Equilibrium and Isomerization in Bicyclic Nitriles[1]

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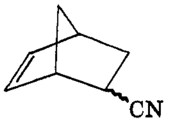
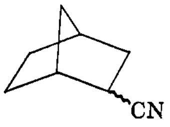
endo- and *exo*-2-cyanobicyclo[2.2.1]-heptene-5 (I) and *endo-* and *exo*-2-cyanobicyclo[2.2.1]heptane (II) have been prepared in greater than 99% purity and the thermodynamic equilibria between the two pairs of nitriles have been determined. The *endo–exo* ratios of I and II obtained from the kinetically controlled neutralization of intermediates common to each isomeric pair have also been determined. Reduction of the *endo* and *exo* isomers of I to the corresponding amines with lithium aluminum hydride has been shown to be accompanied by some isomerization.

Since hydrogen atoms α to nitriles are activated toward abstraction by base, a means is provided to induce isomerization through the intermediate anion produced on treatment of nitriles with base. This method has been used to racemize optically active nitriles[2] and to study the conformational preference of the nitrile group in certain substituted cyclohexyl systems.[3,4] This method has now been extended to show the conformational preference of the cyano group in some bicyclic nitriles.

The *endo* and *exo* isomers of 2-cyanobicyclo[2.2.1]-heptene-5 (I) and 2-cyanobicyclo[2.2.1]heptane (II) have been prepared in greater than 99% purity and the thermodynamic equilibria between the neutral nitriles have been determined. Also the intermediate anions produced by reaction of *endo* and *exo* I and II with an excess of base have been neutralized under conditions which assured that this neutralization was kinetically controlled.



I



II

In the course of another investigation in this laboratory,[5] it was suggested that reduction of I with lithium aluminum hydride may have occurred with some rearrangement. This observation has been substantiated in the present work.

Results

Equilibrium Studies.—*endo-* and *exo*-nitriles I and II were equilibrated with a catalytic amount of potassium *t*-butoxide in *t*-butyl alcohol stirred at reflux for extended periods of time. It was found that the *endo–exo* ratio of I was independent of the configuration of the starting nitrile. The same was true for the saturated nitriles II. Tables I and II contain the results of the equilibrium studies.

Kinetically Controlled Isomerizations.—*endo-* and *exo*-nitriles I and II were added to suspensions of an excess of potassium amide in liquid ammonia, and the ionized nitriles were then added inversely to a saturated solution of ammonium chloride in liquid ammonia. Tables III and IV show that the product ratios of isomerized I and II were independent of the starting nitriles.

TABLE I

EQUILIBRATION OF *endo-* AND *exo*-2-CYANOBICYCLO[2.2.1]-HEPTENE-5 (I) WITH POTASSIUM *t*-BUTOXIDE IN *t*-BUTYL ALCOHOL AT 83°

endo-I			*exo*-I		
Time, hr.	% *endo*	% *exo*	Time, hr.	% *endo*	% *exo*
0	99	1	0	1	99
30.5	51	49	19.5	40	60
68.5	51	49	90	52	48
			118	52	48

TABLE II

EQUILIBRATION OF *endo-* AND *exo*-2-CYANOBICYCLO[2.2.1]-HEPTANE (II) WITH POTASSIUM *t*-BUTOXIDE IN *t*-BUTYL ALCOHOL AT 83°

endo-II			*exo*-II		
Time, hr.	% *endo*	% *exo*	Time, hr.	% *endo*	% *exo*
0	99	1	0	1	99
264	49 ± 3	51 ± 3	264	51 ± 3	49 ± 3

TABLE III

KINETICALLY CONTROLLED ISOMERIZATION OF *endo-* AND *exo*-2-CYANOBICYCLO[2.2.1]HEPTENE-5 (I)

Starting nitriles		Product nitrile	
% *endo*	% *exo*	% *endo*	% *exo*
99	1	73	27
1	99	75	25

TABLE IV

KINETICALLY CONTROLLED ISOMERIZATION OF *endo-* AND *exo*-2-CYANOBICYCLO[2.2.1]HEPTANE (II)

Starting nitrile		Product nitrile	
% *endo*	% *exo*	% *endo*	% *exo*
99	1	64 ± 3	36 ± 3
1	99	64 ± 3	36 ± 3

Reduction with Lithium Aluminum Hydride.—Reduction of *endo-* and *exo*-I by lithium aluminum hydride was accompanied in each case by isomerization. Table V shows the purity of the starting nitrile and the *endo–exo* ratio of 2-methylaminobicyclo[2.2.1]heptene-5.

TABLE V

REDUCTION OF *endo-* AND *exo*-2-CYANOBICYCLO[2.2.1]HEPTENE-5 (I) BY LITHIUM ALUMINUM HYDRIDE

Starting nitrile		Product amine	
% *endo*	% *exo*	% *endo*	% *exo*
99	1	91 ± 2	9 ± 2
9	91	4 ± 2	96 ± 2

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(1) (a) Taken in part from a thesis submitted by D. B. K. to the Graduate School of Duke University in partial fulfillment of the requirements for the M.A. degree, 1964. (b) The support of this research in part by Research Grant CA-4298 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

(2) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 3678 (1961).

(3) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).

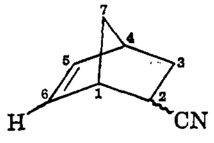
(4) B. Rickborn and F. R. Jensen, *ibid.*, **27**, 4606 (1962).

(5) J. W. Kilgore, unpublished results, Duke University.

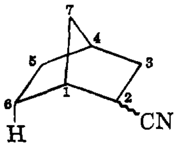
Discussion

Equilibrium Studies.—In the determination of the equilibria between neutral nitriles a catalytic amount of base was used, generally about 4 mole % base. Thus there was the possibility of at least 4% kinetically controlled quenching of the intermediate anions. However, this value of 4% was of the same magnitude as the precision of the method of analysis and could be discounted as it did not add to the uncertainty of the position of the equilibria.

The similarity of the equilibrium mixtures of both the saturated and unsaturated nitriles as shown by Tables I and II indicated that the steric requirements of both types of nitriles were similar. It can be seen from I and II that both nitriles have identical structures as far as the *exo* face of the molecules comprised of C-1, C-2, C-3, C-4, and C-7 is concerned. Pitzer strain arising from the nonbonded interactions of I and II mentioned above should therefore be very similar. The *endo* sides of I and II should differ from one another in that the hydrogen atom attached to C-6 in I is coplanar with C-6, C-1, C-5, and C-4 and is removed from the underside of the bicyclic cage. In II, the hydrogen atom attached to C-6 projects down somewhat under the cage. Models suggest that the *endo*-C-6 hydrogen in II would be nearer the *endo*-cyano group than the C-6 hydrogen of I. Such a situation would destabilize *endo*-II with respect to *endo*-I and would be expected to lead to a difference in the *endo–exo* ratio of II and I at equilibrium. That the same equilibrium ratio of *endo*- and *exo*-nitriles was obtained in both I and II indicates that there is no increase of Pitzer strain of *endo*-II with regard to *endo*-I.



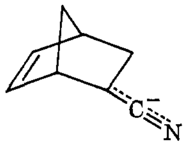
I



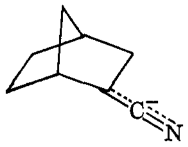
II

It would be predicted that the C-2–nitrile bond should be strongly polarized toward the nitrile group and thus the electron density of the C-2–nitrile bond would be less than a normal C-2–carbon bond. Since there was no apparent destabilization of *endo*-II with respect to *endo*-I, it was concluded that the electron density of the C-2–nitrile bond in both I and II is so small that there is no increase of nonbonded interaction in going from *endo*-I to *endo*-II. Thus it seems that the conformational preference of the cyano group in the bicyclic systems mentioned is slight, with the population of *endo*- and *exo*-I and -II vitually identical. Rickborn and Jensen[4] found that there was also very little conformational preference of the cyano group at equilibrium in 4-*t*-butylcyclohexylcarbonitrile.

A sample of pure *endo* unsaturated nitrile was heated at reflux in *t*-butyl alcohol for 3 days. On analysis by vapor phase chromatography the recovered nitrile was found to be unchanged. This observation eliminates the possibility of a thermally induced isomerization and supports an ionic mode of isomerization.

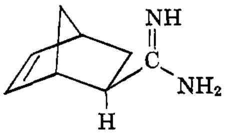


III

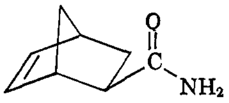


IV

Kinetically Controlled Protonation of Anions.—The reaction of nitriles I and II with excess potassium amide in liquid ammonia would be expected to afford the ionized intermediates III and IV, common to both *endo*- and *exo*-nitriles. Similar intermediates were postulated by Boehme.[6] Inverse addition of the mesomeric anions to liquid ammonia saturated with ammonium chloride, conditions which assure kinetically controlled quenching of the anions, should yield a product mixture of nitriles independent of starting nitrile. Experimental data in Tables III and IV suggest that product ratios of saturated and unsaturated nitriles are independent of the starting isomers and that intermediate III is common to *endo*- and *exo*-I and intermediate IV is common to *endo*- and *exo*-II. Boehme[6] reported that reaction of *endo*-I with sodamide in liquid ammonia yielded amidine V which, on mild hydrolysis gave carboxamide VI in 73% yield. It was observed in this investigation that reaction of *endo*-I and potassium amide in liquid ammonia for 20 min. yielded the mixture of nitriles reported in Table III as well as an amidine, identified by its characteristic infrared absorption. By a semiquantitative method it was found that amidine was the major product of the reaction, comprising at least 75% of the product mixture.



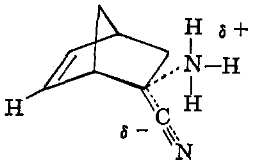
V



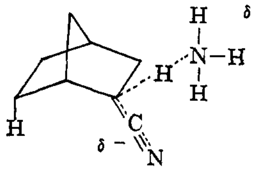
VI

Since it was important to determine the kinetically controlled *endo–exo* ratio of nitriles in the absence of such a large amount of amidine, pure *endo* I was treated with excess potassium amide in liquid ammonia and the anion produced was neutralized after only 20 sec. reaction time. On analysis, the product mixture was found to contain only trace amounts of amidine and a mixture of nitriles that was 75% *endo*-I in excellent agreement with the results recorded in Table III. Thus the kinetically controlled neutralization of intermediates III and IV is independent of the amount of amidine produced in the reaction mixture.

The data in Tables III and IV indicate that there was more *exo* attack affording *endo* product in the unsaturated nitrile anion relative to the saturated case. An explanation of these results can be deduced from a consideration of transition states A, B, C and D.



A



B

Structures A and B represent transition states for protonation from the *exo* side which gives rise to *endo* product. Structures C and D represent transition

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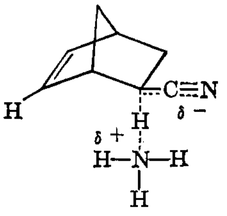
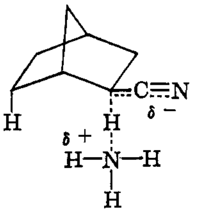
[6] W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *J. Am. Chem. Soc.*, **80**, 5488 (1958).



C



D

states for protonation from the *endo* side which yields *exo* product.

Since equilibrium studies have shown there is no preferred conformation of the nitrile group in either I or II, it would be expected that the products of kinetically controlled protonation of anions III and IV would be chiefly influenced by energy differences in the transition states represented by A and B and by C and D. The nitrile groups in III and IV are not constrained in an *endo* or *exo* conformation and can accommodate the protonating species by moving away from the incoming proton donor. The proton donor approaching from the *exo* side would encounter the same hindrance in A and B. The difference in energy of A and B is due in large measure to the fact that there is in the transition state a partial negative charge associated with the C-2–nitrile bond; hence, there is a larger electron density about this bond than in the neutral nitrile. As the nitrile group moves to the *endo* position, the partial negative charge would be expected to interact to a greater extent with the *endo* hydrogen at C-6 of the saturated nitrile than with the C-6 hydrogen of the unsaturated nitrile. Such an interaction would favor more *endo* product in the unsaturated than in the saturated nitrile, in agreement with the observed results.

On the other hand, in transition states C and D, which represent *endo* protonation to give *exo* product, the environments into which the nitrile group begins to move (*i.e.*, *exo*) are virtually identical and the nitrile group encounters the same hindrance in C and D. It would be expected *a priori* that the approach of the protonating species to IV would be shielded by the *endo* hydrogen at C-6 of II to a greater extent than the C-6 hydrogen of I, thus causing an energy difference between C and D. Data in Tables III and IV, however, show that there is actually less *endo* attack on the unsaturated III than on saturated anion perhaps due to a partial positive charge on the incoming proton donor which reduces the electron density of the incipient C-2–H bond, and in turn the destabilizing effect of nonbonded interaction.

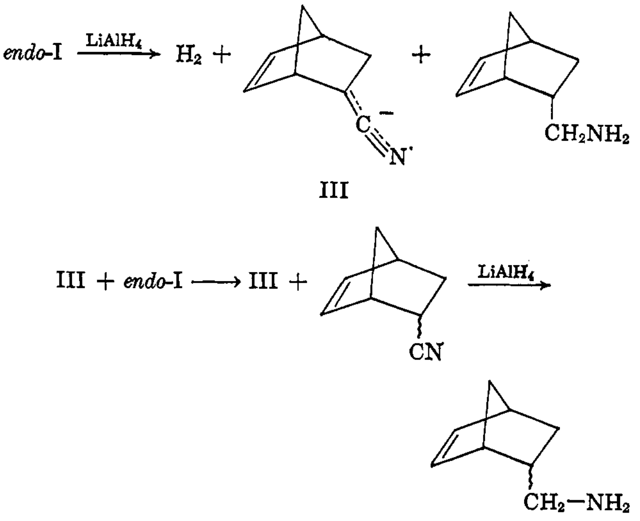
Hence, it is concluded that the difference in energies of transition states A and B representing *exo* protonation and *endo* product are rate determining and thus influence the product ratios of *endo*- and *exo*-nitrile to a greater extent than do the same considerations for *endo* protonation and *exo* product formation.

Attempts to establish the kinetically controlled *endo–exo* ratio of I utilizing excess potassium *t*-butoxide in refluxing *t*-butyl alcohol and also excess sodium hydride in ether were unsuccessful. Thermodynamic mixtures of nitriles were obtained from the reactions with *t*-butoxide regardless of reaction time and mode of neutralization. Starting nitrile was recovered unchanged after reaction with excess sodium hydride in ether for 1 hr. at room temperature. Evidently, under the conditions employed, these bases were not strong enough to ionize the nitrile completely.

Reduction Study.—The *endo* and *exo* unsaturated nitriles were reduced to the corresponding amines by excess lithium aluminum hydride in ether solution. The data in Table V show that the composition of the starting nitrile mixture differed from the *endo-exo* ratio of product amines, indicating that some isomerization occurred during reduction.

The isomerization observed on reduction may be rationalized as shown in Scheme I.

SCHEME I



The lithium aluminum hydride acts like a base to ionize the nitrile, analogous to the action of the *t*-butoxide ion on nitrile. This irreversible ionization, which competes initially with normal reduction, initiates a reversible ionization between the neutral nitrile and its anion, allowing isomerization of the nitrile. Reduction of the isomerized nitrile then gives rise to the isomeric mixture of amines.

Newman and Fukunaga[3] have shown that reduction of unhindered nitriles with lithium aluminum hydride, at least to the imine stage, is extremely rapid. Since nitriles are very rapidly reduced with lithium aluminum hydride, it is significant that 5–7% rearrangement was observed in the reduction of unsaturated nitrile I.

Reactions wherein lithium aluminum hydride reacts like a base are not without precedent. Gaylord[8] records a list of such reactions and Newman[7] has shown that lithium aluminum hydride can initiate a base-induced dehydration of some amides to the corresponding nitriles.

Experimental[9]

Vapor Phase Chromatographic (V.p.c.) Analyses.—The unsaturated nitriles were analyzed by v.p.c. using a Ucon Polar on Chromosorb W column at 150°. The saturated nitriles were analyzed with a polypropylene glycol on firebrick column at 115°. The amines were analyzed using a polypropylene glycol on firebrick column at 90°. Peak areas were determined

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[7] M. S. Newman and T. Fukunaga, *J. Am. Chem. Soc.*, **82**, 693 (1960).

[8] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 92.

[9] Melting points and boiling points are uncorrected. Infrared analyses were obtained by use of Perkin-Elmer Models 137 and 237 recording spectrophotometers. Gas chromatographic analyses were obtained with a Perkin-Elmer Model 154-C vapor fractometer.

by use of a planimeter. The overlap of peaks in the chromatograms of the saturated nitriles and amines complicated the analyses, requiring that an extrapolation of peak areas be made in these cases. The method of Cash[10] was used to make the extrapolations. The precision of the extrapolations is indicated in each case.

2-Cyanobicyclo[2.2.1]heptene-5 (I).—2-Cyanobicyclo[2.2.1]-heptene-5 (I) was prepared from freshly distilled cyclopentadiene monomer and acrylonitrile with no added solvent, after the method of Alder, Krieger, and Weiss.[11] The product mixture of nitriles contained 61% *endo*-I and 39% *exo*-I.

The isomeric nitriles were separated by distillation on a spinning-band column of 23 theoretical plates [*exo*-I, b.p. 77° at 10 mm. (lit.[12] b.p. 80.5° at 12 mm.); *endo*-I, b.p. 86° at 10 mm. (lit.[12] b.p. 86° at 12 mm.)]. Nitriles of greater than 99% purity were obtained by this method. Infrared spectra of the nitriles showed a sharp peak at 4.5 μ.

By a similar method, Alder, Heimbach, and Reubke[12] obtained a product mixture of nitriles that contained 60% *endo*- and 40% *exo*-nitrile. They separated the nitriles by distillation and made configurational assignments by saturating the olefinic double bond and converting the isomeric nitriles to the known *endo*- and *exo*-norbornane-2-carboxylic acids.

2-Cyanobicyclo[2.2.1]heptane (II).—Five grams (0.041 mole) of *endo*-2-cyanobicyclo[2.2.1]heptene-5 (I) was dissolved in 50 ml. of ethyl acetate and a few milligrams of platinum oxide was added. The mixture was then catalytically hydrogenated at an average pressure of 44 p.s.i. The product mixture was treated with activated charcoal and was filtered. The solvent was removed under reduced pressure leaving a light yellow oil which was readily sublimed at 50° (4 mm.). A waxy white solid, *endo*-II, m.p. 57–59° (lit.[12] m.p. 51°), was obtained. Infrared analysis indicated no olefin present.

In a similar manner, *exo*-2-cyanobicyclo[2.2.1]heptene-5 (I) was saturated. *exo*-II was obtained, b.p. 81° (10 mm.) [lit.[12] b.p. 68° (12 mm.)]. Infrared analysis indicated no olefin.

2-Aminomethylbicyclo[2.2.1]heptene-5.—To a suspension of 3.8 g. (0.10 mole) of lithium aluminum hydride in 25 ml. of anhydrous ether was added dropwise with stirring a solution of 2.91 g. (0.024 mole) *endo*-2-cyanobicyclo[2.2.1]heptene-5 (I) in a little dry ether. The mixture was heated at reflux and stirred 22 hr. Excess lithium aluminum hydride was destroyed by addition of wet ether and the suspension of hydroxide was filtered. The filtrate was dried with anhydrous magnesium sulfate and solvent was removed under reduced pressure. Distillation of product under vacuum gave 2.32 g. (78.5%) of amine, b.p. 36–38° (1.1 mm.) [lit.[12] b.p. 71° (12 mm.)], and a brownish tar. Infrared analysis of the crude product indicated no nitrile present.

Similarly, *exo*-2-cyanobicyclo[2.2.1]heptene-5 (I) was reduced with lithium aluminum hydride to give *exo*-2-aminomethylbicyclo[2.2.1]heptene-5 in 71% yield, b.p. 33–36° (1.2 mm.) [lit.[12] b.p. 67–68° (12 mm.)].

Determination of Equilibria.—Samples of approximately 0.8–1.0 g. (0.007–0.008 mole) of *endo*- and *exo*-2-cyanobicyclo[2.2.1]-heptene-5 (I) and *endo*- and *exo*-2-cyanobicyclo[2.2.1]heptane (II) were separately dissolved in 100 ml. of anhydrous *t*-butyl alcohol (distilled over sodium, stored over molecular sieves). To these samples was added by pipet 10 ml. of 0.0324 *M* potassium *t*-butoxide (standardized by weight) in *t*-butyl alcohol. The base added was about 4 mole % with respect to the nitrile. These solutions were stirred at reflux for prolonged periods of time. Periodically, samples were extracted and quenched by adding dilute hydrochloric acid. The samples were then directly analyzed by v.p.c.

Kinetically Controlled Protonations of Anionic Intermediates.—Approximately 1-g. amounts (0.008 mole) of *endo*- and *exo*-2-cyanobicyclo[2.2.1]heptene-5 (I) and *endo*- and *exo*-2-cyanobicyclo[2.2.1]heptane (II) were separately dissolved in 10 ml. of dry ether and added to suspensions of excess potassium amide in liquid ammonia. In all cases, a yellow-green color was produced. These suspensions were stirred 20 min. and then were inversely added dropwise to stirred, saturated solutions of ammonium chloride in liquid ammonia. Ammonia was replaced by ether and the ethereal solutions were extracted with water. The ether layers were dried over anhydrous magnesium sulfate and ether was removed under reduced pressure. The isomerized nitriles were then analyzed by v.p.c.

Semiquantitative Estimation of Amidine (V) **Formation.**—To 75 ml. of a suspension of excess potassium amide in liquid ammonia was added 0.90 g. (0.0075 moles) of *endo*-nitrile I, dissolved in 10 ml. of anhydrous ether. The suspension was stirred for 15 min. and then 5 g. of ammonium chloride was added at one time. Then 75 ml. of dry ether was added and the ammonia was allowed to evaporate. The reaction mixture was extracted with a 50-ml. and then a 25-ml. portion of water. The ethereal layer was dried over anhydrous magnesium sulfate. After the ether was removed, an oily residue which remained was taken up in 5 ml. of acetone and analyzed by v.p.c.

A blank determination was carried out in which 0.90 g. of *endo*-nitrile I was treated in precisely the manner described above, except that the base was omitted. In these reactions it was assumed that only amidine and isomerized nitrile were obtained. Since amidine V could not be analyzed directly by v.p.c., it was assumed that amidine formation could be monitored by determining the disappearance of nitrile.

Analysis by v.p.c. indicated that the product mixture of the sample treated with base contained only 13% as much nitrile as the product mixture of the blank determination. This evidence strongly suggests that amidine is the major product of the reaction and that it may have been formed in 75–85% yield.

Rapid Neutralization of Anionic Intermediate III.—In a separate experiment 1 g. of pure *endo*-nitrile I was added to a suspension of excess potassium amide in liquid ammonia. A yellow-green color pervaded the suspension and, after only 20 sec., the suspension was added inversely to a saturated solution of ammonium chloride in liquid ammonia. The yellow-green color persisted until neutralization occurred. The neutralized mixture was worked up in the manner described and was analyzed directly by v.p.c. The isomerized mixture of nitriles contained 75% *endo*- and 25% *exo*-nitrile. Infrared analysis of the product mixture showed very weak absorption at 3500 cm.$^{-1}$ in the region of N—H stretching frequencies and very weak absorption at 1700–1620 cm.$^{-1}$, the region assigned to —C=N— stretching frequencies.[13] From these spectral considerations it was concluded that only trace amounts of amidine were formed.

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[10] D. J. Cash, unpublished results, Duke University.

[11] K. Alder, H. Krieger, and H. Weiss, *Ber.*, **88**, 144 (1955).

[12] K. Alder, K. Heimbach, and R. Reubke, *ibid.*, **91**, 1516 (1958).

[13] N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p. 284.