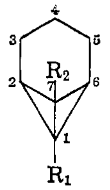

I, $R_1 = R_2 = H$
II, $R_1 = Li$; $R_2 = H$
III, $R_1 = D$; $R_2 = H$
IV, $R_1 = CH_3$; $R_2 = H$
V, $R_1 = CH_3$; $R_2 = Li$
VI, $R_1 = R_2 = CH_3$
VII, $R_1 = COOH$; $R_2 = H$

The remarkably high degree of s-character of the C_1–H bond led us to expect unusual acidity of the hydrocarbon. This prediction was verified when it was observed that I reacted with *n*-butyllithium in ether to form quantitatively the bicyclobutyllithium II,[8] from which I could be regenerated on hydrolysis, and which was converted to III on treatment with deuterium oxide. The n.m.r. spectrum of III establishes the position of the deuterium atom, since the triplet at 8.55 τ in the spectrum of I, attributed to the protons at positions 1 and 7, is replaced in the spectrum of III by an unresolved multiplet of one half the intensity.[9] Reaction of II with methyl iodide gave IV (b.p. 66° (100 mm.), n^{20}D 1.4580; n.m.r.$_{(CCl_4)}$ 7.86 (m), 8.48 (s), 8.75 (m), 9.00 (t) τ, relative areas 2:3:6:1), while carbonation yielded VII (m.p. 84.5–86.0°; n.m.r.$_{(CCl_4)}$ −1.90 (s), 6.89 (m), 7.75 (t), 8.55 (m) τ, relative areas 1:2:1:60; ultraviolet$_{(pentene)}$ end abs. 220 mμ, ϵ 7,700; pK_a 4.6). The carbon-13 hydrogen coupling constants at positions 2 and 7 in IV are identical within experimental error with those measured for I. Again, the high degree of s-character of the C_7–H bond in IV is reflected in the reaction with *n*-butyllithium yielding V. Treatment of V with methyl iodide resulted in the formation of VI (b.p. 72° (20 mm.); n^{20}D 1.4529; n.m.r. 8.20 (m), 8.73, (s), 8.76 (m) τ, relative areas of the 8.20 signal to the sum of the 8.73 and 8.76 peaks 1:6.[10]

Further evidence for the acidity of the bicyclobutane system was obtained from deuterium–hydrogen exchange studies on III carried out in *t*-butyl alcohol with potassium *t*-butoxide as catalyst. Conversion of III to I follows first-order kinetics (k_1 at 99.5° and 0.61 mole/l. potassium *t*-butoxide = 2×10^{-7} sec.$^{-1}$).

The results reported here are in qualitative agreement with the generally accepted theory of bonding in small ring compounds[11] which predicts unusually high degree of s-character for the exocyclic carbon orbitals. Comparison of the data with those obtained for 1,3,3-trimethylcyclopropene ($^{13}C_1$–H 220 c.p.s., corresponding to 44% s-character[3]; deuterium–hydrogen exchange approximately 10^4 times faster than III) indicates a certain qualitative analogy between the two ring systems. However, it remains to be established whether the considerably larger exchange rate of the cyclopropene is caused mainly by the somewhat higher s-character of the $=\overset{|}{C}—H$ bond, or whether the inductive effect of the double bond is a strongly contributing factor.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF CHICAGO
CHICAGO 37, ILLINOIS

G. L. CLOSS[12]
L. E. CLOSS

RECEIVED APRIL 29, 1963

---

[8] At 25° and concentrations of 1 mole/l. of each reactant, the half-reaction point is reached after approximately 3 hr.

[9] The n.m.r. spectrum of I reported by Moore[4] for the neat compound consists of three signals, 7.58 (m) for protons at carbon 2 and 6, 8.33 (t) for protons at 1 and 7 and 8.55 (m) τ for the methylene protons. These values change in carbon tetrachloride to 7.72, 8.55 and 8.71 τ. The assignments of the resonances made by Moore were further supported by spin decoupling experiments carried out in our Laboratory. It was shown that the protons giving the signal at 7.72 τ are coupled with both the methylene protons and the protons whose signal appears at 8.55 τ. The latter are only coupled with the 7.72 resonance.

[10] Compounds I, III, IV and VI were purified by vapor phase chromatography. Satisfactory analyses were obtained for all new compounds.

[11] C. A. Coulson and W. E. Moffitt, *J. Chem. Phys.*, **15**, 151 (1947); A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

[12] Alfred P. Sloan Foundation Fellow.

The Temperature-Independent Factor of the Kinetic Isotope Effect[1]

Sir:

In eq. 1 for the kinetic isotope effect in terms of vibration frequencies of reactants and activated com-

$$\frac{k}{k'} = \frac{\nu_L^*}{\nu_L^{*\prime}} \prod_i^{3n^*-7} \frac{\nu_i^*}{\nu_i^{*\prime}} e^{-\Delta u_i^*/2} \frac{(1 - e^{-u_j^{*\prime}})}{(1 - e^{-u_i^*})} \prod_i^{3n-6} \frac{\nu_i'}{\nu_i} e^{\Delta u_i/2} \frac{(1 - e^{-u_i})}{(1 - e^{-u_j'})}$$

plex, the factor $\nu_L^*/\nu_L^{*\prime}$ has been widely designated[2,3] as "the temperature-independent factor." Bigeleisen and Wolfsberg[2] derived expression 2 for this factor for a linear triatomic activated complex with masses m_1,

$$\frac{\nu_L^*}{\nu_L^{*\prime}} = \left[\frac{(\mu_{23} + p\mu_{12} + 2p^{1/2}\mu_2)}{(\mu'_{23} + p\mu'_{12} + 2p^{1/2}\mu'_2)}\right]^{1/2} \qquad (2)$$

m_2 and m_3 and internuclear distances r_1 and r_2, where $\mu_{12} = m_1^{-1} + m_2^{-1}$, $\mu_{23} = m_2^{-1} + m_3^{-1}$, $\mu_2 = m_2^{-1}$, and $p^{1/2}$, which equals β/α, "determines the relative amount of bond formation to bond rupture"[2] in the reaction coördinate $x_L = \alpha r_2 - \beta r_1$. Yankwich and Ikeda[4] extended the calculation to other transition-state geometries and to $n = 4$.

The actual temperature-independent factor obtained by extrapolation is, however, not usually $\nu_L^*/\nu_L^{*\prime}$ at all, but depends on the experimental conditions and the extrapolation method. If all real vibration frequencies of both reactants and transition state are greater than about $6\mathbf{k}T/h$, eq. 1 becomes

$$k/k' = \tau_*\tau_r^{-1}e^{-\left[\sum_i^{3n^*-7} \Delta u_i^*/2 - \sum_i^{3n-6} \Delta u_i/2\right]} \qquad (3)$$

$$\tau \equiv \prod_i^{3n-6} \nu_i/\nu_i' \qquad (4)$$

where the symbols * and r refer to transition state and reactants, respectively. Under these conditions (high frequencies or low temperature), ln (k/k') *vs.* $1/T$ is linear with infinite-temperature intercept ln $\tau_*\tau_r^{-1}$. For the linear triatomic activated complex the contribution to τ_* from the two linear vibrations (one of which is $\nu_L^*/\nu_L^{*\prime}$) can be calculated, most easily by the **FG**-matrix method of Wilson, Decius and Cross,[5] to be

$$\nu_1\nu_2/\nu_1'\nu_2' = [(\mu_{12}\mu_{23} - \mu_2^2)/(\mu'_{12}\mu'_{23} - \mu'^2_2)]^{1/2} \qquad (5)$$

Note that this is entirely independent of any structural features of the transition state other than the masses and their mutual ordering. Evidently the variations with transition-state structure which are predicted for the imaginary-frequency ratio by eq. 2 are *precisely cancelled by converse variations in the other linear-fre-*

---

[1] Supported in part by the Atomic Energy Commission under Contract No. AT(30-1)-905.

[2] J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **21**, 1972 (1953); **22**, 1264 (1954); J. Bigeleisen and M. Wolfsberg, *Advan. Chem. Phys.*, 1, 15 (1958).

[3] For example, see L. Melander, "Isotope Effects on Reaction Rates," Ronald Press Co., New York, N. Y., 1960, p. 38.

[4] P. E. Yankwich and R. M. Ikeda, *J. Am. Chem. Soc.*, **81**, 1532 (1959).

[5] E. B. Wilson, Jr., J. C. Decius and P. C. Cross, "Molecular Vibrations," McGraw–Hill Book Co., New York, N. Y., 1955, p. 183. From their eq. 3 it follows that $\tau = |\mathbf{G}|^{1/2}/|\mathbf{G}'|^{1/2}$. Tbe **F** determinants cancel because the force constants are the same for isotopic molecules. For this application, the **G** matrices should be written for internal coördinates.

quency ratio and consequently cannot affect the value of the actual temperature-independent factor.

Johnston and co-workers[6] have studied the temperature dependence of kinetic isotope effects and shown that at very high temperatures (>1000°K. for his hydrogen isotope effects) ln (k/k') becomes linear in $1/T^2$ with an infinite-temperature intercept of ln $(\nu_L{}^*/\nu_L{}^{*\prime})$. However, at the intermediate values of $h\nu/\mathbf{k}T$ common in most mechanistic work, plots of ln (k/k') *vs.* $1/T$, although they may appear to be linear over short temperature ranges, have infinite-temperature intercepts which are complex quantities not easily related to theory. Bigeleisen[7] has discussed this phenomenon with respect to equilibrium isotope effects.

Equation 5 may be used generally in combination with an estimate of the temperature-dependent factor in order to calculate an isotope effect at a single temperature. Omission of low bending frequencies for the transition state is then justified because their contribution to τ_* is slightly more than offset by their temperature-dependent contribution, only slightly favoring an inverse effect when they are included. On the other hand, for more rigorous calculations or when bending frequencies are high, the complete contribution τ_* of the transition state to the temperature-independent factor can be calculated by multiplying eq. 5 by eq. 6 for the bending motions ν_3 and ν_4

$$\frac{\nu_3\nu_4}{\nu'_3\nu'_4} = \frac{\mu_{12}r_2{}^2 + \mu_{23}r_1{}^2 + 2\mu_2 r_1 r_2}{\mu'_{12}r_2{}^2 + \mu'_{23}r_1{}^2 + 2\mu'_2 r_1 r_2} = \frac{\mu_{23} + p\mu_{12} + 2p^{1/2}\mu_2}{\mu'_{23} + p\mu'_{12} + 2p^{1/2}\mu'_2} \qquad (6)$$

where p is now $r_2{}^2/r_1{}^2$. The result is not eq. 2 but is its square times eq. 5. When bending frequencies are included in τ_*, care must be taken that the frequencies assigned in calculating the temperature-dependent factor satisfy eq. 5 and 6. If force constants are assumed and the frequencies are *calculated* by the usual methods, consistent results are obtained.[6,8]

(6) H. S. Johnston and E. Tschuikow-Roux, *J. Chem. Phys.*, **36**, 463 (1962); T. E. Sharp and H. S. Johnston, *ibid.*, **37**, 1541 (1962); G. Chiltz, R. Eckling, P. Goldfinger, G. Huybrechts, H. S. Johnston, L. Meyers and G. Verbeke, *ibid.*, **38**, 1053 (1963).

(7) J. Bigeleisen, *Proc. Sec. U. N. Intern. Conf. Peaceful Uses At. Energy*, **4**, 480 (1958).

(8) J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **23**, 1535 (1955); J. Bigeleisen, F. S. Klein, R. E. Weston, Jr., and M. Wolfsberg, *ibid.*, **30**, 1340 (1959); H. S. Johnston, *Advan. Chem. Phys.*, **3**, 131 (1961); F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

DEPARTMENT OF CHEMISTRY AND LABORATORY
FOR NUCLEAR SCIENCE C. GARDNER SWAIN
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASSACHUSETTS RICHARD L. SCHOWEN

RECEIVED APRIL 27, 1963

Protonation of Amide Groups of Polypeptides by "Helix-Breaking" Solvents

Sir:

It has been observed recently[1] that the formation of an amide hydrogen bond may be followed in a model system, N-methylacetamide in a variety of solvents, by the shift in the overtone of the NH stretching vibration; the absorption maximum in the near-infrared moves from 1.47–1.48 μ when the amide is in the unassociated form to a double-peaked band at 1.53–1.57 μ upon the formation of an amide hydrogen bond. Such shifts would also be expected to occur in connection with the transition of polypeptides from the random coil to the helical state. We have therefore undertaken a study of the spectral properties of several synthetic polyamino acids under conditions where changes in the physical properties of these polymers have been interpreted in terms of a helix-coil transformation.

One procedure for producing these transformations employs solvent mixtures containing varying proportions of apolar and polar components—for example, chloroform and an organic acid. The effectiveness of the acids, dichloroacetic and trifluoroacetic, in producing transitions in optical, rotatory and viscosity parameters of solutions of polypeptides in these mixed solvents[2-4] has been attributed to the ability of the acids to break peptide hydrogen bonds primarily by forming their own competing hydrogen bonds with the peptide C═O and NH groups.[4-6] On this basis, one would expect to observe corresponding changes in the position of the NH absorption peak as it shifts from

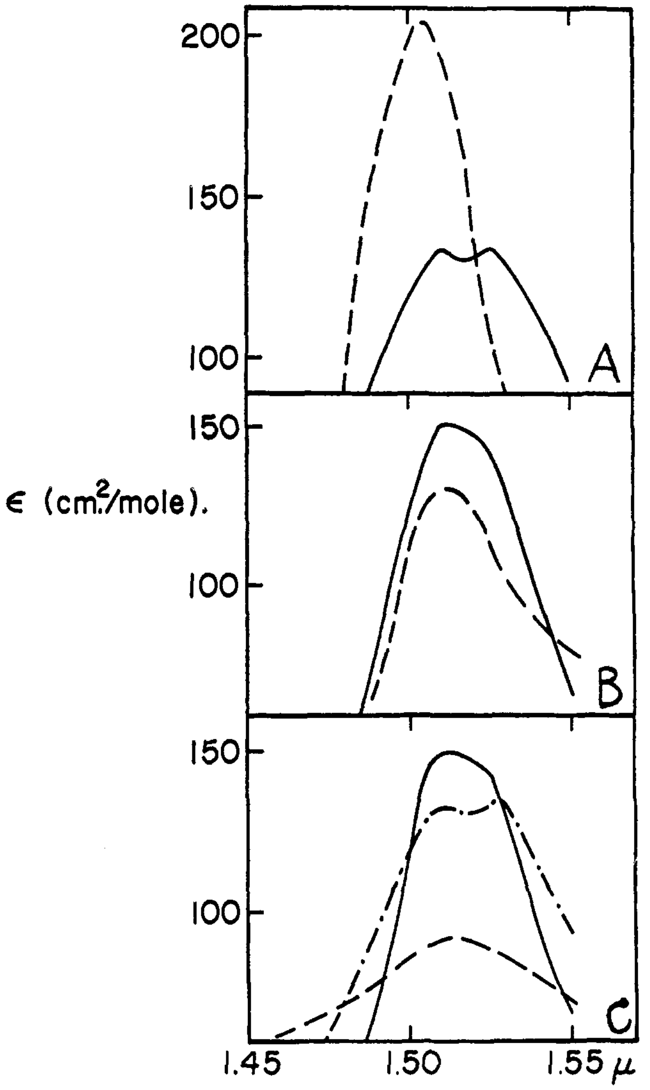

Fig. 1.—Spectra in acidic solvents: A, in CF_3CO_2H: - - - poly-L-alanine (0.442 *M*); ——— N-methylacetamide (0.466 *M*). B, in 8.4 *M* $HClO_4$, 2.5 *M* $C_4H_8O_2$, 19.2 *M* H_2O: - - - poly-L-alanine (0.378 *M*); ——— N-methylacetamide (1.08 *M*). C, N-methylacetamide: - - - in 10.7 *M* HCl, 36.5 *M* H_2O; ——— in 8.4 *M* $HClO_4$, 2.5 *M* $C_4H_8O_2$, 19.2 *M* H_2O; -·-·- in CF_3CO_2H. Spectra are plotted as ε, the extinction coefficient in cm.²/mole, on the ordinate *vs.* an abscissa wave length scale in microns.

---

(1) I. M. Klotz and J. S. Franzen, *J. Am. Chem. Soc.*, **84**, 3461 (1962).

(2) J. T. Yang and P. Doty, *ibid.*, **79**, 761 (1957).

(3) G. E. Perlmann and E. Katchalski, *ibid.*, **84**, 452 (1962).

(4) G. D. Fasman, in "Polyamino Acids, Polypeptides and Proteins," M. A. Stabmann, Ed., University of Wisconsin Press, Madison, Wis., 1962.

(5) C. H. Bamford, W. E. Hanby and F. Happy, *Proc. Roy. Soc.* (London), **A206**, 407 (1951).

(6) S. J. Singer, *Advan. Protein Chem.*, **17**, 1 (1962).