It has been proposed that certain salt effects may be accounted for in terms of complex formation between SH^+ and anions.[33] If an anion replaced a molecule of water in the solvent shell around Ac-ImH^+, to form an ion pair, it would be expected that this complex would undergo hydrolysis at a reduced rate. When the ion concentration becomes sufficiently high that all of the substrate is converted to this species, the rate should level off at a value corresponding to the rate of solvolysis of the ion pair. The further decrease in concentrated acid solutions, which occurs at an H_2O/H^+ ratio of less than 4, may reflect a further replacement of water in the hydration shell, as well as a marked decrease in the availability of water for nucleophilic attack and proton transfer. In these concentrated electrolyte solutions a large fraction of substrate molecules would be expected to be adjacent to anions purely on a statistical basis, as the concentration of anions becomes comparable to the concentration of free water molecules, and even weak electrostatic attractive forces should increase this fraction considerably. The faster rates observed with more basic anions are consistent with the expected greater ability of such ions to aid proton transfer in the transition state by general base catalysis.

Acknowledgments.—We are grateful to the National Cancer Institute of the National Institutes of Health (Grant C-3975) and to the National Science Foundation for financial support. This investigation was carried out by S. M. during the tenure of a Postdoctoral Fellowship from the Division of General Medical Sciences, United States Public Health Service.

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[33] (a) A. R. Olson and T. R. Simonson, *J. Chem. Phys.*, **17**, 1167 (1949); (b) N. N. Lichtin and K. N. Rao, *J. Am. Chem. Soc.*, **83**, 2417 (1961).

[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, MEAD JOHNSON RESEARCH CENTER, MEAD JOHNSON AND CO., EVANSVILLE 21, IND.]

Absolute Configuration of Cycloheximide from Thermal Degradation[1]

BY BERNARD C. LAWES

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Thermal degradation of cycloheximide afforded, in high optical purity, (+)-2,4-dimethylcyclohexanone, different from but epimeric with (−)-2,4-dimethylcyclohexanone from alkaline degradation of cycloheximide. As a consequence, cycloheximide was shown to possess a *trans*-2,4-dimethyl system of the same absolute configuration as the less stable epimeric ketone from thermal degradation. The above, and other reported data permitted a tentative assignment of the glutarimide-containing group at C-6 as being *trans* with respect to the methyl group at C-2. Thermal degradation of cycloheximide also afforded some glutarimide-β-acetaldehyde, and, as an example of a thermally induced reverse aldol reaction, may proceed *via* a cyclic transition state.

Cycloheximide, an antibiotic from streptomycin-producing strains of *Streptomyces griseus*, was first reported[2] as a crystalline solid in 1947. The antibiotic is best known for its action against a variety of yeasts and molds, and as a result has many applications as an agricultural chemical.[3] The degradation work of Kornfeld, Jones and Parke[4] has shown the structure of cycloheximide to be β-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-glutarimide (I), and although this structure has not been confirmed by total synthesis, the simple dehydration product has recently been synthesized in these laboratories.[5]

Although the structure is well established, the stereochemistry of cycloheximide has remained elusive, and difficulties, no doubt, arise from the lack of conformational rigidity of a simple cyclohexyl ring, and from the chemical lability of the molecule, both to degradation and possible epimerization. It has been shown that cycloheximide is degraded by alkali, presumably through a reverse aldol reaction, to yield an optically active ketone, 2,4-dimethylcyclohexanone.[4] Recently the absolute configuration of the asymmetric center at C-4 of this ketone has been related to D-glyceraldehyde.[6] Since the degradation should not have affected the configuration of this center, it is expected that the absolute configuration of the C-4 center in cycloheximide itself would also be related to D-glyceraldehyde.[6] The foregoing would say nothing of the relative stereochemistry of the other asymmetric centers in cycloheximide, since the 2,4-dimethylcyclohexanone formed in hot alkali[4] contains a potentially labile α-methyl group.

It has now been demonstrated in these laboratories that cycloheximide can undergo, in addition to an alkaline degradation, a thermal degradation to break the β-ketol structure in the molecule. At a temperature of 200°, and above, a volatile liquid was smoothly distilled from cycloheximide, and this liquid *was different* from that obtained by alkaline degradation. This thermal product, obtained in greater than 50% yield, was shown to be a ketone closely related to the alkaline degradation ketone because of the virtual identity of infrared absorption below 7.0 μ, the similarity of the ketone-type ultraviolet absorption and the closeness of the boiling points, but the differences in optical rotations,

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[1] Presented in part at the 139th Meeting of the American Chemical Society, St. Louis, Mo., March 30, 1961.

[2] B. E. Leach, J. H. Ford and A. J. Whiffen, *J. Am. Chem. Soc.*, **69**, 474 (1947); referred to as actidione by these authors.

[3] W. Klomparens, J. H. Ford, C. L. Hamner and G. A. Boyack, Abstracts of Papers, 132nd Meeting, American Chemical Society, New York, N. Y., Sept., 1957, p. 24-A.

[4] E. C. Kornfeld, R. G. Jones and T. V. Parke, *J. Am. Chem. Soc.*, **71**, 150 (1949).

[5] B. C. Lawes, *ibid.*, **82**, 6413 (1960).

[6] E. J. Eisenbraun, J. Osiecki and C. Djerassi, *ibid.*, **80**, 1261 (1958).

carbonyl derivatives, and infrared absorption above 7.0 μ clearly showed the two materials to be different. Moreover, both ketones were clearly shown to be epimers, because the ketone from thermal degradation could be isomerized under mild treatment with alkali to afford, in 79% yield, material which was identical with the 2,4-dimethylcyclohexanone obtained from alkaline degradation of cycloheximide. In addition to a comparison of physical constants, identity of the two materials was firmly established by a comparison of the semicarbazones and thiosemicarbazones. The over-all scheme is shown in Chart I and a comparison of the properties of the epimeric ketones, after one distillation, is shown in Table I. It is noted that the rotation of +4.3 for material from the alkaline degradation is lower than reported (+11.52).[4] As reported, however, the alkaline degradation was carried out by distilling the ketone from hot alkali, but in the present study the alkaline degradation was carried out at about 0°. Thus the alkali lability of 2,4-dimethylcyclohexanone to epimerization, and the temperature dependence of equilibrium constants could account for the difference.

TABLE I

PROPERTIES OF EPIMERIC 2,4-DIMETHYLCYCLOHEXANONES FROM CYCLOHEXIMIDE

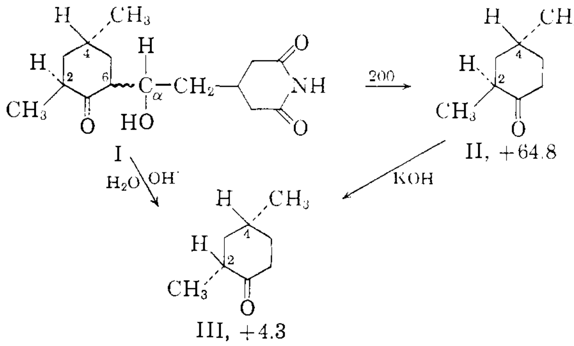
Properties	Alkaline degradation	Thermal degradation
B.p., °C. (766 mm.)	176.3	178.7
$n^{22}\mathrm{D}$	1.4442	1.4488
d^{25}	0.9028	0.9065
$[\alpha]^{25}\mathrm{D}$ (neat)	−1.8°	+57.7°
$[\alpha]^{24}\mathrm{D}$ (EtOH)	+4.3°	+64.8°
$\lambda_{\max}^{\mathrm{EtOH}}$ (ϵ)	283 mμ (19.7)	286 mμ (22.5)
Cotton effect	$[\alpha]_{297.5}$ −278°[6]	$[\alpha]_{315}$ +770°

Both degradation ketones, as represented in Table I, were of high optical purity as indicated by derivative formation and distillation data. Furthermore, a quantitative measure of optical purity was conveniently furnished by vapor phase chromatography. The volatile ketone from either degradation scheme was shown to consist of a mixture of two epimers, the major component from alkaline degradation occurring to the extent of 89% and the major component from thermal degradation occurring to the extent of 93%.

Even though either degradation scheme afforded an epimer of 2,4-dimethylcyclohexanone contaminated with a small amount of the principal epimer of the other degradation scheme, for simplicity each degradation product will be referred to as a single epimer, namely (−)-2,4-dimethylcyclohexanone as the product from alkaline degradation, and (+)-2,4-dimethylcyclohexanone as the product from thermal degradation. It was possible, nevertheless, to obtain indirectly the optical rotations for the pure epimers by consideration of the rotations of mixtures of the epimers as a function of composition (see Experimental). Thus, $[\alpha]^{24}\mathrm{D}$ −3.2° and $[\alpha]^{24}\mathrm{D}$ +70.0°, in ethanol, should represent the rotations for optically pure (−)-2,4-dimethylcyclohexanone and (+)-2,4-dimethylcyclohexanone, respectively.

As a result of the dual scheme (Chart I), it was possible to deduce the stereochemistry, and as a result of earlier work[6] and optical rotatory dispersion, the absolute configuration of both methyl substituents of cycloheximide. Of the two epimers of 2,4-dimethylcyclohexanone, the one from alkaline degradation (and from epimerization of the thermally produced product) is undoubtedly the more stable, and it is interesting to note that such is borne out by the physical constants as related to von Auwer's[7] empirical rule concerning *cis–trans* isomers, as restated by Allinger.[8] As predicted for the less stable isomer, the thermal ketone had the higher boiling point, higher index of refraction and higher density. The more stable (−)-2,4-dimethylcyclohexanone (III) would be expected to possess the *cis* configuration since a diequatorial conformation of the methyl groups would be possible.[9] As a consequence, the epimeric ketone, (+)-2,4-dimethylcyclohexanone (II), must possess the *trans* configuration and, accordingly, for such a 1,3-disubstituted cyclohexyl system presumably in the chair form, one of the methyl groups must be axial and the other must be equatorial.[9] In view of the conformational mobility of such systems, it cannot be said which of the methyl groups is axial, and it is quite likely that a mixture of the chair conformers exists.

CHART I



The *trans* nature, and also the absolute configuration of (+)-2,4-dimethylcyclohexanone was nicely corroborated by the rotatory dispersion curve in methanol. The *cis*-ketone, (−)-2,4-dimethylcyclohexanone, is reported[6] to exhibit a negative Cotton effect, with a trough at 297.5 mμ having a specific rotation of −278°. The epimeric *trans*-ketone, however, was found to exhibit a strong Cotton effect of opposite sign, as a peak at about 315 mμ having a specific rotation of +770°. The Octant rule[10] for cyclohexanones predicts that 4-substituents, and 2- or 6-equatorial substitutents would make "substantially no contribution"[10] to the rotatory dispersion curve, whereas 2- or 6-axial substituents would make significant positive or negative contributions. Thus the strongly positive Cotton effect suggests that a high percentage of the thermally produced ketone, relative to its epimer at least, exists as the 2-axial methyl conformer IIa. This would clearly indicate a *trans* configuration. Further, a positive Cotton effect indicates[10] that the absolute configuration of this ketone is represented

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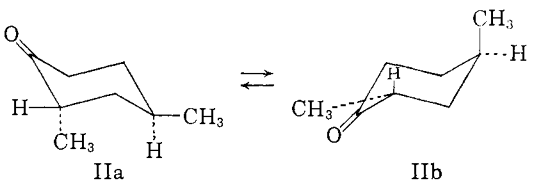
[7] K. von Auwers, *Ann. Chem.*, **420**, 84 (1920).

[8] N. L. Allinger, *Experientia*, **10**, 328 (1954).

[9] W. G. Dauben and K. S. Pitzer, in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 1.

[10] C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 178.

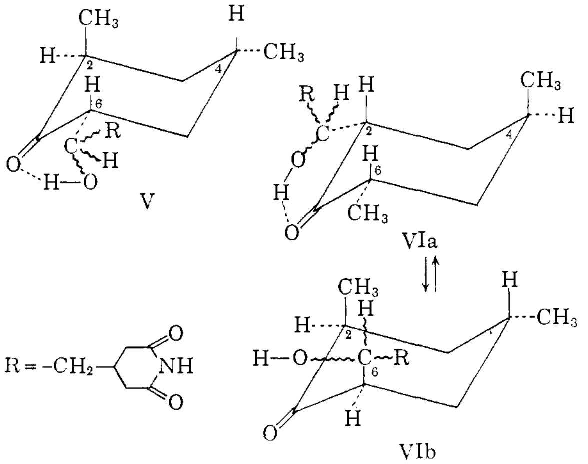


IIa IIb

by IIa, the planar form of which is shown by II. Since the absolute configuration of the *cis*-ketone has been related to D-glyceraldehyde[6] and shown to be represented by III (dotted lines meaning behind the plane of the paper), the present results corroborate a configuration of the *trans*-ketone II, which would be predicted from a knowledge of the absolute configuration of the epimer III.

Since the thermal ketone, (+)-2,4-dimethylcyclohexanone, is the less stable of two possible epimeric degradation products it is clear that cycloheximide possesses the same absolute configuration of methyl substituents at C-2 and C-4 as does the *trans*-(+)-2,4-dimethylcyclohexanone. During a thermal degradation of cycloheximide, one would not expect an intermediate eperimerization at the rather mild conditions (200–225°) of the pyrolysis. When the pyrolysis was interrupted after less than 20% of the (+)-2,4-dimethylcyclohexanone had been liberated, the residual mixture was found to contain at least 35% of unchanged cycloheximide, isolated and identified as the semicarbazone and acetate. Thus, under the conditions of pyrolysis, cycloheximide itself does not readily undergo an epimerization, and in view of the purity of the less stable epimeric ketone, it appears reasonable to assume that thermal degradation did not alter the relative configuration of the methyl groups.

The degradation data alone do not permit assignment of the configuration of cycloheximide at C-6, but because of the *trans* configuration of the methyl groups at C-2 and C-4 there are only two possible configurations involving the cyclohexyl substituents of cycloheximide, and these can be represented by the chair structures V and VIa. The equatorial conformation for the glutarimide-containing side chain at C-6 is reasonable because: (1) An axial conformation at C-6 would result in an unfavorable[9] *cis*-1,3-diaxial form, *e.g.*, as in the conformer VIb. (2) The structurally related 2-(α-hydroxy-*p*-halobenzyl)-cyclohexanones[11] apparently must have the 2-equatorial conformation to accommodate intramolecular hydrogen bonding. The infrared spectrum of cycloheximide in benzene or chloroform showed bonded OH absorption at 2.83 and at 2.97 μ, the former being indicative of intramolecular hydrogen bonding.[11] (3) The bulky side chain at C-6 may be under compulsion to assume the equatorial conformation, by analogy with the *t*-butyl group.[12] It can be appreciated that C-2 and C-6 are potential sites for epimerization, and recently Lemin and Ford[13] have reported that cycloheximide can be isomerized with acetic acid-washed alumina, presumably to an epimer, isocycloheximide. Also, the chromic acid oxidation product (a β-diketone) of cycloheximide can be isomerized with pyridine hydrochloride to the corresponding oxidation product of isocycloheximide.[13] Certainly these results are consistent with an epimerization to a more stable isomer involving the labile sites C-2 or C-6.



V VIa VIb

From the foregoing, it is possible to derive a tentative assignment for the configuration at C-6 in cycloheximide. Of the two possible configurations, V and VIa, an epimerization at C-2 in V should readily afford a more stable product, having all ring substituents in the equatorial conformation. The other possible configuration, however, should be resistant to epimerization for the following reasons. (1) Considering the conformational equilibrium VIa ⇄ VIb, an epimerization at C-2 or at C-6 in conformer VIa would yield a configuration having a less stable conformation because of the added 1,3-diaxial opposition between groups at C-4 and C-2, or C-4 and C-6, respectively. (2) Conformer VIa should be greatly stabilized over conformer VIb by virtue of more effective intramolecular hydrogen bonding (see above) and lower 1,3-diaxial opposition. Consequently, epimerization at C-2 and C-6 to the more stable, all equatorial conformation (or, of course, an initial epimerization at C-6, yielding V) would involve a highly unstable intermediary conformation, VIb. Thus, probable ease of epimerization of V and the unlikelihood of epimerization in VIa (or VIb) makes V the more reasonable structure for cycloheximide, with the glutarimide-containing group at C-6 being *trans* with respect to the methyl group at C-2, or *cis* with respect to the methyl group at C-4. As a consequence, the conversion I → VII should depict the reported[13] isomerization of cycloheximide to isocycloheximide. Lemin and Ford[13] provisionally suggested an epimerization at C-6, from a 2,6-*trans* to a 2,6-*cis* system, for they found both isomers to yield the same anhydro compound on dehydration with pyridine hydrochloride. It is felt, however, that a common anhydro compound could result from epimerization at C-2. Dehydrocycloheximide, for example, is reported to isomerize with pyridine hydrochloride. Certainly the foregoing offers nothing about the configuration of the hydroxyl-bearing carbon (C-α in I), although an assignment has been made from other considerations.[14]

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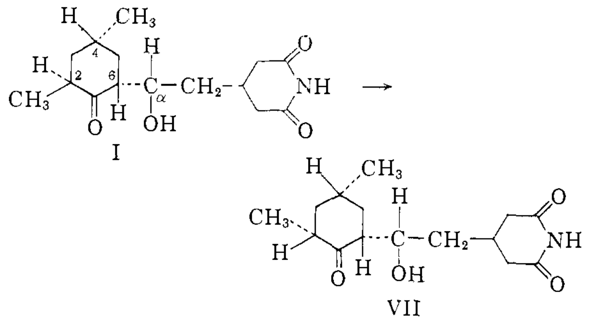
[11] A. C. Huitric and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 1147 (1956.)

[12] S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

[13] A. J. Lemin and J. H. Ford, *J. Org. Chem.*, **25**, 344 (1960).

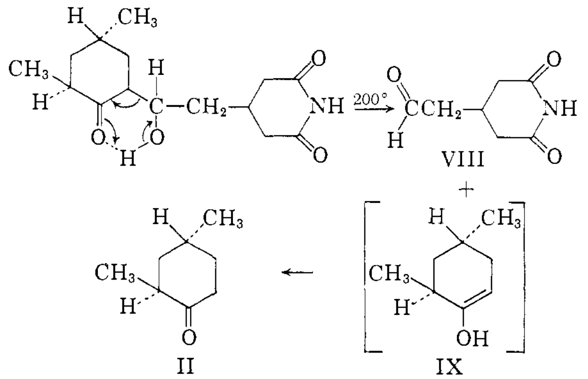
[14] T. Okuda, *Chem. Pharm. Bull.* (*Japan*), **7**, 671 (1959).



Earlier it had been reported[15] that the methyl group at C-4 and the glutarimide-containing group at C-6 possessed the *trans* configuration in Naramycin A, an antibiotic shown to be identical with cycloheximide.[16] This assignment, however, was based partly on the assumption that the 2-methyl substituent of cycloheximide would only make a small contribution to the rotatory dispersion curve, and would not be so strong as to surpass that of 6-substituent. If, however, the 2-methyl group were axial and the 6-substituent equatorial, it could be argued from the octant rule[10] that the methyl group would have the stronger influence on rotatory dispersion. It was also reported[15] that the rotatory dispersion curve of cycloheximide was quite similar to that of the alkaline degradation product, (−)-2,4-dimethylcyclohexanone. It is felt, however, that the presence of two extra asymmetric centers and attendent intramolecular hydrogen bonding in cycloheximide would influence the "asymmetric environment"[17] of the carbonyl chromophore enough, *e.g.*, by hydrogen bonding placing some strain on conformation, so that the similarity of rotatory dispersion curves of cycloheximide and a fragmental ketone would be concidence.

In addition to offering stereochemical evidence, the thermal degradation of cycloheximide was of interest in its own right as an organic reaction. The ketone III from the alkaline degradation of cycloheximide can be accepted as a reverse aldol product, but it can be said that the ketone II from the thermal degradation also can be explained as a reverse aldol product if one makes use of a cyclic six-membered transition state, such as is used to rationalize the thermal decomposition of β-hydroxyolefins[18] or the pyrolytic *cis* elimination of esters.[19] Such a scheme for the thermal degradation of cycloheximide is depicted by the equation giving II. Further credence for this view is given by the fact that a small amount of the other possible fragment, glutarimide-β-acetaldehyde (VIII), was actually isolated. The residue from the reaction was a hard glass, probably arising from polymeric aldolization of the aldehyde VIII.

A cyclic transition state for a pyrolytic reverse aldol reaction of cycloheximide would be analogous to that depicted for the pyrolysis of the β-hydroxyolefin ricinoleic acid,[18] although the olefinic double bond in the β-hydroxyolefin is replaced by a ketonic double bond in cycloheximide. The analogy is furthered by a comparison of the degradation products. The aldehyde VIII from cycloheximide is, of course, quite analogous with the *n*-heptaldehyde from ricinoleic acid. Also, ricinoleic acid yields an olefinic fragment, undecylenic acid, whose double bond has shifted in the same general manner as the ketonic double bond in cycloheximide has shifted to afford the hypothetical vinyl alcohol IX.



The fact that cycloheximide requires a much lower temperature for decomposition than do β-hydroxyolefins gives a further indication of a cyclic transition state. Whereas β-hydroxyolefins are reported[18] to undergo pyrolysis at 450–500°, it was found that cycloheximide smoothly underwent pyrolysis below 230°, and that ketone formation was even detected at a temperature below 180° This lower temperature requirement for cycloheximide may well result from stronger intramolecular hydrogen bonding forces possible with the more electronegative oxygen in the cyclohexanone ring. Such hydrogen bonding, of course, would tend to orient the molecule in a form reasonably close to that envisioned for the transition state, and the probable existence of intramolecular hydrogen bonding in cycloheximide has been noted above.

It is noteworthy that cycloheximide possesses the unstable configuration of methyl substituents, and the cyclic transition state mechanism shows how, after pyrolysis, this configuration is preserved in a fragmentary reaction product, (+)-2,4-dimethylcyclohexanone. On the other hand, it is seen that alkaline degradation should afford the more stable epimer, (−)-2,4-dimethylcyclohexanone. Thus it would seem that this dual scheme of degradation, in conjunction with epimerization and optical rotatory dispersion studies, would be eminently suitable for easily determining the partial configuration of stereoisomers[13,16,20] of cycloheximide, *i.e.*, the configuration of the 2,4-dimethylcyclohexyl system. From the prior data on optical purity of the degradation ketones, it may also be possible to gain information on the relative purity of a stereoisomer of cycloheximide. In addition, it would be expected that antibiotics related to cycloheximide, *e.g.*, E-73[21] and the various

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[15] T. Okuda, *ibid.*, **7**, 659 (1959).

[16] T. Okuda, M. Suzuki, Y. Egawa and K. Ashino, *ibid.*, **6**, 328 (1958).

[17] C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).

[18] R. T. Arnold and G. Smolinsky, *ibid.*, **81**, 6443 (1959).

[19] C. D. Hurd and F. H. Blunck, *ibid.*, **60**, 2419 (1938).

[20] R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 1316 (1955).

[21] K. V. Rao, *J. Am. Chem. Soc.*, **82**, 1129 (1960).

streptovitacins[22] would also undergo pyrolysis to afford substituted 2,4-dimethylcyclohexanones that have maintained their structural and, to a large degree, their configurational integrity.

Experimental[23]

Purification of Cycloheximide.—Commercial cycloheximide of The Upjohn Co. (registered trademark Acti-dione) was most economically purified by one recrystallization from 4:1 water–methanol, permitting slow crystallization, followed by a recrystallization from a mixture of isopropyl acetate–isopropyl ether. White crystals of constant rotation, $[\alpha]^{25}\mathrm{D}$ −3.46° (*c* 9, EtOH),[24] were obtained, m.p. 115–116°.[24]

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.94; H, 8.12; N, 4.98.

Alkaline Degradation of Cycloheximide.—Cycloheximide (19.67 g., 0.070 mole) was dissolved, with swirling, in 150 ml. of an aqueous 10% sodium hydroxide solution maintained at −5° (2–3 minutes), and the resulting solution was maintained at 0 to −4° for 6 hours, and then at −15 to −20° for 16 hours. The mixture (after melting) was extracted with chilled (−15 to −20°) petroleum ether (b.p. 35–40°), first with 150 ml. and then 50 ml. The extracts were washed twice with 100 ml. of chilled (just above freezing point) 10% brine solution, six times with 150 ml. of chilled water, and once more with brine. The extracts were dried (magnesium sulfate), and removal of the solvent followed by distillation at reduced pressure afforded 3.70 g. of (−)-2,4-dimethylcyclohexanone, b.p. 69.5° (17 mm.), 176.3° (766 mm.),[25] $n^{22}\mathrm{D}$ 1.4442, d^{25} 0.9028, $[\alpha]^{25}\mathrm{D}$ −1.8° (neat), $[\alpha]^{24}\mathrm{D}$ +4.3° (*c* 6, EtOH).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.20; H, 11.23.

The thiosemicarbazone was formed in quantitative yield from aqueous ethanol at room temperature, m.p. 161.5–162°, unchanged by two further recrystallizations from aqueous ethanol; $[\alpha]^{24}\mathrm{D}$ +43.7° (*c* 1.6, EtOH).

Anal. Calcd. for $C_9H_{17}N_3S$: C, 54.23; H, 8.60; N, 21.08. Found: C, 54.19; H, 8.44; N, 20.85.

From another run, carried out at 2 to 4° for 4 hours, the (−)-2,4-dimethylcyclohexanone was distilled into four fractions. The first two (total of 3.05 g.) had an $[\alpha]^{25}\mathrm{D}$ +3.4°, the third (12.7 g.), +4.3°, and the fourth (2.10 g.), +6.4° (all in EtOH, *c* 6). For the first fraction, $\lambda^{\mathrm{EtOH}}_{\mathrm{max}}$ 283 mμ (ε 19.7). The semicarbazone, prepared from the third fraction, melted at 198–200° dec., unchanged by further recrystallizations from aqueous ethanol. When taken rapidly, the melting point was 204–206° dec.; $[\alpha]^{24}\mathrm{D}$ +49.8 (*c* 1, DMF). The reported[4] corrected melting point is 212–214°.

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.93. Found: C, 58.98; H, 9.20; N, 22.62.

When (−)-2,4-dimethylcyclohexanone was prepared as reported,[4] by distillation from alkali, the product had an $[\alpha]^{20}\mathrm{D}$ +10.6° (lit.[4] $[\alpha]^{29}\mathrm{D}$ +11.52°), and an infrared spectrum identical with that of material having $[\alpha]^{25}\mathrm{D}$ +3.4°.

Thermal Degradation of Cycloheximide.—A 100-ml. flask containing 22.50 g. (0.080 mole) of cycloheximide, and surmounted by a 6-inch Vigreux column connected to an appropriate condenser and receiving flask, was placed under water aspiration. The flask was immersed in an oil-bath at 198°, and the temperature of the bath was raised to 230° over a 45-minute period, during which time there was collected 6.81 g. (67%) of crude (+)-2,4-dimethylcyclohexanone, b.p. 65–67° (17 mm.).[25] The residue, a dark glass, weighed 15.4 g., and appeared to be polymeric material. The distillate was diluted with 50 ml. of petroleum ether (b.p. 35–40°), and filtered by suction to afford 80 mg. of white crystalline glutarimide-β-acetaldehyde, m.p. 120.5–123.5°, undepressed on admixture with authentic glutarimide-β-acetaldehyde, m.p. 121–123°.[5] The filtrate was washed thrice with chilled water, then with saturated brine solution, and finally dried over anhydrous magnesium sulfate. Removal of the solvent followed by distillation afforded 5.10 g. (50.5%) of (+)-2,4-dimethylcyclohexanone, b.p. 69° (17 mm.), 178.7° (766 mm.),[25] $n^{22}\mathrm{D}$ 1.4488, $[\alpha]^{24}\mathrm{D}$ +64.8° (*c* 6, EtOH); *RD*[26] in methanol (*c* 2.08, *l* 0.1 dm.), 25°: $[\alpha]_{500}$ +28°, $[\alpha]_{400}$ +125°, $[\alpha]_{350}$ +308°, $[\alpha]_{330}$ +558°, $[\alpha]_{315-320}$ +770° (peak), $[\alpha]_{310}$ +673°; there were no extrema above 500 mμ.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.13.

The thiosemicarbazone was formed in 90% yield from aqueous ethanol at room temperature, m.p. 134–136°, followed by resolidification and subsequent remelting at 155–156°. The melting point was unaffected by further recrystallizations from aqueous ethanol; $[\alpha]^{24}\mathrm{D}$ +104.3° (*c* 2, EtOH).

Anal. Calcd. for $C_9H_{17}N_3S$: C, 54.23; H, 8.60; N, 21.08. Found: C, 54.12; H, 8.56; N, 21.08.

From another run, the identity of the glutarimide-β-acetaldehyde obtained was further demonstrated by comparison of the infrared spectrum with that of authentic glutarimide-β-acetaldehyde.[5] Fractionation of the (+)-2,4-dimethylcyclohexanone from this run afforded three fractions having b.p. 80° (28 mm.), $n^{25}\mathrm{D}$ 1.4470; first fraction: $[\alpha]^{25}\mathrm{D}$ +57.3° (neat); mid-fraction: $[\alpha]^{25}\mathrm{D}$ +57.7° (neat), $[\alpha]^{25}\mathrm{D}$ +64.4° (*c* 5, EtOH), d^{25} 0.9065, $\lambda^{\mathrm{EtOH}}_{\mathrm{max}}$ 286 mμ (ε 22.5); third fraction: $[\alpha]^{25}\mathrm{D}$ +57.7° (neat).

The semicarbazone, from aqueous ethanol, melted at either 166.5–167.5 or 170–172° depending on rate of heating; $[\alpha]^{25}\mathrm{D}$ +166.9° (*c* 1.8, DMF).

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.93. Found: C, 59.02; H, 9.47; N, 23.21.

Partial Thermal Degradation of Cycloheximide.—According to the foregoing procedure for thermal degradation, 4.00 g. (0.0142 mole) of cycloheximide was heated at 210–215° (bath temperature) for 10 min., during which time 0.35 g. (19%) of crude volatile ketone was collected. The light yellow glassy residue was thoroughly extracted with 10 ml. of hot *n*-hexane and then 10 ml. of hot water. In both cases the extracting liquid was removed by decantation after chilling in an ice-bath. The residue was then taken up in 50 ml. of 20% aqueous methanol. Into a 20-ml. aliquot of this solution was dissolved 1.50 g. of semicarbazide hydrochloride and 1.60 g. of powdered sodium acetate. After standing overnight, chilling followed by suction filtration afforded 1.06 g. of crude cycloheximide semicarbazone hydrate, m.p. 168.5–169.5° dec. One recrystallization from methanol afforded pure cycloheximide semicarbazone hydrate, m.p. 182–183° dec., unaffected by further recrystallization. Infrared spectrum and mixture m.p. showed this material to be identical with authentic cycloheximide semicarbazone, m.p. 182–183° dec.[24] The 1.06 g. of semicarbazone corresponded to a 55% recovery of cycloheximide. Another 20-ml. aliquot of the foregoing solution was extracted thrice with 9 ml. of chloroform and the combined extracts were washed once with 15 ml. of water, and dried over magnesium sulfate. Removal of the solvent left an oil (1.17 g.) which was dissolved in a mixture of 6 ml. of acetic anhydride and 6 ml. of dry pyridine. After standing at room temperature for 2 days, the volatiles were removed *in vacuo*, and the residual oil was crystallized from 10 ml. of isopropyl alcohol to afford 0.65

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[22] R. R. Herr, *J. Am. Chem. Soc.*, **81**, 2595 (1959).

[23] Melting points and boiling points were uncorrected, but by comparison with the melting points of known compounds (R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 26), the melting points below 200°, reported herein, are correct within 1°. The microanalyses were performed by Arthur Spang, Ann Arbor, Mich.

[24] J. H. Ford and B. E. Leach, *J. Am. Chem. Soc.*, **70**, 1223 (1948).

[25] The boiling point at reduced pressure probably is not accurate because efficient ebullition could not be used (excessive frothing). The boiling point at 766 mm. was taken by the micro capillary technique, and was reproducible within 0.2°, and accurate within 1° (see reference 23).

[26] The rotatory dispersion curve was obtained using a Cary recording spectrophotometer with a Perkin–Elmer optical rotatory dispersion accessory unit. Since the light source was a conventional hydrogen discharge lamp, readings below 310 mμ were not possible. The author is indebted to Mr. John Schmidt for carrying out this measurement in addition to infrared and ultraviolet spectra.

g. of cycloheximide acetate, m.p. 145–146.3°. One recrystallization from isopropyl alcohol raised the melting point to 147–148°, undepressed on admixture with authentic cycloheximide acetate, m.p. 147–148°.[24] Identity was further shown by comparison of infrared spectra. The 0.65 g. of acetate corresponded to a 35% recovery of cycloheximide.

When the pyrolysis, on 2.0 g. of cycloheximide, was carried out at 177–178° (bath temperature) for 75 min. there was obtained a small amount of volatile ketone from which was obtained (+)-2,4-dimethylcyclohexanone semicarbazone (10 mg.), identified by melting point, mixture melting point and infrared spectrum.

Epimerization of (+)-2,4-Dimethylcyclohexanone.—A solution of 2.10 g. of (+)-2,4-dimethylcyclohexanone ($[\alpha]^{24}\text{D}$ +64.8°, *c* 6, EtOH) in 30 ml. of 0.09 *N* potassium hydroxide in absolute methanol was maintained at 26° for 20 min., and then at −10° for 90 min. The solution was dissolved in 50 ml. of cold 10% brine, and the resulting solution was extracted twice with 25 ml. of chilled petroleum ether (b.p. 35–40°), and the combined extracts were washed twice with 25 ml. of cold 10% brine, six times with cold water, and finally with brine again. The extracts were then dried over magnesium sulfate, and removal of the solvent, followed by distillation afforded 1.65 g. (79%) of (−)-2,4-dimethylcyclohexanone, b.p. 67° (17 mm.), 176.3° (766 mm.),[25] $n^{22}\text{D}$ 1.4437, $[\alpha]^{24}\text{D}$ +4.6° (*c* 6.6, EtOH), infrared spectrum identical with that obtained from authentic (−)-2,4-dimethylcyclohexanone by the alkaline degradation of cycloheximide. In addition, both the semicarbazone and thiosemicarbazone (crude) of the epimerized ketone proved to be identical with the same derivatives (purified) of authentic (−)-2,4-dimethylcyclohexanone, by comparison of melting points, mixture melting points, infrared spectra and optical rotations.

Vapor Phase Chromatography.[27]—Chromatography was carried out using a Perkin-Elmer column R (Ucon polyglycol LB-550-X), 6 ft. × 4 mm. column, 120°, helium inlet pressure 20 p.s.i. The ketone from alkaline degradation ($[\alpha]^{24}\text{D}$ +4.3°, EtOH) exhibited two typical peaks corresponding to 89.5% of pure (−)-2,4-dimethylcyclohexanone, and to 10.5% pure (+)-2,4-dimethylcyclohexanone. Ketone from thermal degradation ($[\alpha]^{24}\text{D}$ +64.8°) was shown to consist of 7.2% of pure (−)-2,4-dimethylcyclohexanone, and 92.8% of pure (+)-2,4-dimethylcyclohexanone. Mixtures of the foregoing ketones having rotations of +43.6° and +24.0° were shown to consist of 35.2% and 63.4%, respectively, of pure (−)-2,4-dimethylcyclohexanone. A plot of the preceding optical rotations as a function of composition of the epimers, as determined by vapor phase chromatography, afforded a straight line having intercepts at −3.2 and at +70.0 (optical rotations in ethanol). Typical retention times for pure (−)-2,4-dimethylcyclohexanone and for pure (+)-2,4-dimethylcyclohexanone were 25.0 and 27.9 minutes, respectively. The following experiment ruled out epimerization on the column. A sample of (−)-2,4-dimethylcyclohexanone ($[\alpha]^{24}\text{D}$ +4.3°, EtOH) was injected and allowed to stand on the column at 120° for 1 hour with no helium flow. When the gas flow was resumed the results obtained were identical (within 1%) with those obtained using the standard conditions described above.

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(27) I am indebted to Mr. William Stevenson for his skillful development of a suitable method.

[Contribution from the Department of Chemistry, University of California, Berkeley, Calif.]

Acidity of Hydrocarbons. I. Kinetics of Exchange of Toluene-α-*d* with Lithium Cyclohexylamide[1]

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The kinetics of the proton exchange reaction between toluene-α-*d* and lithium cyclohexylamide in cyclohexylamine have been studied at 50°. The reaction is first order each in toluene-α-*d* and in monomeric lithium cyclohexylamide. Free ions are apparently not involved to a significant extent in the concentration range studied. Lithium cyclohexylamide appears to be in equilibrium with relatively inert dimers, trimers, etc.

Introduction

This paper introduces an extensive investigation of the relative acidities of hydrocarbon derivatives through the study of the rates and equilibria of proton exchange reactions. Compared to the numerous and detailed studies of carbonium ion stabilities, surprisingly little has been done with hydrocarbon anions. However, many hydrocarbons are so weakly acidic that the meaning of the term, acidity, must be questioned. Ideally, for use in the theory of organic chemistry, we would like to know the relative energetics of the gas phase reaction

$$\text{RH} \longrightarrow \text{R}^- + \text{H}^+$$

Such values are derivable from the bond dissociation energies, the ionization potential of hydrogen atom and the electron affinity of the alkyl radical. The first two are known or accessible numbers; the last is exceedingly difficult to measure.

We are forced to rely instead on quantities that may be expected to parallel variations in the gas phase energetics, such as the relative equilibrium constants for the metal exchange reaction

$$\text{RH} + \text{R'M} \rightleftarrows \text{RM} + \text{R'H}$$

in which the metal is chosen to be such that the R–M bond has substantial ionic character.

This approach was developed by Conant and Wheland[4] and culminated in the work of McEwen[5] who proposed a rough set of *pK* values for a number of hydrocarbons. These values, important as they are in the theory of organic chemistry, are now a quarter of a century old, and have come down to us without significant further study or elaboration.

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(2) Alfred P. Sloan fellow.

(3) (a) Shell Development Co. fellow, 1957–1958; (b) National Science Foundation Co-operative fellow, 1959–1960.

(4) J. B. Conant and G. W. Wheland, *J. Am. Chem. Soc.*, **54**, 1212 (1932).

(5) W. K. McEwen, *ibid.*, **58**, 1124 (1936).