THE ORIGIN OF THE REACTIVITY OF CYCLOHEXANONE

W. D. Cotterill and M. J. T. Robinson

The Robert Robinson Laboratories,

University of Liverpool

REACTIONS of cyclohexane derivatives involving a single carbon
atom in the ring are generally favoured or disfavoured
compared with analogous reactions of acyclic compounds
depending on whether the hybridisation of the carbon atoms
changes from sp^2 to sp^3 or from sp^3 to sp^2.   Brown [1] has
explained this empirical generalisation, which includes rates
of reaction, equilibrium constants, and heats of reaction, by
supposing that Pitzer strain results from the near eclipsing
of the group on a trigonal carbon atoms in the ring, e.g., in
cyclohexanone (I) or in a cyclohexyl carbonium ion, but we
believe that quite different explanations are required
depending upon whether the trigonal carbon atom is or is not
part of a double bond.   In this letter we consider only the
reactivity of cyclohexanone in carbonyl addition reactions,
but because of the correlations between various types of
reaction for cyclic ketones [2] the results have wider
significance.

          I   II   III   IV
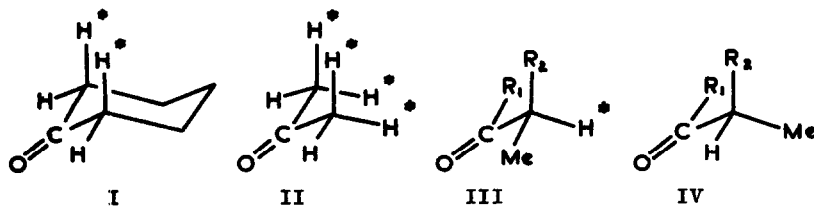
     Because of the absence of solvation effects, the clearest
example of the high reactivity of cyclohexanones in carbonyl
addition reactions is the difference, about 2.0 kcal.mole^{-1},
in the heats and free energies of hydrogenation of cyclo-
hexanones and acyclic ketones (3), (see Table 1).   We have
not attempted to correct these heats and free energies of
hydrogenation by Taft's equation for differences in the
inductive effects of the alkyl groups because the polar
reaction constant ρ^{x} and the hyperconjugation parameters h_{H}
and h_{C} for the free energies of hydrogenation of ketones
evaluated by Kreevoy and Taft (5) were based on a mistaken
interpretation of the experimental data (6), but the
qualitative effect would be to increase rather than decrease
the difference between the cyclic and acyclic ketones.   The
supposition that the eclipsing of the carbonyl group by the
equatorial 2- and 6-substituents causes strain in cyclo-
hexanone has been widely accepted (2,7), although there is no
direct evidence to support it.   On the contrary, in all
acyclic compounds with a single bond between a tetrahedral
carbon atom and a doubly bonded trigonal carbon atom, the
double bond is eclipsed by an atom or group on the
neighbouring tetrahedral carbon atom in the preferred
conformation where this has been determined; pertinent

TABLE 1

Heats and Free Energies of Hydrogenation of Ketones

in the Gas Phase.

Ketone	H_{298} (kcal.mole^{-1})	F_{298} (kcal.mole^{-1})	Reference
Cyclohexanone	15.23	6.84	3a
2-Methyl- "	15.11	6.70	3a
3-Methyl- "	15.03	6.69	3a
Acetone	13.20 [a]	5.04 [a]	3b,4
Methyl ethyl	12.96	4.81	3b
" "	12.96 [a]	4.94 [a]	3b,4

[a]   Calculated (ref.3b) from earlier equilibrium data (ref.4).

examples are acetaldehyde (8) and diethyl ketone (9).   The
highly improbable possibility that acyclic and cyclic compounds
might differ fundamentally in this respect is eliminated by
Pitzer and Donath's quantitative comparison of the
dissociation constants of the cyanhydrins of cyclopentanone
and cyclohexanone (10), and by our study of the conformational
equilibrium in the latter (11).   The high heat and free
energy of hydrogenation of cyclohexanone, however, is consistent
with the properties of acyclic carbonyl compounds if it is
assumed that each axial (but not equatorial) α-carbon-hydrogen
bond in cyclohexanone and each analogously situated bond in
acyclic ketones and aldehydes, i.e., the C-H^{x} bonds in (I),
(II), and (III), stabilise these molecules relative to isomers
or conformations with axial or similarly situated α-carbon-

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TABLE 2

Stabilisation of Aldehydes and Ketones by Axial or

Analogously Situated α-Carbon-Hydrogen Bonds.

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Type of evidence	Stabilisation (kcal.mole^{-1} per effective bond)
Heats of hydrogenation of ketones	1.0
Conformational equilibrium in	
a. Propionaldehyde	1.0
b. Isobutyraldehyde	1.2
c. Ethyl ketones	$>$0.41
d. 2-Bromocyclohexanone	0.9

carbon bonds by about 1 kcal.mole^{-1} (Table 2).   Thus acetone

in its preferred conformation (II)[†] has four C-H^{x} bonds but

cyclohexanone has only two.   Electron diffraction studies of

methyl ethyl ketone and diethyl ketone show that the preferred

conformations are (III; R_1=Me, R_2=H^{x}) and (III; R_1=Et, R_2=H^{x})

(each with four C-H^{x} bonds) (9).   These conformations must

have enthalpies substantially lower, i.e., at least 0.5 and

probably nearer 1.0 kcal.mole^{-1} lower, than the less stable

conformations (IV;R_1=Me, R_2=H^{x}) and (IV; R_1=Et, R_2=H^{x}) (each

with three C-H^{x} bonds) because the latter occur as mirror

image pairs and are therefore favoured by an entropy term

Rln 2 = +1.38 cal.deg.$^{-1}$mole^{-1} equivalent to a free energy

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[†]   The preferred conformation of acetone does not appear to
have been established by Swalen and Costain's microwave study
(12) and we have assumed the conformation (II) by analogy
with other acyclic carbonyl compounds.

difference of -0.41 kcal.mole^{-1} at 25^{0}.   Similarly proton
magnetic resonance spectra show that the preferred
conformations of propionaldehyde (III; R_1=H, R_2=H$^{\overline{x}}$) and of
isobutyraldehyde (III; R_1=H, R_2=Me) are approximately
1 kcal.mole^{-1} more stable than the conformations (IV; R_1=H,
R_2=H$^{\overline{x}}$) and (IV; R_1=H, R_2=Me) (12,13) which each have one
fewer C-H$^{\overline{x}}$ bond.   A study of the conformational equilibrium
in 2-methylcyclohexanone (11) has shown that the difference
in stability of the two chair conformations is greater than
would be predicted from steric hindrance alone.   It is
probably also significant that attempts to predict the
conformational equilibrium in 2-halo-cyclohexanones from
estimates of steric repulsions and electrostatic interactions
always predict that the axial conformation should be more
favoured than is experimentally observed.   For 2-bromocyclo-
hexanone in heptane Allinger and Allinger calculated that the
conformation with the bromine axial would be the more stable
by 1.53 kcal.mole^{-1} whereas the observed free energy
difference was only 0.62 kcal.mole^{-1} (15).

The effect we have postulated has the steric properties
of hyperconjugation but 1 kcal.mole^{-1} for each effective bond
is very large for the difference between carbon-hydrogen and
carbon-carbon bonds and we will defer further discussion of
the origin of this effect until we have more experimental
evidence.   Because some of the observations we have cited as
evidence for special stabilisation associated with axial and
analogous α-carbon-hydrogen bonds in aldehydes and ketones
may be explained in other ways, which are, however, neither

very satisfactory nor broad in scope but which will be

discussed in a full paper later, we are seeking further

evidence about the preferred conformations of alkyl groups

and the reactivity of aldehydes and ketones.

REFERENCES

[1] H.C. Brown, R.S. Fletcher, and R.B. Johannesen, J. Amer.
Chem. Soc., 73, 212 (1951); H.C. Brown, J.H. Brewster,
and H. Schechter, ibid., 76, 467 (1954).

[2] E.g., J. Sicher, "Progress in Stereochemistry, Volume III",
ed. P.B.D. de la Mare and W. Klyne, Butterworths, London,
1962, p. 225 et seq.

[3] A.H. Cubberley and M.B. Mueller, (a) J. Amer. Chem. Soc.,
69, 1535 (1947); (b) ibid., 68, 1149 (1946).

[4] H.J. Kolb and R.L. Burwell, J. Amer. Chem. Soc., 67, 1084
(1945).

[5] M.M. Kreevoy and R.W. Taft, J. Amer. Chem. Soc., 79, 4011,
4016 (1957); R.W. Taft, Tetrahedron, 5, 210 (1959).

[6] H. Adkins, R.M. Elofson, A.G. Rossow and C.C. Robinson,
J. Amer. Chem. Soc., 71, 3622 (1949).

[7] E.g., E.L. Eliel, "Stereochemistry of Carbon Compounds",
McGraw-Hill, New York, 1962, pp. 245, 267; N.L. Allinger,
J. Amer. Chem. Soc., 71, 5727 (1959).

[8] R.W. Kilb, C.C. Lin, and E.B. Wilson, J. Chem. Phys., 26,
1695 (1957).

[9] C. Romers and J.E.G. Creutzberg, Rec. Trav. Chim., 75,
331 (1956).

[10] K.S. Pitzer and W.E. Donath, J. Amer. Chem. Soc., 81,
3213 (1959).

[11] W.D. Cotterill and M.J.T. Robinson, unpublished work.

[12] J.D. Swalen and C.C. Costain, J. Chem. Phys., 31, 1562,
(1959).

[13] R.J. Abraham and J.A. Pople, Mol. Phys., 3, 609 (1960).

[14] R.J. Abraham, personal communication.

[15] J. Allinger and N.L. Allinger, Tetrahedron, 2, 64 (1958).