252.

(18) C. W. L. Bevan and G. C. Bye, *J. Chem. Soc.*, 3091 (1954).

(19) J. F. Bunnett and T. Okamoto, *J. Am. Chem. Soc.*, 78, 5363 (1956).

(20) W. Wachter, *Ber.*, 26, 1744 (1893).

(21) E. Bergmann and A. Bondi, *ibid.*, 64, 1474 (1931).

(22) Analysis by Micro-Tech Laboratories, Skokie, Ill.

(23) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 199.