factor as compared with the experimental value of 4.9×10^{12}. Such close agreement is regarded as fortuitous, but substantially supports the theory proposed to account for the isomerization. The introduction of hindered rotation in the activated complex to the extent of about 3000 calories would result in an increase in the frequency factor by about 1.2 fold. In addition, the activated complex possesses two unshared electrons capable of forming singlet and triplet states. This probably leads to an electronic multiplicity factor of four for the activated complex, which of course increases the frequency factor fourfold. In any event the frequency factor has been calculated within a factor of fivefold and thus justifies serious consideration of the Olson theory as an explanation for all geometrical isomerization reactions incapable of proceeding by tautomerization.

An obvious corollary of this theory is the proposition that 43,000 calories represents the energy required to open the carbon–carbon double bond in a molecule. The values obtained for structurally different molecules support this figure.

Summary

The thermal isomerization of gaseous *trans*-dichloroethylene into the *cis* form was found to be approximately homogeneous and of first order in the temperature range of 566 and 608°K. A pressure range of 700 to 200 mm. was investigated. The rate of the reaction was expressed by the equation

$$k = 4.9 \times 10^{12} e^{-41,900/RT} \text{sec.}^{-1}$$

The activation energy compared favorably with those found by Kistiakowsky for the isostilbene and methyl cinnamate isomerizations.

A mechanism is proposed to account for the isomerization of geometrical isomers. The isomerization is a consequence of the activation of the carbon–carbon double bond to form a single bond with two free valences. Free rotation of the H–C–Cl groups takes place and a double bond is reformed in the *cis* molecule by an inversion of a free carbon valence.

WASHINGTON, D. C. RECEIVED AUGUST 26, 1940

[CONTRIBUTION FROM THE LABORATORY OF BIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BUFFALO]

The Rates of Reaction of the Stereoisomeric Oximes of Cholestenone and of Benzal-*p*-bromoacetophenone with Iodine Monobromide

BY J. O. RALLS

Introduction

Among the many manifestations of steric hindrance, we are concerned only with steric hindrance effects in the reactions of certain types of stereoisomers. Some interesting observations have been made upon the rates of esterification and of hydrolysis of *cis* and *trans* isomers of cyclopentanols[1] and cyclohexanols[2,3] and the influence of steric hindrance in those cases. In general, the *trans* form esterified and hydrolyzed the more rapidly. Steric hindrance seemed to modify, also, the rates of hydrolysis of[4] esters of *cis* and *trans* cinnamic acid and[5] of certain stereoisomeric hydrazones and oximes. The *anti* oximes hydrolyzed considerably more rapidly than did the *syn* oximes. More pertinent, however, are the observations of Merz[6] on the rates of hydrogenation of the oximes of isovanillalacetone (α,β unsaturated ketone). He observed that the *syn* form was, whereas the *anti* form was not, readily hydrogenated. Since the relation between oxime configuration and the Beckmann rearrangement was not fully clarified until a year later,[7,8] it is probable that his *syn* and *anti* designations were in error.

In a previous paper,[9] the author suggested that the failure of cholestenoneoxime to halogenate in glacial acetic acid and its easy halogenation in carbon tetrachloride could be due to the existence of one form (*syn*) in one solvent and of another form (*anti*) in the other solvent. This was contrary to the belief of K. v. Auwers[10] that the addition of halogen to α,β unsaturated ketoximes

(1) Vavon and Flurer, *Bull. soc. chim.*, **45**, 754–762 (1929).
(2) Vavon and Mitchovitch, *ibid.*, **45**, 961–972 (1929).
(3) Vavon and Guedon, *ibid.*, **47**, 901 (1930).
(4) Manta, *ibid.*, **53**, 1277–1286 (1933).
(5) Johnson and Stieglitz, THIS JOURNAL, **56**, 1904 (1934).
(6) Merz, *Ber.*, **63B**, 2951–2953 (1930).
(7) Blatt, THIS JOURNAL, **53**, 1133 (1931).
(8) Blatt and Stone, *ibid.*, **53**, 4134 (1931).
(9) Ralls, *ibid.*, **60**, 1748 (1938).
(10) K. v. Auwers and Muller, *J. prakt. Chem.*, **137**, 65–66 (1933).

was normal. Blatt,[8] on the other hand, found that the bromination of *syn*- and *anti*-benzal-*p*-bromoacetophenoxime did not proceed normally in that the *syn* dibromo product always resulted regardless of which was the starting material. None of the authors made a study of the rates of halogenation of the *syn* and *anti* oximes in question. We, therefore, decided to make such studies using the benzal-*p*-bromoacetophenoximes and the cholestenoneoximes. Fortunately, it has been established that the latter are indeed *syn* and *anti* isomers.[11] Under special conditions, we found that *anti* oximes halogenated somewhat more rapidly than did the *syn* oximes.

Discussion

(a) **The Benzal-*p*-bromoacetophenoximes.**—A definite difference between the rates of reaction of the two forms of benzal-*p*-bromoacetophenoxime with iodine monobromide in carbon tetrachloride was observed (Curves 2 and 3, Fig. 1). The *anti* form reacted the more rapidly. In the presence of glacial acetic acid, the difference was considerably diminished (Curves 4 and 5, Fig. 1). The rate of reaction of the *syn* oxime, under the latter conditions, was somewhat greater than was expected. This might have been due to the partial conversion of the *syn* form to *anti*-benzal-*p*-bromoacetophenoxime, of which change there was some evidence. The *syn* compound, after treatment with glacial acetic acid, gave a color with concentrated sulfuric acid somewhat suggestive of the presence of the *anti* oxime.

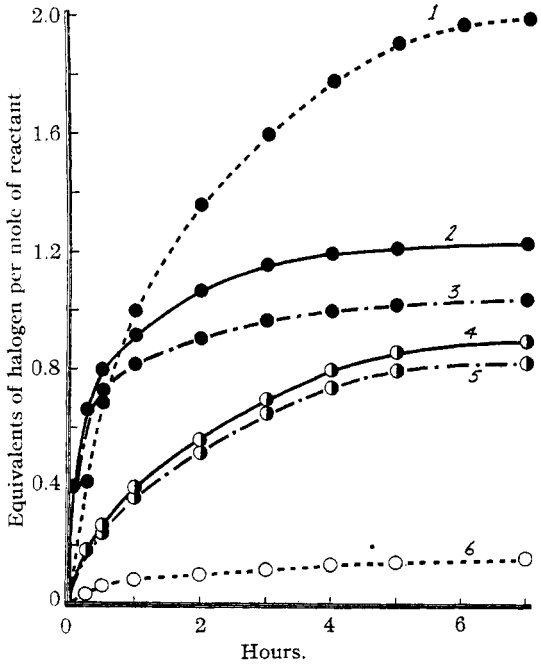


Fig. 1.—The halogen consumed by benzal-*p*-bromoacetophenone, and the *syn* and *anti* oximes, in a medium of varying proportions of carbon tetrachloride and glacial acetic acid: 1, ----● ketone in CCl_4; 2, ——● *anti* oxime in CCl_4; 3, — - —● *syn* oxime in CCl_4; 4, ——◑ *anti* oxime in 4 parts CCl_4 and 2 parts CH_3COOH; 5, — - —◑ *syn* oxime in 4 parts CCl_4 and 2 parts CH_3COOH; 6, ----○ ketone in CH_3COOH.

(11) Ralls, THIS JOURNAL, **62**, 2459 (1940).

The diminished rates of reaction of the oximes in glacial acetic acid was in line with the effect of that solvent upon the reaction of the ketone with iodine monobromide (Curves 1 and 6, Fig. 1).

The more rapid reaction of the *anti* oxime and the slower reaction of the *syn* form could be explained on the basis of steric hindrance effects. It is possible that even a greater difference in the rates would have been observed if it were not for the fact that *syn* dibromobenzal-*p*-bromoacetophenoxime was the product from both the *syn* and the *anti* oxime.

(b) **The Cholestenoneoximes.**—Unfortunately, we observed no real difference between the rates of reaction of the *syn* and *anti* cholestenoneoximes with iodine monobromide, either in carbon tetrachloride or in carbon tetrachloride–glacial acetic acid mixtures (Curves 3, 5, 6, and 7, Fig. 2). However, in view of the ready interconvertibility of these compounds in the solvents used,[11] no other results should have been expected especially when twelve hours were allowed to elapse between the solution of the oximes and the start of the halogenation. When the reaction was started immediately after solution in carbon tetrachloride was effected, some difference in the reaction rates was detected (Curve 3, *syn* delayed, and 4, *syn* immediate, Fig. 2).

Attempts to utilize the solvents ethyl alcohol and formic acid in which the stereoisomeric cholestenoneoximes exist without apparent change[11] were unsuccessful because of large and erratic reactions between these solvents and the reagent.

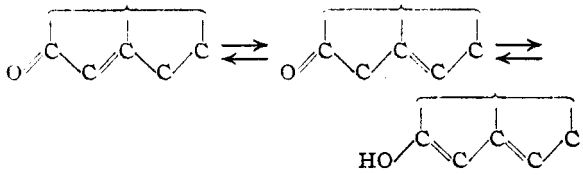
As in the case of the benzal-*p*-bromoacetophenoximes, increasing the proportion of acetic acid in the medium caused a marked diminution in the rate of halogenation of the cholestenoneoximes. Since cholestenone was more reactive in glacial acetic acid than in carbon tetrachloride (Curves 1 and 2, Fig. 2), it would seem that the effect of the acetic acid upon the rate of halogenation of its oximes might have been due to the

known predominance of the *syn* form in that solvent[11] and the lesser reactivity of the latter. The only real evidence of this lesser reactivity was obtained when the dry oximes were exposed to bromine vapors.[12,13] In a given time, the *anti* cholestenoneoxime combined with approximately twice as much bromine as did the *syn* oxime; but neither one was fully saturated, even after two hours of exposure to the bromine.

When *syn* and *anti* cholestenoneoxime, separately, were brominated under conditions which did not permit the conversion of the one into the other, or *vice versa*, the bromo derivatives of the one differed from those of the other.[11] In this respect, the behavior of the *syn* and *anti* cholestenoneoximes was different from that of the *syn* and *anti* benzal-*p*-bromoacetophenoximes.

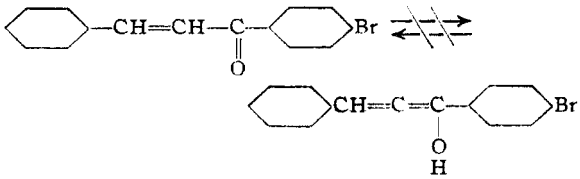
(c) **The Influence of Glacial Acetic Acid upon the Halogenation of Cholestenone and of Benzal-*p*-bromoacetophenone.**—There may be some question as to why glacial acetic acid accelerated the halogenation of cholestenone whereas it retarded the halogenation of benzal-*p*-bromoacetophenone. It is believed that the explanation is quite simple.

It is known that the halogenation of cholestenone proceeds through its enolization which process is catalyzed by hydrogen bromide.[9,14] The enolization of cholestenone occurs easily because its double bond readily shifts as shown below.



Moreover, the acetic acid favors this process by reason of its being a good solvent for the hydrogen bromide catalyst.

The situation in regard to benzal-*p*-bromoacetophenone is totally different, for it cannot readily enolize because the double bond already present has no place to shift to in order to permit of enolization.



(12) Becker, *Z. angew. Chem.*, **36**, 539 (1923).
(13) Rossman, *Ber.*, **65B**, 1847–1851 (1932).
(14) Inhoffen, *ibid.*, **69B**, 2141–2147 (1936).

The acetic acid retards the direct addition to the double bond near the carbonyl group.[15]

Materials.—Cholestenone, $\Delta^{4,5}$, m. p. 81°, prepared according to Schoenheimer.[16]

Cholestenoneoxime, *anti*(*anti* 3-hydroxylimino cholesten-4,5),[11] m. p., 151.8°, prepared according to Diels and Abderhalden.[17]

Cholestenoneoxime, *syn*(*syn* 3-hydroxylimino cholesten-4,5), m. p. 65°, prepared by recrystallizing the *anti* form from glacial acetic acid.[11]

Benzal-*p*-bromoacetophenone, m. p. 102–103°, was prepared according to the directions given for the preparation of benzalacetophenone[18] except that *p*-bromoacetophenone was the starting material.

syn-Benzal-*p*-bromoacetophenoxime, m. p. 145–158°, and *anti* benzal-*p*-bromoacetophenoxime, m. p. 150–163°, were prepared through the oxime acetates in the manner described by Blatt and Stone[8] and compared favorably with authentic samples.[19]

Experimental

The Reaction of Benzal-*p*-bromoacetophenone, of *syn*-Benzal-*p*-bromoacetophenoxime, and of *anti*-Benzal-*p*-bromoacetophenoxime with Iodine Monobromide in Various Proportions of Carbon Tetrachloride and Glacial Acetic Acid.—One-third millimole of the organic reactant was weighed out and quantitatively transferred to one arm of a T-tube. This was dissolved in 20 cc. of a mixture of carbon tetrachloride and glacial acetic acid of the desired proportions. Forty cc. of 0.05 *M* iodine monobromide, in the same mixture of solvents as above, was added to the other arm of the T-tube. When the two solutions had come to a temperature of 25°, they were quickly mixed. At definite intervals of time, 6 cc. aliquot portions (containing $^1/_{30}$ millimole of organic reactant) were removed and the residual halogen was titrated with standard thiosulfate after the addition of 5 cc. of 0.05 *M* potassium iodide. In Fig. 1, the equivalents of halogen consumed per mole of organic substance are plotted against the reaction period in hours.

Dibromobenzal-*p*-bromoacetophenone, m. p. 184°,[20] was isolated from the reaction mixture containing benzal-*p*-bromoacetophenone and iodine monobromide; while *syn*-dibromobenzal-*p*-bromoacetophenoxime, m. p. 173°,[8] was obtained when either the *syn*- or the *anti*-benzal-*p*-bromoacetophenoxime reacted with iodine monobromide.

The Effect of Glacial Acetic Acid upon *syn*- and upon *anti*-Benzal-*p*-bromoacetophenoxime.—Fifty milligrams of *syn*-benzal-*p*-bromoacetophenoxime was dissolved in 3 cc. of glacial acetic acid. After several minutes, water was added and the precipitate was filtered off and dried by suction. Some of the product was dissolved in concentrated sulfuric acid. The color produced was yellow with a slight orange tinge. Untreated *syn*-benzal-*p*-bromoacetophenoxime gave a clear yellow color in concentrated sulfuric acid.[8]

(15) Böeseken and Gelber, *Rec. trav. chim.*, **46**, 158 (1927).
(16) Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935).
(17) Diels and Abderhalden, *Ber.*, **37**, 3101 (1904).
(18) Kohler and Chadwell, "Organic Syntheses," Collected Vol. I, John Wiley and Sons, Inc., New York, 1932, p. 71.
(19) We wish to thank Dr. Blatt for the samples which he so kindly supplied.
(20) Weygand, *Ann.*, **459**, 118 (1927).

Fifty milligrams of *anti*-benzal-*p*-bromoacetophenoxime was similarly dissolved in glacial acetic acid and reprecipitated with water. The dry product was dissolved in concentrated sulfuric acid. A distinctly orange yellow color resulted. This color was like that obtained when untreated *anti* oxime was dissolved in sulfuric acid.[8]

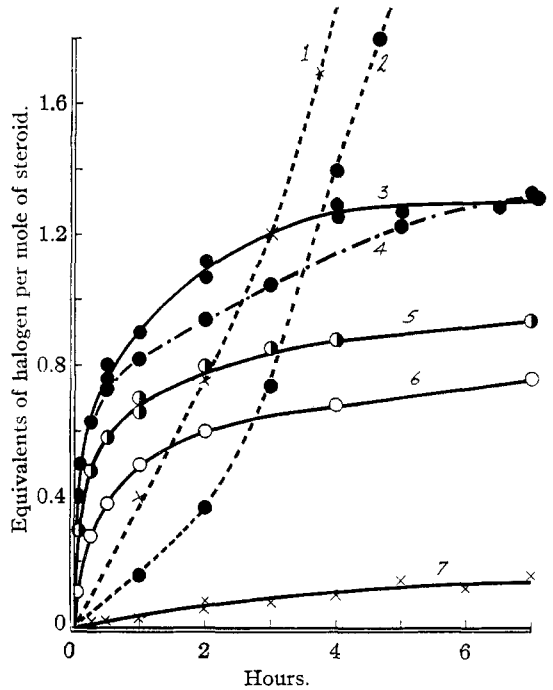


Fig. 2.—The halogen consumed by cholestenone and the *syn* and *anti* oximes thereof in a medium of varying proportions of carbon tetrachloride and glacial acetic acid: 1, ----● ketone in CCl_4; 2, -----× ketone in 2 parts CCl_4 and 4 parts CH_3COOH; 3, ——● *syn* and *anti* oximes in CCl_4, solution stood overnight and then reaction started; 4, —·—● *syn* oxime in CCl_4, immediate reaction; 5, ——◑ *syn* and *anti* oximes in 4 parts CCl_4 and 2 parts CH_3COOH, delayed reaction as in CCl_4 alone; 6, ——○ *syn* and *anti* oximes in 3 parts CCl_4 and 3 parts CH_3COOH, delayed reaction as above; 7, ——× *syn* and *anti* oximes in 2 parts CCl_4 and 4 parts CH_3COOH, delayed reaction as above.

The Reaction of Cholestenone, of *syn*-Cholestenoneoxime, and of *anti*-Cholestenoneoxime with Iodine Monobromide in Various Proportions of Carbon Tetrachloride and Glacial Acetic Acid.—One-third of a millimole of the steroid substance was carefully transferred to one arm of a T-tube and dissolved in a mixture of carbon tetrachloride and glacial acetic acid of the selected proportions. The next morning, to the other arm was added 40 cc. of 0.05 *M* iodine monobromide in a like mixture of the solvents. When the two solutions had come to a temperature of 25°, they were mixed. At definite intervals of time, 6 cc. aliquot portions of the reaction mixture (containing $^1/_{80}$ millimole of steroid) were removed and the residual halogen was titrated with standard thiosulfate.

Four reactions of *syn*-cholestenoneoxime with iodine monobromide in an exclusively carbon tetrachloride medium were run immediately after the solution of the steroid was effected.

All the results of the above runs and those described in the previous paragraph were plotted as equivalents of reacted halogen per mole of steroid against the reaction time in hours (Fig. 2).

The Reaction of the *syn* and the *anti* Cholestenoneoxime (in the Dry State) with Bromine Vapors.[12,13]—Thin layers of the cholestenoneoxime were spread upon weighed cover glasses. The loaded glasses were then reweighed and placed in a desiccator containing bromine vapors. Samples of *syn*- and *anti*-cholestenoneoxime were simultaneously exposed to bromine for two hours. At the end of this time, the plates were removed and warmed at 60° for fifteen minutes, then cooled and weighed. If the oximes had not been exposed to excessive amounts of bromine, reasonably comparable results were obtained. In no test did the *syn*-oxime ever consume as much halogen as did the *anti* form. An example of the results is given below.

Oxime	Weight of sample, mg. Before Br_2	After Br_2	Gain, mg.	Theory, mg.	Per cent. of theory
syn-Cholestenone-	13.70	15.34	1.64	5.48	30
anti-Cholestenone-	13.70	16.72	3.02	5.48	55

In all four such experiments were carried out. The samples varied from 10 to 15 mg. The *syn* samples consumed from 24 to 30% of the theoretical quantity of bromine, while the *anti* form consumed from 50 to 55% of the theoretical amount.

Summary

1. A small but definite difference in the rates of reaction of the two stereoisomeric benzal-*p*-bromoacetophenoxime with iodine monobromide was noted. The *anti* form was somewhat more reactive.

2. In the dry state or in *freshly* prepared solutions in carbon tetrachloride, there was a detectable difference in the rates of reaction of the *syn*- and *anti*-cholestenoneoxime with a halogenating agent. The *anti* oxime reacted somewhat the more rapidly. Under no other conditions could any differences be detected.

3. Glacial acetic acid markedly depressed the bromination of benzal-*p*-bromoacetophenone and of its oximes, as well as that of the *syn*- and *anti*-cholestenoneoximes.

4. Glacial acetic acid accelerates the reaction of cholestenone with iodine monobromide.

BUFFALO, NEW YORK RECEIVED SEPTEMBER 30, 1940