The Stability toward Racemization of Optically Active Compounds—with Especial Reference to Trivalent Nitrogen Compounds

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Although a tremendous amount of work has been done in attempts to resolve trivalent nitrogen compounds into optically active forms, the attempts have been uniformly unsuccessful.[1] On the other hand, other compounds in which the central atom is surrounded by only three groups have been resolved. Thus active forms of the sulfoxides, sulfinic esters, and sulfonium salts have been obtained. The present investigation was undertaken in order to explain this apparent anomaly as well as to gain information which would lead to a prediction of the stability toward racemization of a substituted ethyleneimine of the type (I), which is being investigated at the present time by Dr. T. L. Cairns of this Laboratory.[2]

$$H_2C—CR_2$$
$$\diagdown \diagup$$
$$N$$
$$|$$
$$R \qquad I$$
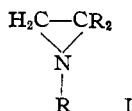
Since all previous attempts to prepare optically active nitrogen compounds have proved fruitless, the energy required to bring about a planar configuration, through vibrations, must be low. The computations which are to follow are based on the fact that one of the normal modes of vibration, v_3 of Fig. 1, leads to such a configuration. A
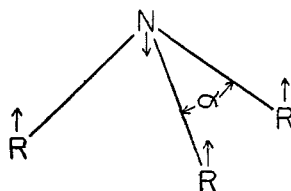

Fig. 1.—A diagrammatic representation of the normal vibration v_3.

similar type of calculation by Rice and Teller[3] of the amount of energy required to bring three of the hydrogen atoms of the methane molecule into a plane containing the carbon has led to an approximately correct value of the activation energy of the reaction $D + CH_4 \rightarrow CH_3D + H$.[4]

Let us consider a compound of the type R_3N. If the nitrogen is not in the plane of the R groups, then the potential energy of the molecule as a function of the distance of the nitrogen atom from the plane of the other groups will have the form illustrated by the dotted curve in Fig. 2.
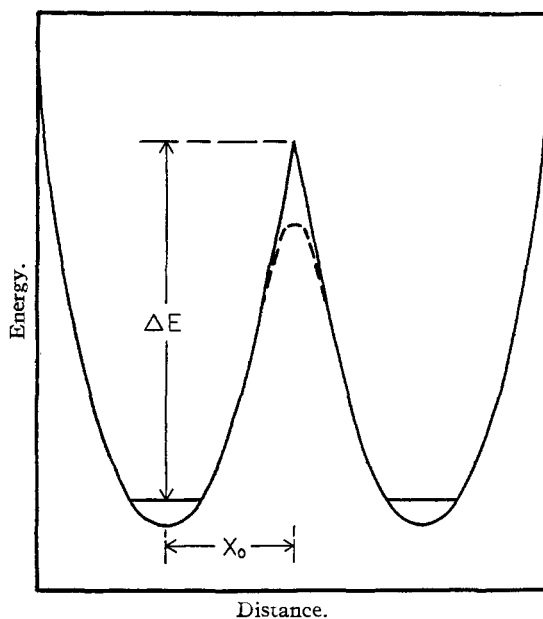

Fig. 2.—The energy, V, as a function of the displacement, x, for the normal vibration v_3.

Therefore, racemization may take place either by passing over or through the potential hill. The rate of racemization by either of these mechanisms is determined by the dimensions of the barrier, the frequency v_3, and the temperature. For ammonia several methods have been employed to obtain these dimensions.[5,6,7] By far the simplest of these leading to agreement between theory and experiment is that employed by Wall and Glockler[7]; and it is this function which has been used in these computations. Their expression for the potential energy, V, is

$$V = {}^1/_2 k(|x| - |x_0|)^2 \qquad (1)$$
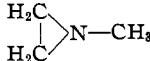
where x is the distance of the nitrogen from the

(1) Gilman, "Organic Chemistry, an Advanced Treatise," John Wiley and Sons, 1938, Chapter 3 by Shriner, Adams, and Marvel.
(2) Cf. Adams and Cairns, This Journal, 61, 2464 (1939).
(3) Rice and Teller, J. Chem. Phys., 6, 489 (1938).
(4) Gorin, Kauzman, Walter and Eyring, ibid., 7, 633 (1939).

(5) (a) Morse and Stueckelberg, Helv. Phys. Acta, 4, 373 (1931); (b) Dennison and Uhlenbeck, Phys. Rev., 41, 313 (1932); (c) Rosen and Morse, ibid., 42, 210 (1932).
(6) Manning, J. Chem. Phys., 3, 136 (1935).
(7) Wall and Glockler. ibid.. 5 314 (1937).

TABLE I

Compd.	Bond distance in Å.	Bond angle see Figs. 1 and 3	Equil. height in Å. x_0	Frequency[d] in cm.$^{-1}$, ν_3	Reduced mass in g., μ	Activ. energy in kcal.
NH₃	N–H = 1.01[9]	α = 109.5°[9]	0.34	945	2.5	11
N(CH₃)₃	C–N = 1.47[10]	α = 109.5°[10]	.49	374	11	15
H₂C⟩N—CH₃ (H₂C)	C–N = 1.47[a] C–C = 1.54	α = 109.5°[a] β = 63°	.77	~374[e]	11	38
(CH₃)₃S⁺	C–S = 1.82[10]	α ≈ 109.5°[c]	.61	~600[f]	19	100
PH₃	P–H = 1.40[b]	α ≈ 100°[c]	.65	990	2.7	47
P(CH₃)₃	C–P = 1.87[11]	α = 100°[11]	.87	~340[g]	18	67
PCl₃	P–Cl = 2.00[12]	α = 101°[12]	.91	260	24	57
PBr₃	P–Br = 2.24[12]	α = 100°[12]	1.04	162	28	34
C(CH₃)₄[h]	C–C = 1.54[13]	α = 111.5°[13]	0.87	377	9.6	88

[a] The angle β, see Fig. 3, is uniquely determined by the bond distances. Since the C–C bond distance in cyclopropane has been found to be 1.53 Å.,[13] it is quite reasonable to assume that the above bond distances for ethyleneimine are correct. Angle α, see Fig. 3, has been assumed to have the normal tetrahedral value. This assumption is substantiated by the value of 110° found for the C—N≡N angle of azomethane by Boersch.[15]   [b] This distance has been calculated from the covalent radii of the atoms.[14]   [c] From a comparison of homologous compounds, values of 100° for the HPH angle and 109.5° for the C–S–C angle are upper limits. A smaller angle would only make the calculated activation energies higher.   [d] All of the experimental frequencies are those summarized by Hibben.[16]   [e] Since the vibrational levels for ethyleneimines are unknown, the value for N(CH₃)₃ has been used. Due to the formation of a three-membered ring the actual frequency for this vibration must be somewhat greater; however, this would only lead to a higher activation energy than that calculated.   [f] The vibrational spectrum of this ion has not been determined. Since the C–C bending frequencies,[16] 377 cm.$^{-1}$ for (CH₃)₂CH₂ and 413 cm.$^{-1}$ for (CH₃)₂NH are very close to the respective values of the normal mode corresponding to ν_3, 372 cm.$^{-1}$ for (CH₃)₃CH and 374 cm.$^{-1}$ for (CH₃)₃N; a good approximation for ν_3 of (CH₃)₃S⁺ can be obtained from the 648 cm.$^{-1}$ bending frequency of dimethyl sulfide. 600 cm.$^{-1}$ is probably a lower limit, and a higher value would only tend to increase the activation energy.   [g] The vibrational frequencies for this compound are also unknown. A comparison of ν_3 for PH₃ and NH₃ together with the known value for N(CH₃)₃ (see table) yield 390 cm.$^{-1}$ for P(CH₃)₃. A similar comparison using the corresponding frequencies[16] of 1304 cm.$^{-1}$ and 372 cm.$^{-1}$ for methane and isobutane, respectively, yields a value of 300 cm.$^{-1}$. An average value, 340 cm.$^{-1}$, has been used; even if ν_3 were as low as 300 cm.$^{-1}$, the calculated ΔE would still be 55 kcal.   [h] The method of calculating the activation energy for this compound is given later. α is the C–C–C angle in propane, and ν_3 its bending frequency; x_0 is the height of one carbon from a line joining the other two; $1/\mu \approx (1/14) + 1/(2 \times 15)$.

plane of the R groups, x_0 is this distance at equilibrium, and k, the force constant, is given by the expression

$$k = 4\pi^2\nu_3^2\mu \qquad (2)$$

where ν_3 (Fig. 1) is the frequency leading to inversion of the molecule and μ is the reduced mass defined by

$$\mu \approx 3ab/(3a + b) \qquad (3)$$

where a is the mass of the R group and b that of nitrogen.[8]

(8) It is a well-known fact that a potential curve of the form illustrated in Fig. 2 leads to a quantum mechanical interaction, *tunneling*, and gives rise to a separation of the ν_3 vibrational levels into doublets. Previous investigations have been made with the view in mind of obtaining these observed doublet separations. In order to obtain the observed separation of the first vibrational level of ν_3, Wall and Glockler[7] used an arbitrary equilibrium distance, x_0, for ammonia. It is of interest to compare their activation energy of 9.5 kcal./mole with our value for ammonia of 11 kcal. Both these values are possibly high since the form of the curve given by equation (1) is that of the solid curve rather than the dotted curve of Fig. 2. The more elaborate function, $V = A(\csc^2 \Theta - \csc^2 \Theta_0)^2$, was employed by Manning and gives rise to a smooth curve. The arbitrary parameters in this function were chosen so as to give the observed doublet separations of the zero-th and first vibration levels. Manning[6] obtained 6 kcal./mole for the height of the potential hill, 0.38 Å. for x_0, and 1050 cm.$^{-1}$ for ν_3 (see also Howard, *J. Chem. Phys.*, **3**, 208 (1935)). Although this value of 6 kcal./mole is considerably lower than our value, it should be noted that Manning's
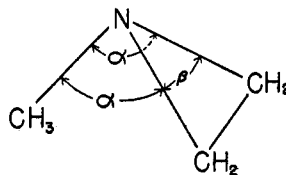

Fig. 3.—A diagrammatic representation of N-methyl ethyleneimine.

The results of the computations are given in Table I. A necessary condition for resolution is that the intramolecular first order rate constant for racemization be less than 10^{-5} sec.$^{-1}$. Thus values for x_0 and ν_3 are both too high. Since the doublet separation for a fixed reduced mass is a function of the area under the barrier, it is clear that a more reasonable value for x_0 and the correct value for ν_3 would lead to a considerably higher activation energy. These considerations lead to the conclusion that about 8 kcal./mole is the most probable barrier height for ammonia.

(9) Wright and Randall, *Phys. Rev.*, **44**, 391 (1933).
(10) Brockway and Jenkins, THIS JOURNAL, **58**, 2036 (1936).
(11) Springall and Brockway, *ibid.*, **60**, 996 (1938).
(12) Creeg, Hampson, Jenkins, Jones and Sutton, *Trans. Faraday Soc.*, **33**, 852 (1937).
(13) Pauling and Brockway, THIS JOURNAL, **59**, 1223 (1937).
(14) Pauling, "Nature of Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.
(15) Brockway, *Rev. Mod. Phys.*, **8**, 261 (1936).
(16) Hibben, "The Raman Effect and its Chemical Applications," Reinhold Publishing Corp., New York, N. Y., 1939.

one readily obtains from the Arrhenius equation

$$k \approx 10^{13} \exp.(-\Delta E/RT) \qquad (4)$$

that ΔE must be greater than 25 kcal./mole if resolution at room temperature is to be possible. For the moment tunneling through the barrier has been neglected. It will be shown later that for room temperature and above the effective activation energy for tunneling is only a few % lower than the height of the barrier.

Before discussing specific cases it should be emphasized that our method of obtaining ΔE leads to rather approximate results and values which are too high. However, the relative values are undoubtedly quite significant. An estimate of the probable error may be obtained by comparing our value of 11 kcal. for ΔE for NH_3 with the more reasonable value of 8 kcal.[8] Due to mutual repulsions, neopentane is an exception, the calculated ΔE being too low.

Compounds Similar to Trimethylamine.—The activation energy obtained for trimethylamine is 15 kcal./mole. One would expect other compounds of the type $NR_1R_2R_3$ to have a somewhat lower value for the following reasons. (1) The activation energy calculated for ammonia is less than that of trimethylamine. Thus if R_1, R_2, or R_3 is a hydrogen atom, ΔE should be slightly less than 15 kcal. (2) If R_1, R_2, and R_3 are aliphatic groups, the force constant, k, which appears in equation (1) will be approximately independent of the weight, *i. e.*, an increase in the reduced mass will be compensated by a corresponding decrease in the numerical value of ν_3. However, due to mutual repulsions, x_0, the height of the pyramid, will actually tend to decrease with increasing size of the R groups, thus lowering ΔE. Hence, three large normal saturated aliphatic groups attached to nitrogen would not lower the activation energy as much as would branched groups, such as *t*-butyl radicals. (3) Aromatic groups attached directly to nitrogen tend to lower ΔE through making the molecule more planar both because of the size of the groups, and the contribution to the stability of the compound through the resonance structure involving a double bonded nitrogen. This effect has been pointed out by Pauling.[17] (4) A comparison of ΔE for PH_3, PCl_3, and PBr_3 indicates that the attachment of an electronegative group to the central atom will not result in an appreciable increase in stability.

(17) Gilman, *loc. cit.*, p. 334.

The resolution of a compound of the type NR_1-R_2R_3 is impossible at room temperature.

From the reasons given above, the activation energy for inversion of these compounds is certainly no more than 15 kcal./mole. This value almost suffices for resolvability at $-80°$ (dry-ice temperature). Since, however, 15 kcal./mole is an upper limit for the activation energy, it appears very improbable that these compounds can be resolved even at dry-ice temperatures.[1]

Cyclic Compounds.—The activation energy obtained for N-methyl ethyleneimine was 38 kcal./mole. Even if rounding off the barrier should decrease it as much as 10 kcal., this compound would be stable with respect to racemization at room temperature. It can be shown that the increase in the rate of racemization through tunneling is negligible.[18] Thus a substituted ethyleneimine containing an asymmetric nitrogen atom appears to offer an excellent possibility for the resolution of a trivalent nitrogen compound.

Many attempts have been made to resolve cyclic compounds in which the nitrogen is enclosed in a five- or six-membered ring.[1] From simple considerations of strain it is evident that such systems will be only slightly more stable than the analogous open chain compounds.

Trivalent Phosphorus Compounds.—Although no examples of activity due to trivalent phosphorus have been reported, the values of ΔE recorded in Table I for these compounds are so high that it appears certain that they can be

(18) The B. K. W. approximation for tunneling rate is given by Rojansky ("Introductory Quantum Mechanics," Prentice-Hall, New York, N. Y., 1938, p. 221).

$$T_{\epsilon_i} = f(\epsilon_i) \exp. \left(-(4\pi/h) \int_{x_1}^{x_2} \sqrt{2\mu(V - \epsilon_i)}\, dx \right)$$

where T_{ϵ_i} is the probability of penetration through the barrier for a harmonic oscillator with energy ϵ_i, and V is defined by equation (1). It is easy to show that in our case $f(\epsilon_i)$ is about two. Assuming a Boltzmann distribution, the rate constant for tunneling is

$$k_t = cv_3 \sum_i T_{\epsilon_i} \exp. (-\epsilon_i/kT) / \sum_i \exp (-\epsilon_i/kT)$$

where v_3 has been previously defined and c is the velocity of light. From the above equations it is found that for trimethylamine the ratios of the rate of tunneling to that of going over the barrier, k_t/k, at 300, 200, and 150°K. are 60, 3 × 10³, and 10⁵, respectively. The numerical values of k_t at these temperatures were, respectively, 10³, 10⁻¹ and 6 × 10⁻⁵ sec.⁻¹ and resolution should be possible only at or below 150°K. For the ethyleneimine considered, k_t/k at 300, 400, and 500°K. is 300, 30, and 10, respectively. Since the rate in the reverse direction has been neglected, these computations are an upper limit for the rate of tunneling. It should be pointed out that if the calculations had been based on the type of potential function illustrated by the dotted line in Fig. 2, the tunneling rate would be much smaller, but the thermal rate would be correspondingly greater. Thus for the type of barrier employed, the effect of tunneling is essentially to round off the barrier.

resolved if the chemical difficulties can be overcome. Comparison of the values recorded for $P(CH_3)_3$, phosphorus trichloride, and phosphorus tribromide lead to the conclusion that the most favorable case is one in which three alkyl groups are attached directly to phosphorus.[19]

Active Sulfonium Salts.—The calculated activation energy is so high that racemization through an intramolecular conversion is out of the question. In fact, not only have these compounds been resolved,[20] but it has also been demonstrated that the mechanism by which they racemize is dissociation of the molecule, $R_3S^+X^-$, into the compounds R_2S and RX.

Asymmetric Carbon Atoms.—A mechanism which has been suggested[21] for the racemization of a compound of the type $CR_1R_2R_3R_4$ is one in which the four R groups and the asymmetric carbon atom are postulated to assume momentarily a planar configuration during inversion. Computations of the energy required show that this mechanism is entirely unreasonable.

From inspection of models it is clear that ΔE for this mechanism should be approximately twice the energy required to bend the propane molecule so that the three carbons lie on a line. Using the carbon bending frequency for propane[16]

and the appropriate reduced mass, ΔE is found to be 88 kcal./mole. A value computed directly from data for neopentane is even higher. Since the attachment of groups other than methyls would not be expected to reduce greatly this value it may be stated *that the racemization of an asymmetric carbon cannot occur except through some process which results in the breaking of a bond attached to the central carbon.* A search through the literature has revealed no clear-cut experimental evidence for inversion through an intramolecular process.

Summary

1. Approximate calculations of activation energy from spectroscopic data have shown that no compound of the type $NR_1R_2R_3$ can be resolved into active forms at room temperature.

2. Substituted ethyleneimines appear to offer the best possibility for the resolution of trivalent nitrogen compounds since the calculated activation energy is considerably above the minimum value required for stability.

3. Trivalent compounds of phosphorus can be resolved if the chemical difficulties can be overcome.

4. The calculations provide an explanation of the observation that the mechanism of racemization of active sulfonium salts is through dissociation of the molecule, $R_3S^+X^-$, into RX and R_2S, rather than through an intramolecular mechanism.

5. It is concluded that the activated complex for racemization of a compound of the type $CR_1R_2R_3R_4$ cannot be a planar structure, and thus that the racemization of a compound of this type cannot occur except through some process which results in the breaking of a bond attached to the central atom.

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(19) Sutherland, Lee and Wu (*Trans. Faraday Soc.*, **XXXV**, 1373 (1939)) have recently computed about 4 kcal./mole for the height of the barrier in PH_3 from a doublet observed by Fung and Barker (*Phys. Rev.*, **45**, 238 (1934)) at 990 cm.$^{-1}$. The separation of 2.4 cm.$^{-1}$ was interpreted as arising from a splitting of the ν_3 vibrational levels. We do not agree with this interpretation since it leads to a ten-fold reduction in the barrier height, thus necessitating an unreasonable anharmonicity. It should be noted that if the same anharmonicity were employed in the calculation of ΔE for R_3S^+, a value of 10 kcal./mole would be obtained compared to a minimum value of 25 kcal./mole required for stability at room temperature. There is no reason to expect much difference in the behavior of S^+ and P since the orbitals available for bond formation are the same in each case.

(20) (a) Gilman, *loc. cit.*, p. 344; (b) Balfe, Kenyon and Phillips, *J. Chem. Soc.*, 2554 (1930).

(21) Gilman, *loc. cit.*, p. 177.