[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF PURDUE UNIVERSITY AND THE OHIO STATE UNIVERSITY]

# An Interpretation of the Chemical Behavior of Five- and Six-membered Ring Compounds[1]

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It is postulated that exo double bonds stabilize a 5-membered ring and destabilize a 6-membered ring. The generalization is made that reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in a 5-ring and to avoid the formation or retention of an exo double bond in a 6-ring. With few exceptions the generalization accounts for the available data on equilibria involving exo and endo double bond isomers and tautomers, olefin formation in the terpenes and related compounds, the stability of cyclic esters, lactones, hemiacetals and imides and, finally, the preference for furanose and pyranose structures in the sugars and sugar acids. The generalization is shown to be in accord with available thermochemical data. The theoretical implications are examined. The evidence favors the conclusion that an oxygen atom in a ring system can result in the same type of conformational effects as a methylene group.

## Introduction

Ring compounds, from small[2] to large,[3] exhibit numerous unusual chemical characteristics. In previous papers it was pointed out that a great deal of the chemistry dealing with reaction at one of the ring atoms can be systematized in terms of the change in internal strain accompanying the change in coördination number of the ring atom participating in the reaction (I-strain).[4,5] For small rings (3 to 4 ring members) the internal strain arises primarily from the distortions of the normal bond angles.[6] In 5- and 6- and larger rings the strain is attributed primarily to repulsion terms arising from unfavorable conformations.[7]

In the present paper we wish to suggest a simple generalization which serves to correlate many of the unusual chemical characteristics of rings of five or six members. The generalization includes such diverse substances as the cyclic ketones, lactones and lactals, cyclic imides, the sugar aldehydes and acids, exo and endo tautomers and isomers, and the terpene hydrocarbons.

An empirical approach will be utilized in developing the generalization. Following a survey of its applicability and utility, it will be shown to be consistent with available thermochemical data. Finally the theoretical implications will be explored.

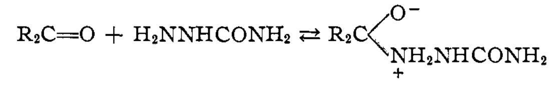
## The Generalization

Considerable data now exist to establish that reactions involving a change in coördination number of a ring atom from four to three proceed rapidly in cyclopentane and slowly in cyclohexane derivatives.[4] A typical example is furnished by the solvolysis of tertiary halides in aqueous (80%) ethanol.[5] (Only the rate-determining stage is indicated.)

$$RCl + H_2O \rightleftarrows R^+ + Cl^-$$

$k_1^{25°}$ (hr.$^{-1}$) 1.32 0.0106

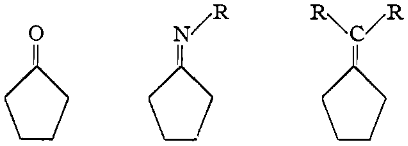
Conversely, reactions involving a change in coordination number from three to four proceed slowly in 5- and rapidly in 6-rings.[4] Typical data are furnished by the reaction of ring ketones with semicarbazide.[8] (Only the rate-determining stage is indicated.)



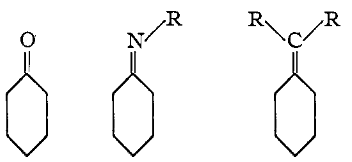
$$R_2C{=}O + H_2NNHCONH_2 \rightleftarrows R_2C{<}^{O^-}_{\overset{+}{N}H_2NHCONH_2}$$

$k_2^{25°}$ (l. mole$^{-1}$ sec.$^{-1}$) 0.0153 0.152

It follows that in the 5-membered ring the trigonal structure for one of the ring atoms is strongly favored over the tetrahedral arrangement, whereas the reverse is true in the 6-membered ring. Let us assume that this result will be generally true for all derivatives of 5- and 6-membered rings. In other words let us assume that an exo double bond in all 5-membered ring systems will be more stable toward changes involving loss of the exocyclic double bond than will the corresponding exo double bonds in 6-membered ring systems.



More stable, less reactive



Less stable, more reactive

Let us further assume that the difference in stability between double bonds exo to 5- and 6-membered rings is larger than the difference in stability between endo double bonds in these ring systems.[9] It follows that for a first approximation attention may be focused on the relative stabilities of the exo double bonds and the smaller

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[1] Chemical Effects of Steric Strains. IX.

[2] J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 3176, 5034 (1951).

[3] V. Prelog, *J. Chem. Soc.*, 420 (1950).

[4] H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951).

[5] H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952).

[6] A. Baeyer, *Ber.*, **18**, 2269, 2277 (1885).

[7] K. S. Pitzer, *Science*, **101**, 672 (1945); J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2483 (1947).

[8] F. Price and L. P. Hammett, *ibid.*, **63**, 2387 (1941).

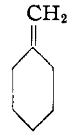
[9] This assumption will be justified later on the basis of thermochemical data.

difference in stabilities of the endo double bonds may be ignored.

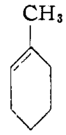
The postulate is therefore made that exo double bonds in 5-rings are relatively stable; exo double bonds in 6-rings, relatively unstable. The generalization follows: *reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in the 5-ring and to avoid the formation or retention of the exo double bond in the 6-ring systems.*

## Applications

**Equilibria Involving Exo and Endo Isomers.**—In the simple hydrocarbons, endocyclic are far more stable than exocyclic double bonds. Thus Wallach demonstrated in a number of investigations that alkylidine cyclanes (*e.g.*, I) are readily isomerized under the influence of acids to 1-alkylcyclenes (*e.g.*, II).[10]



I

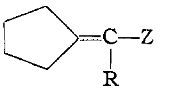


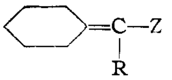
II

In order to obtain a measurable equilibrium between endo and exo isomers, it is necessary to introduce groups which can conjugate strongly with the exo double bond. A number of systems of this kind have been investigated by Dieckmann, Kon, Linstead and others.[11] Representative results are summarized in Table I.

TABLE I

PER CENT. OF EXO FORM AT EQUILIBRIUM[a]



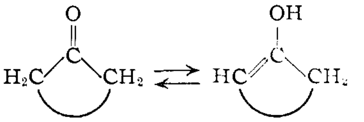


| Z | R = H | R = Me | R = H | R = Me |
|---|---|---|---|---|
| -$COCH_3$ | 84 (d) | 64 (i) | 30 (e) | *ca.* 0(i) |
| -$COCH_2CH_3$ | 85–90 (d) | . . | 30 (e) | . . |
| -$CO_2Et$ | 60 (f) | 88 (f) | 38 (e) | 5 (f) |
| -$CO_2H$ | 14 (g) | 38 (i) | 12 (h) | 32 (i) |

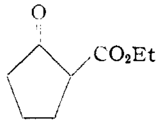
[a] References in parentheses refer to footnote 11.

Dieckmann[11a] and Kon[11bc] considered that the relative position of the equilibrium reflected a greater tendency for the accommodation of a double bond in the cyclohexane ring (the Dieckmann–Kon Rule). According to the generalization here proposed, the greater instability of the double bond exo to the cyclohexane ring is the more important factor. Justification for this view will be advanced later in the paper.

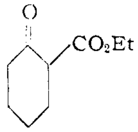
The relative tendency for cyclopentanone and cyclohexanone to exist in the enol form should also reflect the relative stabilities of the two exo double bonds.



It has been reported that in water the per cent. of enol in cyclohexanone is $20 \times 10^{-3}$ as compared to a value of $4.8 \times 10^{-3}$ for cyclopentanone.[12a] Similarly in the carbethoxy derivative (III, IV) the cyclopentane derivative exists primarily in the



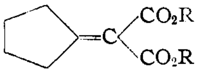
III



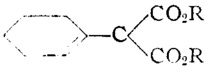
IV

form of the keto derivative (4.5% enol) whereas the cyclohexane compound exists primarily as the enol (76%)[11a]; in 95% ethanol the values are 5 and 57%.[12b]

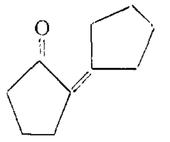
The generalization may be further illustrated by a consideration of the structures of the most stable forms of the malonic acids[13] and esters[11b] (V, VI), of the bimolecular condensation products of cyclopentanone (VII) and cyclohexanone (VIII),[11c] and by the behavior of the two acid chlorides (IX, X)[14] on distillation.



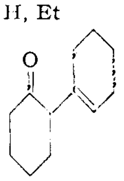
V
R = H, Et



VI
R = H, Et

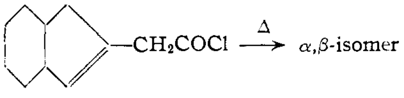


VII

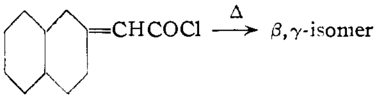


VIII

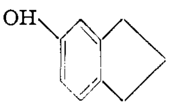
IX



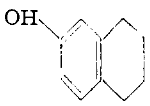
X



It is of interest that the generalization can be extended to predict the direction of operation of the Mills–Nixon Effect.[15] In the two phenol derivatives, the preferred forms are those with the double bonds exo to the 5-membered ring (XI) and endo to the 6-membered ring (XII).



XI



XII

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[10] O. Wallach, *Ber.*, **39**, 2504 (1906); O. Wallach, A. Fels and W. Lange, *Ann.*, **353**, 284 (1907); O. Wallach and K. Fleischer, *ibid.*, **353**, 304 (1907); O. Wallach and W. Lange, *ibid.*, **359**, 287 (1908); O. Wallach, E. Evans, J. B. Churchill, M. Rentschler and H. Mallison, *ibid.*, **360**, 26 (1908).

[11] (a) W. Dieckmann, *Ber.*, **55**, 2470 (1922); (b) G. A. R. Kon and E. A. Speight, *J. Chem. Soc.*, 2727 (1926); (c) G. A. R. Kon and J. H. Nutland, *ibid.*, 3101 (1926); (d) A. H. Dickins, W. E. Hugh and G. A. R. Kon, *ibid.*, 572 (1929); (e) G. A. R. Kon and R. P. Linstead, *ibid.*, 1269 (1929); (f) G. A. R. Kon, R. P. Linstead and G. W. G. Maclennan, *ibid.*, 2454 (1932); (g) A. A. Goldberg and R. P. Linstead, *ibid.*, 2343 (1928); (h) R. P. Linstead, *ibid.*, 2579 (1927); (i) G. A. R. Kon and R. S. Thakur, *ibid.*, 2217 (1930).

[12] (a) G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 656, 669 (1947); (b) G. Schwarzenbach, M. Zimmermann and V. Prelog, *ibid.*, **34**, 1954 (1951).

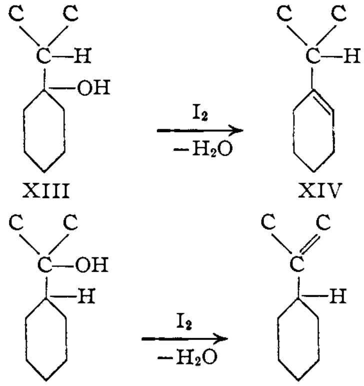
[13] W. E. Hugh and G. A. R. Kon, *J. Chem. Soc.*, 775 (1930).

[14] R. S. Thakur, *ibid.*, 2157 (1932).

[15] For a summary of the literature see L. F. Fieser in "Organic Chemistry," 2nd Ed., Vol. I., H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 134–142.

**Olefin Formation in Monocyclic Terpenes and Related Compounds.**—Elimination of the elements of water from dimethylisopropylcarbinol yields tetramethylethylene almost exclusively. In other words loss of the tertiary hydrogen occurs in preference to that of the primary. This is a typical example of elimination to give the more highly branched olefin (Saytzeff Rule).[16]

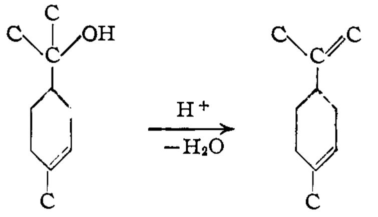
On the other hand, similar elimination of the elements of water from tertiary alcohols containing a cyclohexane ring (XIII, XV) appears to involve either the secondary hydrogen of the ring (XIV) or the primary hydrogen of the methyl groups (XVI).



XV XVI

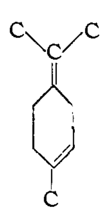
Thus Mosher observed that in the dehydration of XIII with iodine, there was obtained predominantly 1-isopropylcyclohexene (XIV); only 2.5% of isopropylidenecyclohexane was identified in the product. On the other hand, dehydration of XV resulted in the identification in the product of 53% of the isopropenyl derivative (XVI).[17]

Considerable additional evidence from work with terpene derivatives can be cited to support the conclusion that tertiary alcohols of this type resist the establishment of a double bond exo to the cyclohexane ring. Thus Flawitzky[18] observed that α-terpineol (XVII) was dehydrated by alcoholic sulfuric acid to form an optically active hydrocarbon identified[19] as limonene (XVIII).

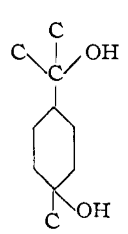


XVII XVIII

Optical activity was also retained when this dehydration was carried out with potassium hydrogen sulfate.[18] These observations indicate that the compound with the non-cyclic double bond (XVIII) is sufficiently stable to resist equilibration with the symmetrical terpinolene (XIX).



XIX

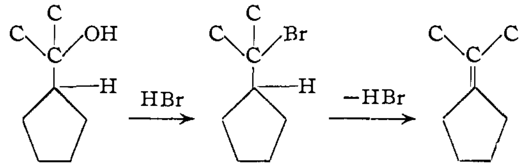


XX

Limonene (XVIII) of high optical purity can also be obtained as one product of the alkaline hydrolysis of the hydrogen phthalate ester of terpineol (XVII).[20] The dehydration of terpin hydrate (XX) with acetic anhydride at 200° is reported to give dipentene (*dl*-XVIII) in nearly quantitative yield[21]; terpin hydrate also gives dipentene as the main product upon dehydration at 180° with potassium acid sulfate.[22] Finally the dihydrochloride of dipentene is dehydrohalogenated to dipentene by the use of aniline.[23]

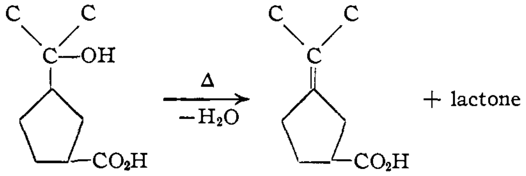
Unfortunately, there is much less work reported for comparable cyclopentane derivatives. Nevertheless the available data support the conclusion that elimination in compounds with the dimethylcyclopentylcarbinyl structure XXI occurs preferentially to give the isopropylidine derivatives XXIII.

Thus the carbinol XXI is reported to form the bromide XXII which spontaneously loses hydrogen bromide on distillation to form isopropylidenecyclopentane (XXIII).[24]



XXI XXII XXIII

Semmler[25] and Komppa[26] have reported similar results for a carboxylic acid derivative XXIV.



XXIV

It would be highly desirable to have quantitative data involving kinetically controlled reactions. However, even in the absence of such data the available results clearly support the proposed generalization. Elimination in cyclohexane derivatives occurs in such a manner as to avoid the formation of an exo double bond, whereas in related cyclopentane derivatives elimination to form the exo bond does not appear to offer similar difficulties.

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[16] For a recent review of directive effects in elimination reactions, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapt. VIII.

[17] W. A. Mosher, THIS JOURNAL, **62**, 552 (1940).

[18] F. Flawitzky, *Ber.*, **20**, 1956 (1887).

[19] E. Kremers, *Pharmaceut. Rev.*, **26**, 102 (1908); *Chem. Zentr.*, **80**, [I] 21 (1909).

[20] A. T. Fuller and J. Kenyon, *J. Chem. Soc.*, **125**, 2304 (1924).

[21] A. Ginsberg, *J. Russ. phys. chem. Ges.*, **29**, 249 (1897); *Chem. Zentr.*, **68** (II), 417 (1897).

[22] O. Wallach *Ann.*, **230**, 257 (1885).

[23] O. Wallach, *Ber.*, **40**, 600 (1907).

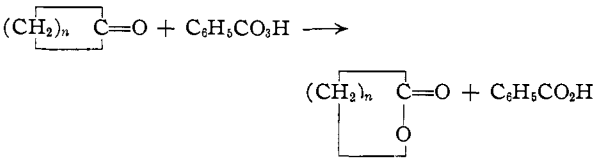
[24] S. S. Nametkin and D. M. Gabriadze, *J. Gen. Chem.* (*USSR*), **13**, 560 (1943).

[25] F. W. Semmler, *Ber.*, **42**, 246 (1909).

[26] G. Komppa, *Ann. Acad. Sci. Fennicae*, **Ser. A58, No. 2, 3** (1941); *C. A.*, **39**, 290 (1945).

**Ring Opening in Cyclic Esters, Lactones, Lactams and Imides.**—It is usually considered that 6-membered rings are more stable than 5-. However, this conclusion appears to be correct only in cases where no exo double bond is present in the molecules. In agreement with the proposed generalization, 6-membered rings with an exo double bond appear to be generally less stable and more susceptible to ring opening than 5-membered derivatives of this kind.

The reaction of cyclopentanone and cyclohexanone with perbenzoic acid may be an example of ring opening of this kind.

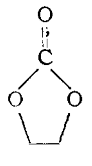


$$(CH_2)_n\,C{=}O + C_6H_5CO_3H \longrightarrow (CH_2)_n\,C{=}O + C_6H_5CO_2H$$

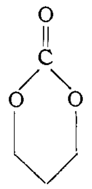
Friess has found that in this reaction cyclohexanone reacts at a rate some sixfold greater than cyclopentanone.[27] Unfortunately, the reaction is a complex one and it is uncertain to what extent the relative stabilities of the two rings affect the reaction rate.

More reliable data are offered by the ring opening reactions of cyclic esters, lactones, lactams, imides and related substances. In these compounds the relative ease with which the ring may be opened permits a clear-cut comparison of the relative stabilities of 5- and 6-membered rings with exo double bonds.

For example, the two cyclic esters, ethylene carbonate (XXV) and trimethylene carbonate (XXVI), differ markedly in their chemical behavior.



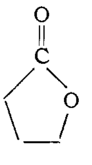
XXV



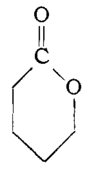
XXVI

Ethylene carbonate is highly stable and exists indefinitely as the monomeric 5-membered ring compound,[28] whereas trimethylene carbonate is readily converted under the influence of heat and catalysts into a linear polymer.[29] Similarly, the 6-membered ring compound, ethylene oxalate, is unstable and polymerizes on standing.[30]

The lactones behave similarly. The 5-membered derivative, γ-butyrolactone (XXVII) has been heated with catalysts at 80° for as long as 12 months without noticeable polymerization.[31] On the other hand, the corresponding 6-membered derivative, δ-valerolactone (XXVIII), slowly polymerizes on standing at room temperature.[32]



XXVII



XXVIII

Following the generalization it would be predicted that δ-valerolactone should be far more readily hydrolyzed than γ-butyrolactone. Sebelius observed that the δ-lactone hydrolyzed in basic solution at a rate 22 times that of the γ-derivative In acid solution the effect is even greater—the factor is 170.[33,34]

The prediction that the δ-lactones should be much less stable and more reactive than the corresponding γ-lactones can be supported by a wealth of data in the sugar derivatives. Typical data are summarized in Table II.[35]

TABLE II

EQUILIBRIUM AND RATE DATA FOR SUGAR LACTONES

| Lactone | Lactone at equil., % Gamma | Delta | Time for 25% hydrolysis at 18-22° (hr.) Gamma | Delta |
|---|---|---|---|---|
| Tetramethylglucono- | 13 | 5 | 75 | 1 |
| Tetramethylgalactono- | .. | 1.5 | 600 | 1 |
| Tetramethylmannono- | 89 | 36 | Never reached | 17 |
| Trimethylxylono- | 69 | 36 | 430 | 22 |
| Trimethylarabono- | 55 | 0.5 | 60 | 1 |

Replacement of the oxygen member of the ring by sulfur or nitrogen leads to additional results in excellent agreement with the generalization. Thus, a kinetic study of the corresponding thiolactones shows that at 25° δ-thiovalerolactone hydrolyzes at a rate some 50-fold greater than that of γ-thiobutyrolactone. The energy of activation for the 6-ring is 2.5 kcal. lower than that for the 5-ring derivative.[36] It is also of interest that the reactions of glutarimide and succinimide with aqueous sodium hydroxide show the 6-ring derivative to be the more reactive by a factor of 100.[37]

A possible exception to the generalization is offered by the behavior of the 5- and 6-membered lactams. Both of these substances are stable and show no tendency to undergo ring opening with polymerization.[38] Unfortunately, a search of the literature failed to reveal any quantitative data which could be used for a comparison of the relative

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[27] S. L. Friess, THIS JOURNAL, **71**, 2571 (1949).

[28] D. Vorländer, *Ann.*, **280**, 186 (1894).

[29] W. H. Carothers and F. J. Van Natta, THIS JOURNAL, **52**, 314 3292 (1930).

[30] W. H. Carothers, J. A. Arvin and G. L. Dorough, *ibid.*, **52**, (1930).

[31] W. H. Carothers, G. L. Dorough and F. J. Van Natta, *ibid.*, **54**, 761 (1932).

[32] F. Fichter and A. Beisswenger, *Ber.*, **36**, 1200 (1903).

[33] H. Sebelius, Dissertation, Lund, 1927. Unfortunately the original source was not available to us. The data are summarized in W. Hückel. "Theoretische Grundlagen der Organischen Chemie," 3rd Ed., Akademische Verlagsgesellschaft Geest und Portig K.-G., Leipzig, 1943, Vol. II, p. 562.

[34] N. Thon, Ed. "Tables of Chemical Kinetics Homogeneous Reactions," Circular of National Bureau of Standards, 1951, reports values of $k_2$ (l. mole$^{-1}$ sec.$^{-1}$) at 0°: 0.0196 for γ-butyrolactone and 0.00823 for δ-valerolactone. These values would be directly contrary to the prediction of the generalization. However, an examination of the original source, D. S. Hegan and J. H. Wolfenden, *J. Chem. Soc.*, 508 (1939), revealed that the "valerolactone" used in their experiments must have been the gamma isomer.

[35] H. D. K. Drew, E. H. Goodyear and W. N. Haworth, *ibid.*, 1237 (1927). See also S. R. Carter, W. N. Haworth and R. A. Robinson, *ibid.*, 2125 (1930).

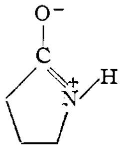
[36] E. Schjanberg, *Ber.*, **75**, 468 (1942).

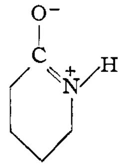
[37] S. S. G. Sircar, *J. Chem. Soc.*, 600, 1252 (1927).

[38] W. H. Carothers and G. J. Berchet, THIS JOURNAL, **52**, 5286 (1930).

reactivity of γ-butyrolactam with δ-valerolactam.[39]

It may be that the great tendency of the nitrogen atom to donate an electron pair to the carbon atom of the carbonyl group results in a considerable contribution of resonance structures such as XXIX and XXX. This effect might then stabilize the 5- and 6-rings and minimize the usual destabilizing effect of the exo double-bond in the 6-ring system.


XXIX


XXX

There is also the possibility that these compounds may exist in the tautomeric lactam structure.[40]

The available kinetic data on ring opening of 5- and 6-membered rings are summarized in Table III.

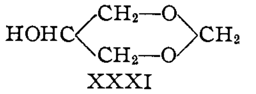
TABLE III

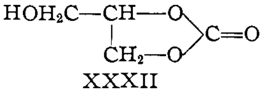
RATE CONSTANTS FOR THE RING OPENING REACTIONS OF FIVE- AND SIX-MEMBERED RINGS

| Compound | Rate constant[b] | | Reaction conditions | Ref.[a] |
|---|---|---|---|---|
| Cyclopentanone | $k_2 \times 10^5$ | 17.3 | Perbenzoic acid, moist chloroform, dark, 27° | 27 |
| Cyclohexanone | | 106 | | |
| γ-Butyrolactone | $k_2 \times 10$ | 8.3 | Water, OH⁻, 25° | 33 |
| δ-Valerolactone | | 183 | | |
| γ-Butyrolactone | $k_2 \times 10^4$ | 2.3 | Water, H+, 25° | 33 |
| δ-Valerolactone | | 397 | | |
| γ-Thiobutyrolactone | $k_2 \times 10^5$ | 1.21 | Water, H+, 25° | 36 |
| δ-Thiovalerolactone | | 58.8 | | |
| Succinimide | $k_2 \times 10^6$ | 3.87 | Water, OH⁻, 25° | 37 |
| Glutarimide | | 412 | | |

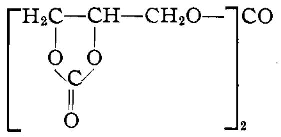
[a] Number refers to reference in footnote. [b] Units of $k_2$ = 1. mole$^{-1}$ sec.$^{-1}$.

**Ring Formation in Cyclic Esters, Lactones and Hemiacetals. Application of Generalization to Sugar Chemistry.**—According to the proposed generalization, we should expect quite different results in the reaction of formaldehyde, on the one hand, and carbonyl chloride, on the other, with a polyhydroxy compound such as glycerol. Formaldehyde would be expected to yield a cyclic formal which, in the absence of an exo double bond, should consist predominantly of the 6-membered ring derivative XXXI. Contrariwise, the carbonate from the acid chloride contains an exo double bond and therefore should preferentially form a 5-membered derivative XXXII.


XXXI


XXXII

Some evidence that this is the case is available in the literature. It is reported that in the reaction of formaldehyde with glycerol the 1,2- and 1,3-formals (XXXI) are formed in a ratio of 40:60.[41] The reaction product of glycerol and carbonyl chloride has been shown to have the structure (XXXIII), with the carbonate group forming a 5-membered ring.[42]


XXXIII

Far more definite data are available from investigation of the reactions of these two reagents with the sugars.

Sugars react with formaldehyde to yield mono- or dimethylene derivatives.[43] The structure of these compounds was investigated by Hudson and his co-workers[44] and the conclusion was reached that formaldehyde condenses most readily with *cis* secondary hydroxyl groups located 1,3 to each other. For example, the formal of *d*-sorbitol is considered to have the structure: 1,3;2,5;4,6-trimethylene *d*-mannitol. Other simple aldehydes, such as acetaldehyde and benzaldehyde, behave similarly. Thus benzaldehyde reacts with glucose and with methyl α- and β-glucopyranosides to form the 4,6-benzylidene derivative.[45,46]

In marked contrast to the preferred reaction of formaldehyde with 1,3-situated hydroxyls, carbonyl chloride reacts preferentially with 1,2-hydroxyls.[47] Thus the structures assigned are: glucofuranose, 1,2;5,6-dicarbonate; mannofuranose, 2,3;5,6-; galactopyranose, 1,2;3,4-; fructopyranose, 1,2;4,5-; arabinopyranose, 1,2;3,4.[48]

The I-strain concept[4,5] offers an explanation for the marked difference in behavior of the furanose and pyranose forms of the sugars. Under ordinary circumstances the sugars exist in solution as the hemiacetals in an equilibrium mixture of ring structures, with the pyranose form greatly predominating. However, treatment of the mixture with methanol and hydrogen chloride under mild conditions results in the preferential formation of the

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(39) It is of interest to point out that the 4-membered derivative, β-propiolactam, is much more reactive toward alkaline hydrolysis than the 5-ring derivative, γ-butyrolactam, or the corresponding open-chain derivative, N-methylacetamide [R. W. Holley and A. D. Holley, *ibid.*, **71**, 2129 (1949)]. This high reactivity of a 4-membered ring compound containing a carbonyl group is in agreement with the predictions of the I-strain concept (ref. 4, 5).

(40) G. W. Wheland, "Advanced Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 617–621.

(41) H. Hibbert and N. M. Carter, THIS JOURNAL, **50**, 3120 (1928). J. D. van Roon [*Rec. trav. chim.*, **48**, 173 (1929)], attempted to determine the composition of the equilibrium mixture. However, he was unable to obtain quantitative data and could only conclude that the isomer XXXI was present in the greater amount at all temperatures.

(42) R. Scheuble and A. Hochsteller, German Patent, 252,758; *Chem. Zentr.*, **83**, [II] 1756 (1912); A. Contardi and A. Ercoli, *Gazz. chim. ital.*, **64**, 522 (1934); *C. A.*, **29**, 1392 (1935).

(43) M. Schulz and B. Tollens, *Ann.*, **289**, 20 (1896); B. Tollens, *Ber.*, **32**, 2585 (1899).

(44) A. T. Ness, R. M. Hann and C. S. Hudson, THIS JOURNAL, **66**, 665, 670 (1944).

(45) L. Zervas, *Ber.*, **64**, 2289 (1931); J. C. Irvine and J. P. Scott, *J. Chem. Soc.*, **103**, 575 (1913); H. Ohle and K. Spencker, *Ber.*, **61**, 2387 (1928).

(46) It is well known that acetone reacts preferentially with hydroxyls located on adjacent carbon atoms to form the 5-membered ring isopropylidine derivatives. This difference between acetone, on the one hand, and formaldehyde and other simple aldehydes on the other, is probably the result of steric strains. A six-membered isopropylidine derivative would have a *gem*-dimethyl in a homomorphic cyclohexane structure. One methyl group must then be in the polar position. Presumably this results in sufficient destabilization to render the 5-ring preferable.

(47) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 2796 (1929); *ibid.*, 151 (1930).

(48) For a concise summary of the cyclization and other pertinent reactions of the sugars see W. W. Pigman and R. M. Goepp, "Chemistry of the Carbohydrates," Academic Press, Inc., New York, 1948.

methyl furanosides. On more extended treatment the methyl pyranoside is obtained.[48]

It was previously pointed out that the solvolysis of 1-methyl-1-chlorocyclopentane proceeds at a rate some 100-fold greater than that of the corresponding cyclohexane derivative.[4,5] The greater reactivity of the 5-ring derivative was accounted for in terms of the I-strain concept. Presumably the same factors operate to render the 5-membered furanose form far more reactive than the pyranose form. Therefore, in the initial stages of the reaction the furanose derivative will react preferentially.[49] At equilibrium, however, with no exo double bond, the pyranoside will be the more stable and will constitute the bulk of the product.

In a recent study Hurd and Saunders examined the ring-chain tautomerism of hydroxy aldehydes.[50] They observed that both γ-hydroxybutyraldehyde and δ-hydroxyvaleraldehyde exist in aqueous dioxane solution predominantly in the ring hemiacetal form, in contrast to the higher members, which exist predominantly as the free aldehyde. In this system also there is no exo double bond and the 6-ring is evidently more stable than the 5-ring. At 25° there is present 11.4% of the γ-hydroxybutyraldehyde in the equilibrium mixture as compared to 6.1% of the δ-hydroxyvaleraldehyde.

In the corresponding hydroxy acids, the situation is reversed. At 25° an aqueous solution of γ-hydroxybutyric acid contains 27.2% of the free acid, whereas δ-hydroxyvaleric acid contains 91% of the free acid.[33] The data are summarized in Table IV.

TABLE IV

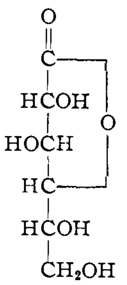
EQUILIBRIA DATA FOR HYDROXY ALDEHYDES AND ACIDS

| Compound | Open chain at equil., % | Equil. constant,[a] $K_{eq.}$ |
|---|---|---|
| γ-Hydroxybutyraldehyde[b] | 11.4 | 7.77 |
| δ-Hydroxyvaleraldehyde[b] | 6.1 | 15.4 |
| γ-Hydroxybutyric acid[c] | 27.2 | 2.68 |
| δ-Hydroxyvaleric acid[c] | 91.0 | 0.099 |

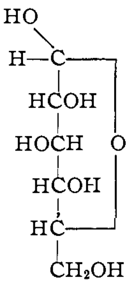
[a] $K_{eq.}$ = [ring]/[open-chain]. [b] Aqueous dioxane (75% dioxane), 25°. [c] Water, 25°.

We therefore observe that in agreement with the generalization the 6-membered ring is preferred in the hemiacetal with no exo double bond, whereas the 5-membered ring is preferred in the lactone with its exocyclic carbonyl double bond.

We are now in position to rationalize, in terms of the proposed generalization, a long-standing anomaly in sugar chemistry. Both the sugar acids and the sugar aldehydes tend to exist naturally in the ring form. However, it has been quite puzzling that the lactones from the sugar acid and the hemiacetal from the sugar aldehyde prefer to form rings of different sizes. To quote from Pigman and Goepp: "Oddly enough, the 1,4- or gamma lactones are the more stable, while the 1,5- or pyranose sugars are the favored form."[51] Again we see, in accordance with the generalization, that the sugar lactone, with its exo double bond, prefers the 5-membered ring (XXXIV), whereas the hemiacetal, with no exo double bond, favors the 6- (XXXV).



XXXIV



XXXV

## Discussion

**Thermochemical Data.**—The proposed generalization has been developed primarily as an empirical correlation based upon chemical observations. It is of interest to examine the available thermochemical data to ascertain what support, if any, they offer to the generalization.

Pertinent thermochemical data are summarized in Table V.

TABLE V

THERMOCHEMICAL DATA FOR CYCLOPENTANE AND CYCLOHEXANE DERIVATIVES

| | $\Delta H_f$ (gas, 25°) | $\Delta H_H$ (gas, 82°)[a] | Increment[b] $\Delta H_f$(6-) − $H_f$(5-) |
|---|---|---|---|
| Cyclopentane | −18.46[c] | | |
| Cyclohexane | −29.43[c] | | −11.0 |
| Cyclopentanol | −59.3[d] | | |
| Cyclohexanol | −70.5[d] | | −11.3 |
| Cyclopentanone | −47.2[e] | −12.50[f] | |
| Cyclohexanone | −55.6[e] | −15.42[f] | − 8.4 |
| Cyclopentene | 7.87[g] | −26.92[h] | |
| Cyclohexene | − 1.70[g] | −28.59[i] | − 9.6 |

[a] $\Delta H_H$ = heat of hydrogenation. [b] Difference between heat of formation values for the cyclopentane and cyclohexane derivatives. The values should be compared with the increment per $CH_2$ group for the normal paraffins, −4.926 kcal. [E. J. Prosen and F. D. Rossini, *J. Research Natl. Bur. Standards*, **34**, 263 (1945)]. [c] "Selected Values of Properties of Hydrocarbons" Circular of the National Bureau of Standards, C461, U. S. Printing Office, Washington, D. C., 1947. R. Spitzer and H. M. Huffman, THIS JOURNAL, **69**, 211 (1947). [d] G. S. Parks, J. R. Mosley and P. V. Peterson, Jr., *J. Chem. Phys.*, **18**, 152 (1950). [e] Calculated by E. J. Prosen, National Bureau of Standards, from heats of combustion of cyclopentanol and cyclohexanol[d] and heats of hydrogenation of the corresponding ketones, with estimated or literature values for heats of vaporization. Private communication from E. J. Prosen. [f] J. B. Conn, G. B. Kistiakowsky and E. A. Smith, THIS JOURNAL, **61**, 1868 (1939). [g] M. B. Epstein, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **42**, 379 (1949). [h] M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, THIS JOURNAL, **59**, 831 (1937). [i] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *ibid.*, **58**, 146 (1936).

The difference in the heats of formation of cyclohexane and cyclopentane is −11.0 kcal. as compared to the incremental value per $CH_2$ group of −4.9 observed in the normal paraffins. The increment in cyclohexanol and cyclopentanol, −11.3 kcal., is approximately the same, whereas in the corresponding ketones that observed, −8.4 kcal., is considerably closer to the paraffin value. The

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(49) P. A. Levene, A. L. Raymond and R. T. Dillon, *J. Biol. Chem.*, **95**, 699 (1932).

(50) C. D. Hurd and W. H. Saunders, Jr., THIS JOURNAL, **74**, 5324 (1952).

(51) W. W. Pigman and R. M. Goepp, ref. 48, p. 10.

difference in the incremental values observed in these cyclic hydrocarbons and the paraffins has been attributed to strains in the cyclopentane molecule resulting from unfavorable conformations.[7] Presumably these strains are not altered by replacing one of the hydrogen atoms by an hydroxyl group. However, the smaller increment observed in the ketones suggests that the replacement of two hydrogen atoms in the hydrocarbon by the carbonyl oxygen must either reduce the strain in the 5-ring derivative, or increase it in the 6-ring compound, or both.

The argument may be made clearer by another approach. The difference in the heats of formation of cyclohexane and cyclohexanol is 41.2 kcal. This is practically identical with the difference between cyclopentane and cyclopentanol, 40.8 kcal. Thus replacement of one of the hydrogens in the hydrocarbon by an hydroxyl group has not altered the strains significantly. On the other hand, the difference between cyclohexane and cyclohexanone is 26.17, as compared to 28.74 for the corresponding cyclopentane derivatives. Therefore, there has been a change of approximately 2.6 kcal. in strain energy accompanying the introduction of the carbonyl group into the parent hydrocarbons.

The change in strain could arise from a decrease in strain in cyclopentanone over that present in cyclopentane, or an increase in strain in cyclohexanone over that present in the strain-free hydrocarbon, or both. That this last conclusion must be the case is suggested by similar data for open-chain compounds. The difference between propane (−24.82)[52a] and acetone (−51.8)[52b] is 27.0, a value intermediate between the quantities previously calculated of 26.2 and 28.7 for the cyclopentane and cyclohexane derivatives, respectively. The same conclusion is reached in a comparison of the values of $\Delta H_{298}$ obtained from equilibrium data[53] for the reaction

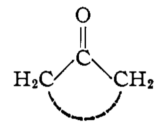
$$>C{=}O + H_2 = >CHOH$$

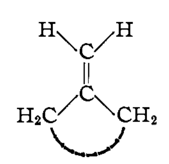
Here also the values for the open chain compounds fall between the corresponding values for the cyclopentyl and cyclohexyl systems. The values are: acetone, −13.2 kcal.; 2-butanone, −13.0; cyclopentanone, −12.3; cyclohexanone, −15.2.

It was proposed earlier in the paper that the difference between the stabilities of exo double bonds in the 6- and 5-membered rings is probably greater than that for endo double bonds in these rings. Good heat of hydrogenation data are available for cyclopentene and cyclohexene (Table V).

Unfortunately, good modern thermochemical values are not available for methylenecyclopentane and methylenecyclohexane. In the absence of such data we may take the difference between the heats of hydrogenation of cyclopentanone and cyclohexanone as a lower limit to the difference in the heats of hydrogenation of the methylene derivatives.

In comparing the two cyclic structures





we should expect some interaction between the two hydrogen atoms of the double-bonded methylene groups and the two equatorial hydrogen atoms in the $\alpha$-position of the cyclohexane ring. The existence of such interaction is suggested by the data of Roth and his co-workers[54] in Table VI.

TABLE VI

HEATS OF COMBUSTION OF ISOMERIC UNSATURATED COMPOUNDS OF THE CYCLOHEXANE SERIES

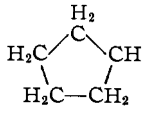
| $R_1$ | $R_2$ | Heat of combustion of liquid at constant vol., kcal./mole | | Increment $\Delta H$(exo) − $\Delta H$(endo) | Ref. |
|---|---|---|---|---|---|
| H | H | −1051.0 | −1047.9 | −3.1 | 53a |
| $CH_3$ | H | −1207.1 | −1203.4 | −3.7 | 53ab |
| $CH_3$ | $CH_3$ | −1348.1 | −1338.5 | −9.6 | 53c |

The corresponding interaction in the cyclopentane ring should be smaller. Therefore this interaction should result in an increased instability of the exo double bond of the methylene derivatives as compared to that of the carbonyl group. The treatment here presented will therefore serve only to set a lower limit to the relative instability in the two ring system of the exo *versus* endo double bonds.

We observe that the difference in the heats of hydrogenation of the two cyclic olefins (Table V) is 1.67 kcal. The difference in the heats of hydrogenation of the two cyclic ketones is 2.9 kcal. We have suggested reasons for believing that the difference will actually be considerably greater than 2.9 kcal. in the methylene compounds. However, even without allowing for this further increase, the calculation fully justifies the neglect, as a first approximation, of the differences in stability of endo bonds in the two cyclic systems in favor of the larger difference in stability of the exo double bonds

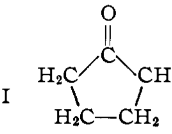
**Theoretical Implications.**—The effect of the carbonyl group in stabilizing the cyclopentane ring is attributed to a decrease in the number of bond oppositions.[7] In the idealized planar structure for cyclopentane the number of bond oppositions will be 10 (XXXVI). In cyclopentanone the carbonyl group will be in the staggered conformation with respect to the two alpha methylene groups (XXXVII). The number of bond oppositions will therefore be reduced to 6. Although the situation will be altered by readjustment of the structure to

XXXVI



10 bond oppositions
10 kcal. strain
(idealized planar model)

XXXVII



6 bond oppositions
6 kcal. strain
(idealized planar model)

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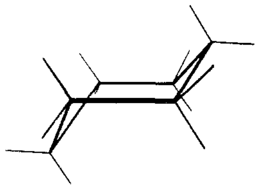
(52) (a) E. J. Prosen and F. D. Rossini, *J. Research Natl. Bur. Standards*, **34**, 263 (1945); (b) K. A. Kobe, R. H. Harrison and R. E. Pennington, *Petrolum Refiner*, **30**, 119 (1951).

(53) A. H. Cubberley and M. B. Mueller, THIS JOURNAL, **68**, 1149 (1946); *ibid.*, **69**, 1535 (1947). See also M. A. Dolliver, T. L. Gresham and G. B. Kistiakowsky, *ibid.*, **60**, 440 (1938).

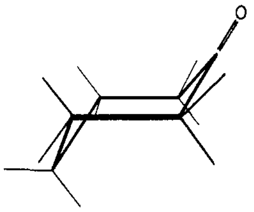
(54) (a) W. A. Roth, *Z. Elektrochem.*, **17**, 791 (1911); (b) W. A. Roth and Ellinger, Landolt-Börnstein, Hauptw., Vol. II, pp. 1587–1611; (c) W. A. Roth and Ellinger, Landolt-Börnstein, Suppl. I, p. 868.

a somewhat less strained, non-planar structure,[7] there is little reason to doubt that the ring ketone will continue to be stabilized relative to the hydrocarbon by the reduction in the number of unfavorable conformations.[55]

The parent cyclohexane structure is nicely staggered with no bond oppositions (XXXVIII). Introduction of a trigonal atom alters this nice symmetrical arrangement and introduces some measure of unfavorable conformations (XXXIX).[56]



XXXVIII



XXXIX

According to this physical interpretation, the introduction of the carbonyl group stabilizes the cyclopentane ring and destabilizes the cyclohexane ring largely by altering the number and degree of unfavorable conformations involving the two alpha methylene groups. We have observed, however, that the effect is not restricted to carbon rings with alpha methylene groups. The lactones with but one alpha methylene group show the effect. Ethylene and trimethylene carbonates (XV, XVI), *with no alpha methylene groups*, exhibit the same effect of ring size on stability as that of the corresponding carbocyclic derivatives.

This observation suggests that the two alpha methylene hydrogen atoms are not essential for the production of these strained conformational effects. In the carbonates the two lone pairs of each oxygen atom must produce a conformational effect similar to that produced by the two carbon-hydrogen bonds in the parent structure.

A comparison of the potential barrier to rotation in dimethyl ether with that in propane should offer a suitable test of this proposal. The potential barrier in the oxygen derivative is reported to be 2700 cal.,[57] not significantly smaller than the value of 3400 cal. reported for propane.[58,59]

**Conclusion.**—In conclusion it may be stated that a large number of different experimental observations, with remarkably few exceptions, are satisfactorily correlated with the aid of the proposed generalization. The generalization is in accord with the available thermochemical data. Moreover, it appears to have a sound theoretical basis. A systematic search for apparent exceptions and experimental study of the many predictions should provide a rigorous test of its adequacy and utility.

**Acknowledgment.**—We wish to acknowledge the invaluable assistance of E. J. Prosen of the National Bureau of Standards in assembling and interpreting the thermochemical data.

(55) In this treatment it is assumed that in the staggered arrangement the interaction of the doubly-bonded carbonyl group with the two alpha methylene groups will be quite small and not significantly greater than the interactions which occur with a singly-bonded group in the same position. Justification for this view is offered by a comparison of the potential barrier in acetone, 1400 cal./mole with that in propane, 3300 cal./mole. Thus replacement of the two hydrogen atoms in the methylene groups by a doubly-bonded oxygen atom has decreased the potential barrier by 1900 cal., or 950 cal. per carbon-hydrogen bond. This is practically identical with the estimated barrier per carbon-hydrogen bond in ethane. [For a summary of the available data on potential barriers see J. A. McCoubrey and A. R. Ubbelohde, *Quart. Rev.*, **5**, 364 (1951)].

(56) For a recent discussion of the conformations of substituted cyclohexanones, see E. J. Corey, THIS JOURNAL, **75**, 2301 (1953).

(57) F. A. French and R. S. Rasmussen, *J. Chem. Phys.*, **14**, 389 (1946).

(58) K. S. Pitzer, *ibid.*, **12**, 310 (1944).

(59) A similar comparison of the potential barrier in methanol with that in ethane appears to involve difficulties arising from the highly ionic character of the hydrogen-oxygen bond and its resulting strong tendency to form hydrogen bonds. See W. Weltner, Jr. and K. S. Pitzer [THIS JOURNAL, **73**, 2606 (1951)] for a discussion of the barrier in methanol and pertinent literature references.

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# Preparation and Reactions of Perfluoroalkyllithiums[1]

BY O. R. PIERCE, E. T. McBEE AND G. F. JUDD

RECEIVED SEPTEMBER 21, 1953

The conditions of formation of heptafluoropropyllithium and trifluoromethyllithium by interchange with butyl- or methyllithium have been studied and an over-all yield of the perfluoropropyllithium reagent of 77% was obtained as shown by hydrolysis to heptafluoropropane. Reaction of this reagent with carbonyl compounds having an active hydrogen led to aldol-type products as well as the expected addition product, the best yield occurring with propionaldehyde (50%) and the lowest, benzophenone (0%). The scope and limitations of the reactions are discussed.

## Introduction

Earlier attempts to prepare a lithium reagent directly from lithium and iodotrifluoromethane[2] were unsuccessful. Studies involving the direct formation of perfluoropropyl Grignard reagents,[3-6] however, have demonstrated the existence of a fluorine-containing organometallic compound and such materials as carbon dioxide, acetone, acetaldehyde and formaldehyde have reacted with

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(2) R. N. Haszeldine, *J. Chem. Soc.*, 2952 (1949).

(3) A. L. Henne and W. C. Francis, THIS JOURNAL, **73**, 3518 (1951).

(4) *Ibid.*, **75**, 992 (1953).

(5) R. N. Haszeldine, *J. Chem. Soc.*, 3423 (1952).

(6) O. R. Pierce and M. Levine, THIS JOURNAL, **75**, 1254 (1953).