[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Stereochemistry of Aminocyclanols. Reaction of Epimeric Aminocyclanols with Glycol-splitting Reagents[1]

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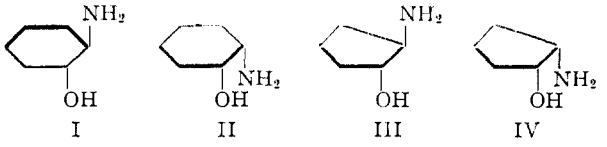
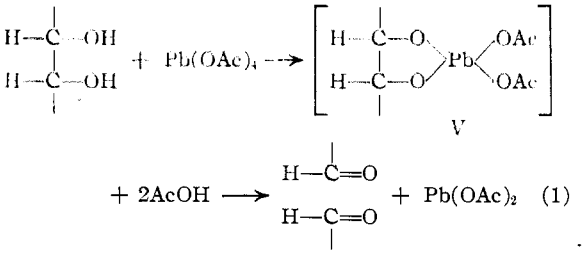
Lead tetraacetate under specified conditions oxidizes *cis*-2-aminocyclohexanol about twenty times more rapidly than *trans*- and *cis*-2-aminocyclopentanol at least twenty times more rapidly than *trans*. However, even the *trans*-cyclopentane derivative is oxidized more rapidly than the *cis* cyclohexane derivative. Periodate oxidations of the aminocyclopentanols show a smaller *cis*/*trans* rate-ratio than above, and with the aminocyclohexanols rate differences are negligible. The reduction of periodate is accompanied by a rise in *p*H. Experiments using different initial *p*H values and buffered solutions showed that the aminocyclanol oxidation is markedly accelerated by an increase in *p*H. At high *p*H the reaction is immeasurably fast and at low *p*H immeasurably slow. Near neutrality the oxidation rate is roughly proportional to the concentration of non-protonated aminocyclanol present at the *p*H used.

A number of recent communications[3] have described our investigations of methods for the chemical differentiation of diastereomeric (epimeric) aminocyclanols, *e.g.*, I–II or III–IV. It is well known that the glycol-splitting reagents lead tetraacetate and sodium periodate show steric specificity in their rates of oxidation of epimeric cyclanediols. While numerous aminoalkanols, some of them alicyclic,[4] have been oxidized with periodate and a few with quadrivalent lead, apparently little attention has been given to the rates of these reactions.[5a,b] The possibility of applying such rate-studies to the configurational characterization of aminocyclanols has therefore now been investigated.



I II III IV

Lead Tetraacetate Studies.—Lead tetraacetate presumably oxidizes a vicinal diol with formation of two aldehyde groups according to the equation



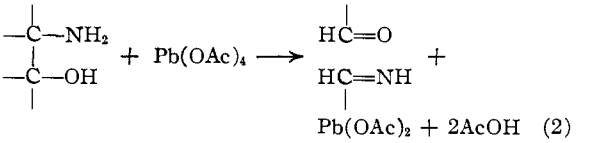
(1)

Criegee, Kraft and Rank[6] found that under identical conditions *cis*-cyclohexanediol was oxidized faster than *trans*- and *cis*-cyclopentanediol (in a polycyclic compound) much faster than *trans*.

We have now carried out such experiments on aminocyclanols. The rate of oxidation of *cis*-2-aminocyclohexanol (II) with excess lead tetraacetate under the conditions used is about 20 times greater than for *trans* (I), during the first half of the reaction. That of *cis*-2-aminocyclopentanol (IV) is at least 20 times greater than for *trans* (III). The results (Fig. 1) show not only that *cis*-epimers are oxidized much faster, but that cyclopentane derivatives react much faster than those of cyclohexane. Even the *trans*-C_5 compound was oxidized more rapidly than *cis*-C_6. The *cis*-C_5 reaction was immeasurably fast.

On the basis of the results so far obtained (Fig. 1) it appears that the lead tetraacetate reaction should be useful in distinguishing *cis*- and *trans*-2-aminocyclanols, at least when both epimers are available.[4]

The reaction of a diol with lead tetraacetate in acetic acid is reportedly[6] second order, even though the rate-determining step is a monomolecular cyclization of —CHOHCHOPb(OAc)$_3$— to V. By analogy with the diol reaction one may postulate an iminealdehyde as initial product of the aminocyclanol reaction



(2)

Possibly a cyclic intermediate such as V with hetero-oxygen replaced by NH may account for the rate differences. However, we observed a continued though slower decrease in the quadrivalent lead titer after the calculated amount for oxidizing

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(3) For related publications in this series see: (a) G. E. McCasland, THIS JOURNAL, **73**, 2293 (1951); (b) G. E. McCasland, *ibid.*, **73**, 2295 (1951); (c) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950); (d) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949); (e) H. E. Carter, R. K. Clark, Jr., Betty Lytle and G. E. McCasland, *J. Biol. Chem.*, **175**, 683 (1948); (f) G. E. McCasland and E. Clyde Horswill, THIS JOURNAL, **73**, 3744 (1951); *ibid.*, **73**, 3923 (1951).

(4) Very recently T. Posternak has reported periodate and lead tetraacetate rate studies on the epimeric compounds, *cis*-(1,3,5)- and *cis*-(1,3,5,6)-inosamine, see *Helv. Chim. Acta*, **33**, 1062 (1951). The latter epimer was oxidized more rapidly than the former by each reagent and the difference was more pronounced with lead tetraacetate. Thus the results are closely similar to those observed by us on the 2-aminocyclanols.

(5) (a) For periodate oxidations of aminoalkanols see the publications of A. E. O. Menzel, *et al.*, 1949; P. Fleury, *et al.*, 1949; H. E Carter, *et al.*, 1947-1948; R. L. Peck, F. A. Kuehl and K. Folkers, *et al.*, 1946; D. D. Van Slyke, *et al.*, 1940–1941; B. H. Nicolet and L. A. Shinn, 1939. For convenient reviews see G. F. Smith, "Analytical Applications of Periodic Acid and Iodic Acid," 5th ed., G. Frederick Smith Chemical Co., Columbus, Ohio, 1950; E. L. Jackson, "Organic Reactions," Vol. II, p. 341, 1944. (b) Few publications have appeared on the reaction of lead tetraacetate with aminoalkanols. See R. Criegee, Chap. 1 in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948; N. Leonard and M. A. Rebenstorff, THIS JOURNAL, **67**, 49 (1945).

(6) R. Criegee, L. Kraft and Bodo Rank, *Ann.*, **507**, 159 (1933); Criegee, *Angew. Chem.*, **53**, 321 (1940).

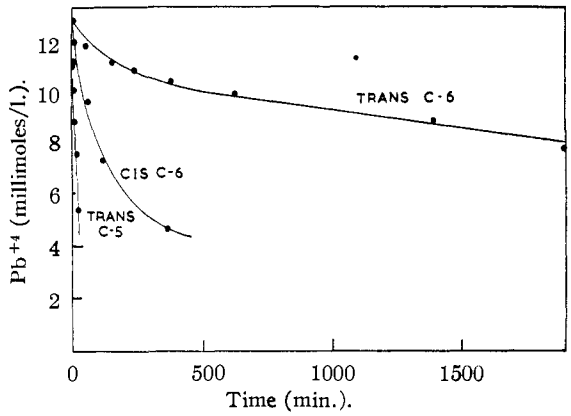

Fig. 1.—Quadrivalent lead concentration *vs.* time. Oxidation of 0.008 *M* epimeric 2-aminocyclohexanols and -pentanols by excess lead tetraacetate in acetic acid at 25° (*cis*-C-5 too fast to show).

aminocyclanol was consumed. This may be attributed to dehydrogenation of the iminealdehyde to a nitrile-aldehyde by excess lead tetraacetate.[6] Attempts to isolate pure reaction products have thus far been unsuccessful. Because of these (and possibly other) complications in the mechanism, it is not surprising that our kinetic data show generally poor agreement with the second or first order rate-equations.

Oxidations by Periodate.—The oxidation rate of *cis*-2-aminocyclopentanol (IV) with periodate at *p*H 7 was about four times as great as for *trans* (III) (during first half of reaction). However, the rate of oxidation of *cis*-2-aminocyclohexanol (II) under certain conditions was equal to or even less than that for *trans* (I) (see Fig. 3). For this reason it does not appear that periodate studies will be a very reliable indicator of aminocyclanol configurations.

In all experiments equimolar amounts of periodate and aminocyclanol were used. It was soon discovered that the rate of oxidation of aminocyclanols by periodate is markedly dependent on the initial *p*H and that a *p*H rise of one to three units regularly accompanies the reaction (Fig. 2).

A similar increase in *p*H has been reported[7] in the reaction of periodate with epimeric cyclohexanediols. Since the increase occurred only with initial *p*H values from 7.5 to 10, Price, *et al.*, attributed it to the conversion of diprotic paraperiodate[8] ($H_3IO_6^=$) to monoprotic iodate during the reaction

$$H_3IO_6^= + \text{—CHOHCHOH—} + H^+ \longrightarrow \text{—CHO} + \text{—CHO} + IO_3^- + 3H_2O \quad (3)$$

However, increasing *p*H decreased the rate of diol oxidation, an effect opposite to that now observed in aminocyclanol oxidations. It is reasonable that the presence of a salt-forming amino group should reverse the *p*H effect. The epimeric cyclohexanediols (despite higher concentration) reacted less

(7) C. C. Price, *et al.*, THIS JOURNAL, **64**, 552 (1942); **60**, 2726 (1938).

(8) There is some disagreement (perhaps partly due to differing ionic strengths) in the dissociation constants for paraperiodic acid reported by Price, *et al.*[7] (pK_1 0.96; pK_2 7.6); by N. Rae, *J. Chem. Soc.*, 876 (1931) (pK_1 1.63; pK_2 about 6); and by C. R. Crouthamel, *et al.*, THIS JOURNAL, **71**, 3031 (1949) (pK_1 1.63; pK_2 8.36; pK_3 14.98); see also Crouthamel, *et al.*, *ibid.*, **73**, 83 (1951).

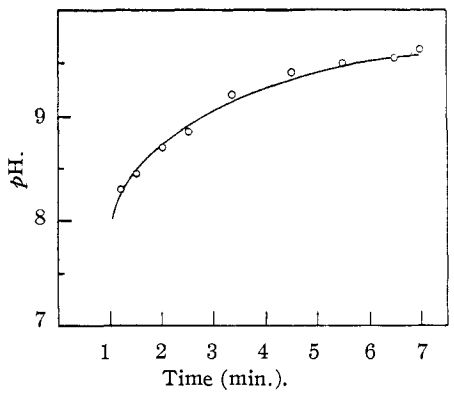

Fig. 2.—*p*H *vs.* time: oxidation of *trans*-2-aminocyclohexanol by sodium periodate (each 1.0 millimolar) in water at 25°; no added acid or buffer.

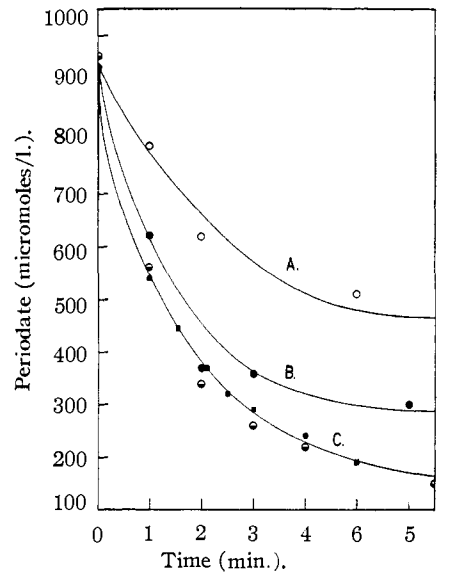

Fig. 3.—Periodate concentration *vs.* time: oxidation of epimeric 2-aminocyclohexanols and -pentanols with sodium periodate (each 1.0 millimolar) in citrate buffer solution at 25°; *p*H 6.75 for *cis*-C-6; 7.00 for other aminocyclanols; Curve (A), *trans*-C-5; (B) *cis*-C-6; (C) *cis*-C-5 (■) and *trans*-C-6 (◒).

rapidly[7] than the 2-aminocyclohexanols at *p*H 7–10.

We first studied the effect of *p*H on the aminocyclanol oxidation rates by adding varying amounts of sulfuric acid to the reaction mixtures at time zero. As the initial *p*H was decreased the rate also decreased (Fig. 4). At low *p*H the reaction was immeasurably slow, and at high *p*H immeasurably fast. Near neutrality the reaction was measurable.

In each of a further series of experiments the initial *p*H was maintained substantially constant throughout each reaction by use of citrate buffers. Here also, the rate increased greatly when the *p*H was increased (Fig. 5). Acetate buffers gave similar results but were not effective above *p*H 6.

To explain the *p*H effect one may reasonably assume that only the free aminocyclanol reacts rapidly and that its ammonium ion resists oxidation. The rate should then increase with the

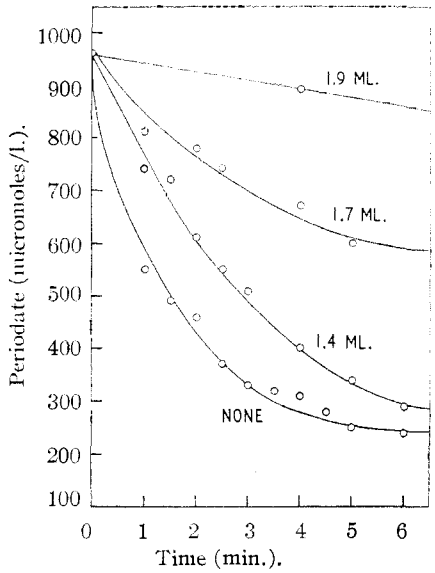

Fig. 4.—Periodate concentration *vs.* time: effect of various volumes (ml.) of 0.02 *M* sulfuric acid added to the reaction mixture (100 ml. total) at time zero. Oxidation of *trans*-2-aminocyclohexanol by sodium periodate (each 1.0 millimolar) in water at 0°; not buffered.

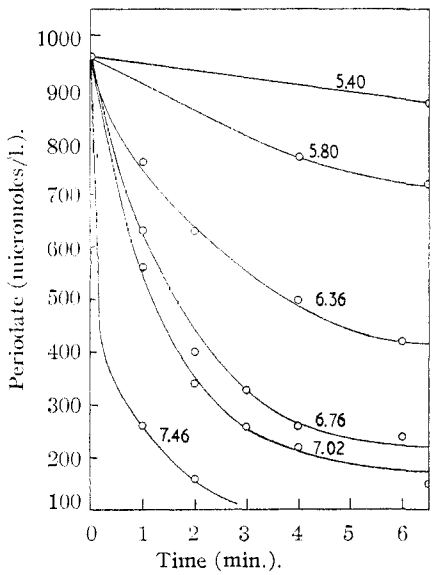

Fig. 5.—Periodate concentration *vs.* time: effect of *p*H in buffered reaction mixtures. Oxidation of *trans*-2-aminocyclohexanol by sodium periodate (each 1.0 millimolar) in water at 25°. Acetate buffer for *p*H 5.80; citrate buffer for other runs.

fraction (y) of dissociated 2-hydroxycyclohexylammonium ion. The fraction y can be calculated from the *p*H and the previously reported[3b] pK_a values for the 2-aminocyclohexanols, using the equilibrium equations

$$K = \frac{(H^+)(RNH_2)}{(RNH_3^+)} = \begin{cases} 10^{-9.5} & (trans) \\ 10^{-9.6} & (cis) \end{cases} \quad (4)$$

$$\frac{(RNH_2)}{(RNH_2) + (RNH_3^+)} = \frac{K}{K + (H^+)} = y \quad (5)$$

The variation of the initial rates (derived from reciprocal of concentration *vs.* time curves) with the initial concentration of *free* aminocyclanol calculated from fraction y is shown in Fig. 6.

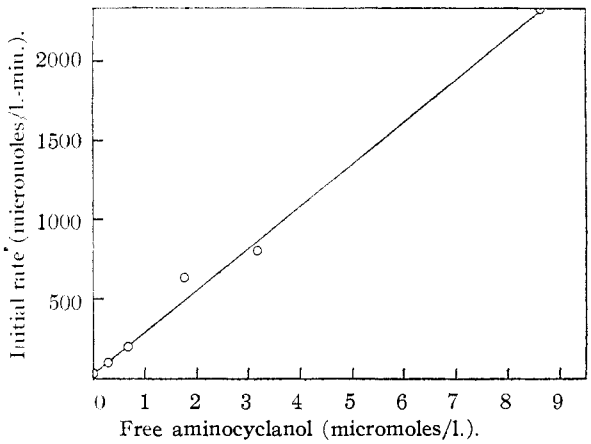

Fig. 6.—Initial rate *vs.* initial *free* aminocyclanol concentration: oxidation of *trans*-2-aminocyclohexanol by sodium periodate (each 1.0 millimolar) in citrate-buffered solutions of various *p*H's at 25°.

Except at the lowest *p*H values used the periodate oxidations were too fast for measurements of high precision. To decrease the rate, low concentrations (1 millimolar) were used. In some experiments the temperature was also reduced, from 25 to 0°. However, this temperature change reduced the rate by only a single power of two.

Attempts to isolate pure reaction products from the aminocyclanol oxidations by periodate have thus far been unsuccessful.

Apparently little is known about the mechanism of the periodate oxidation of amino-alcohols, whether acyclic or alicyclic. The apparent conformity of many of our periodate oxidations with the second order rate equation (Table I), might tempt one to speculate on the mechanism. However, we believe this conformity is misleading,[9] as suggested by the fact that both the buffered and non-buffered periodate runs appear to be second order when so calculated. Probably neither the lead tetraacetate nor the periodite oxidation of aminocyclanols has a simple mechanism. It will, no doubt, be necessary to isolate the products and to study exhaustively the effect of varied concentrations for all reactants present before reliable conclusions on the orders and mechanisms can be drawn.

Experimental

Preparation of Aminocyclanols.—The *d,l-trans* and *cis* forms of 2-aminocyclohexanol and of 2-aminocyclopentanol were prepared as previously described.[3c,3d]

Standard Lead Tetraacetate Solution.—Fourteen grams of lead tetraacetate[10] wet with acetic acid, was dissolved in 100% acetic acid and diluted to 500 ml. The solution was standardized by addition of an aliquot to acidified potassium iodide and titration of the liberated iodine with standard 0.1064 *N* sodium thiosulfate.

Standard Sodium Periodate Solution.—A 6.7-g. portion of sodium metaperiodate (G. Frederick Smith Co.) was

(9) Regarding the frequent unreliability of the "method of integration" in determining the order of a reaction, see K. V. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 17.

(10) O. Dimroth, *et al.*, *Ber.*, **53**, 484 (1920).

dissolved in a liter of water and the solution standardized by the following method. A 3.00-ml. aliquot was diluted to 100.0 ml. and a 4.00-ml. aliquot of this solution run into acidified potassium iodide. The liberated iodine was determined by titration with standard 0.1064 *N* sodium thiosulfate.

TABLE I

Apparent conformity of kinetic data with the integrated second order equation (see text). Oxidation of *trans*-2-aminocyclohexanol by sodium periodate (each 1.0 millimolar) in water. (A) Not buffered, 0°, 1.9 ml. of 0.02 *M* H_2SO_4 added at time zero. (B) Citrate buffer, *p*H 6.36, 25°.

Time, min.	Rate constant 10^4k, l./micromole-min. (A)	(B)
0	..	...
1	..	2.7
2	..	2.7
4	0.20	2.4
6	..	2.2
10	0.22	2.1
13	..	2.4
20	0.22	2.0
26	..	2.2
30	0.23	...
50	.24	...
60	.28	...
70	.26	...
80	.26	...
95	.25	...
111	.28	...

Citrate–Phosphate Buffer Solution.—Stock solutions of 0.100 *M* citric acid and 0.200 *M* disodium hydrogen phosphate were prepared. For any desired *p*H the solutions were mixed in the proportions specified by MacIlvaine.[11] The *p*H values were checked with a *p*H meter. Control experiments indicated that reduction of periodate by the buffer solution itself is negligible.

Acetate Buffer Solutions.—Stock solutions of 0.100 *M* sodium acetate and 0.100 *M* acetic acid were made up and combined in varying proportions.

Kinetic Studies with Lead Tetraacetate.—A weighed sample of 0.001 mole of redistilled aminocyclanol was dissolved in 70 ml. of glacial acetic acid in a 100.0-ml. volumetric flask. A 25.0-ml. portion of the standard lead tetraacetate solution was then added, the solution made up to 100.0 ml., shaken vigorously and placed in the 25.0° thermostat. Aliquots were periodically removed and the excess lead tetraacetate estimated by iodimetry.

(11) T. C. MacIlvaine, *J. Biol. Chem.*, **49**, 183 (1921); "Handbook of Chemistry," 5th Edit., Handbook Publishers, Inc., Sandusky, O., 1944, p. 1118.

The results are given in Fig. 1.

Kinetic Studies with Sodium Periodate. A. Reaction Rates in Non-buffered Solutions.—A 10.0-ml. sample of standard 0.01 *M* aqueous aminocyclanol solution was pipetted into the reaction flask. The reaction mixture was then diluted to about 95 ml. with water and a 3.00-ml. aliquot of standard sodium periodate solution added. The solution was quickly diluted to the mark, shaken vigorously, and returned to the 25.0° or 0.0° thermostat. Experiments at 0° were conducted in a cold room. Aliquots of 4.00 ml. were periodically removed and run into excess acidified potassium iodide solution. The liberated iodine was determined by titration with standard 0.1064 *N* thiosulfate and the amount of periodate present calculated, making allowance for the iodate present after reduction.

The results for *trans*-C-6 are given in Fig. 4. Comparable results (not shown) were obtained with *cis*-C-6 and *cis*- and *trans*-C-5.

B. Increase in *p*H Caused by the Reaction.—The *p*H of the reaction mixture was followed during the reaction by means of a Coleman Model 3D *p*H meter, calibrated against buffers of known concentration. Due to the speed of the reaction it was found impractical to measure the periodate concentration and the *p*H simultaneously. Consequently, identical reaction mixtures were separately examined for *p*H increase (Fig. 2) and periodate decrease. Due to the speed of the reaction reliable measurements of initial *p*H were not obtained.

C. Effect of Variation of Initial *p*H in a Non-buffered Solution.—The procedure was the same as in (A) except that quantities of 1–2 ml. of 0.0200 *M* sulfuric acid were added to the reaction vessel immediately following the addition of aminocyclanol. The rate results for *trans*-C-6 at 0° are given in Fig. 4. The results (not shown) at 25° and with *cis*-C-6 were similar.

D. Reaction Rates at Constant *p*H (Citrate Buffer).—A 10.0-ml. sample of standard aminocyclanol solution was added to the reaction flask and then diluted to 95 ml. with the particular buffer selected. The periodate solution (3.00 ml.) was then added, volume adjusted to 100.0 ml. and the experiment carried out as before. The *p*H of the solution was checked before and after reaction and found to be substantially constant.

The results for *trans*-C-6 at six *p*H values are given in Fig. 5. The results (not shown) at *p*H 6.02, and for *cis*-C-6 and for *cis*- and *trans*-C-5, were similar (see Fig. 3).

E. Reaction Rates at Constant *p*H (Acetate Buffer).—The procedure was similar to the previous one except that an acetate buffer of the desired *p*H was used as a diluent. The *p*H was again determined before and after the reaction and found to be constant. The limit of effective buffering action was found to be about *p*H 6.02 (obtained by combining 100 ml. of 0.1 *M* sodium acetate with 3.4 ml. of 0.1 *M* acetic acid). The result for *trans*-C-6 at *p*H 5.80 is shown in Fig. 5. The results (not shown) at *p*H 5.64 and 6.02 were similar.

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