expect the isotropic coupling constant for the two α protons to be 20 G, assuming Q_α for the $R\dot{C}H_2$ configuration is 24.4 G.[8] Unfortunately, the extraction of the isotropic splitting from the anisotropic (largely polycrystalline) spectrum in Figure 1 is made difficult by the overlapping brought about by the nitrogen triplet substructure. Even though the spectrum indicates that the two protons are equivalent, the line shapes of the individual components in the outer triplets do not resemble those which normally characterize an axially symmetric hyperfine tensor.[6] Also, the structure of the group at low field appears to consist of two inner and two outer features in addition to the more intense triplet. Faced with these facts, we have obtained a tentative value for the isotropic splitting a_H simply from the center of gravity of each flanking group. This procedure results in a value of 26 ± 2 G which is appreciably greater than the 20 G estimated from the Q_α value, but we must concede that the discrepancy could well be due to our oversimplified analysis.

After this note was submitted for publication, we learned that Wood and his coworkers[9] have obtained the isotropic spectra of several isocyanatoalkyl radicals in an adamantane matrix. Their values of a_β^H (21.1 G) and a^N (4.2 G) for the isocyanatoethyl radical agree with our results almost within experimental error, so this supports the inference that the coupling to nitrogen in our spectrum is largely isotropic. The isotropic spectrum of the isocyanatomethyl radical would be of particular interest, but this has not been reported.[9]

Acknowledgment. We thank Professor D. E. Wood for sending us a preprint of his work on the isocyanatoalkyl radicals and for helpful correspondence about the possible interpretations of the powder spectrum of the isocyanatomethyl radical.

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Protolysis Kinetics of Ethyl *N*-Methylcarbamate[1]

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There has been a recent surge of interest in the study of proton exchange kinetics of biologically important classes of organic compounds.[2-6] To date these compounds have been principally amines, carboxylic acids and amides, mercaptans, and peptides. For example, the study of H–D exchange kinetics of polypeptides[7-9] and synthetic polyamides[10] has been useful to biochemists in elucidating chemical behavior of these compounds as a function of their substituents and conformational properties.

We became interested in proton exchange kinetics of biologically active compounds because of the recogniton that physical chemical properties such as oil–water partitioning, dissociation constants, dielectric constants, and electron densities of molecules are important in determining the type and magnitude of their biologic activity.[11] As a prelude to an extensive investigation of the role of proton exchange in biological activity of certain N–H bearing drugs we studied *N*-methylpropionamide and ethyl *N*-methylcarbamate. The title compound is a known general anesthetic[12] and a carcinogen[13] and possesses antileukemic activity.[14] *N*-Methylpropionamide was studied because of (1) its structural and chemical similarity to the title compound, and (2) because of its low degree of biologic activity. The analytical technique used herein was high-resolution nmr spectroscopy.

Experimental Section

All spectra were obtained in the frequency sweep mode on a Hitachi Perkin-Elmer R20A high-resolution nmr spectrometer operating at 60 MHz and equipped with a variable-temperature probe and digital frequency counter. Temperatures reported are within ±1° and were calibrated with ethylene glycol. Spectra were recorded at 30-Hz sweep width at 1000-sec

(1) (a) The authors wish to thank the Office of General Research and the School of Pharmacy, University of Georgia, for partial financial support of this research. (b) Presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., Mar 1971.

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sweep time and were checked to assure saturation did not occur.

pH measurements were determined with a Corning Model 12 pH meter equipped with a Corning Triple Purpose Ag/AgCl electrode and a saturated KCl reference electrode. NBS buffers were used as calibration standards. All pH measurements and nmr spectra were obtained in CO_2 free triply distilled water which was stored under argon. Measurements were determined in a water-jacketed vessel at 34 ± 0.5°. The pH of the solutions were varied using HCl or KOH in CO_2 free water.

Values of τ were computed from individual spectra using an IBM 360/65 computer programmed with the general equations of Arnold,[15] which corrects for T_2 effects; T_2 was obtained from the N–CH_3 line width under slow proton exchange conditions and is limited by the field inhomogeneity.

N-Methylpropionamide. The amide was obtained commercially (Eastman reagent grade) and used without further purification.

Ethyl N-Methylcarbamate. Ethyl chloroformate (0.1 mol) and methylamine hydrochloride (0.1 mol) were added to a mixture of water–ether containing triethylamine (0.2 mol) and stirred for 1 hr. The ether layer was separated, dried over $MgSO_4$, and filtered, and the excess ether was removed to give a yellow oil. Distillation afforded a 65% yield of the carbamate ester, bp 164° at 754 mm [lit.[16] bp 170° (760 mm)].

Results and Discussion

Equations for the probable mechanisms of proton exchange were adapted from the published work on *N*-methylacetamide[17] and are listed below.

$$RH^* + H_3{}^+O \overset{k_{H^+}}{\rightleftharpoons} RH + H_2\overset{+}{O}H^* \text{ (acid catalyzed)} \quad (1)$$

$$RH + \bar{O}H \overset{k_{OH}}{\rightleftharpoons} R^- + HOH \text{ (base catalyzed)} \quad (2)$$

$$RH + HOH + RH^* \overset{k_2}{\rightleftharpoons} RH^* + HOH + RH \text{ (bimolecular)} \quad (3)$$

$$RH^* + HOH \overset{k_3}{\rightleftharpoons} RH + H^*OH \text{ (water catalyzed)} \quad (4)$$

Using these mechanisms, the overall rate expression is

$$\frac{\text{rate}}{RH} = \frac{1}{\tau} = k_{H^+}[H_3O^+] + k_{-OH}[\bar{O}H] + k_2[RH] + k_3[H_2O] \quad (5)$$

The overall rate ($1/\tau$) was determined by following the collapse of the N–CH_3 doublet. The exchange mechanisms were investigated as a function of pH and concentration of exchanging species. Activation energies were determined by measuring the rate of collapse of a doublet by varying the temperature at a fixed pH.

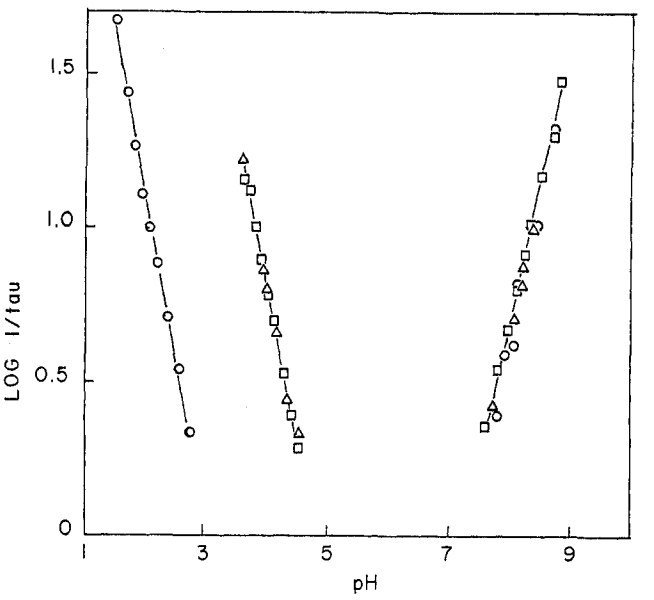

Figure 1. Log rate of proton exchange *vs.* pH:

○, 0.5 *M* $CH_3CH_2\overset{O}{\overset{\|}{C}}-\underset{H}{N}-CH_3$ in H_2O;

□, 0.5 *M* $CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-CH_3$ in H_2O;

△, 1.0 *M* $CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-CH_3$ in H_2O.

From a plot of log $1/\tau$ *vs.* pH, Figure 1, it can be seen that carbamate esters are subject to specific acid- and base-catalyzed proton exchange. In this respect they behave similarly to amides.[15] In Figure 1 it can also be seen that again like amides, carbamate ester proton exchange is not a function of concentration, either under acidic or basic conditions. This rules out the possibility of bimolecular mechanisms significantly contributing to any proton exchange rate either under basic or acidic conditions.

It is reported that with amides in water k_3 is small compared to k_{H^+} or k_{-OH}.[18] It was observed by us that k_3 is also small for carbamate esters in water. In a solution where neither $[H_3O^+]$ or $[^-OH]$ is large the

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Table I: Rate Constants for N-H Proton Exchange and Energies of Activation[a]

Compound	k_{-OH}, M^{-1} sec^{-1}	k_{H^+}, M^{-1} sec^{-1}	E_a (acid), kcal/mol	E_a (base), kcal/mol
$CH_3CH_2CONHCH_3$	$3.81 \pm 0.26 \times 10^6$	$1.08 \pm 0.1 \times 10^3$	10.66 ± 0.46	...[b]
$CH_3CH_2OCONHCH_3$	$5.87 \pm 2.07 \times 10^6$	$5.62 \pm 1.23 \times 10^4$	8.56 ± 0.55	11.07 ± 0.50

[a] Rate constants and energies of activation were determined on 0.5 M solutions of amide and carbamate esters. Rate constants were determined at 34°. [b] Hydrolysis occurred at elevated temperatures.

exchange is slow (a sharp well-resolved doublet is observed).

On the basis of these data the overall rate expression is simplified to

$$\frac{\text{rate}}{RH} = \frac{1}{\tau} = k_{H^+}[H_3O^+] + k_{-OH}[\bar{O}H] \quad (6)$$

Under acidic conditions hydroxide concentration is insignificant, simplifying the expression to

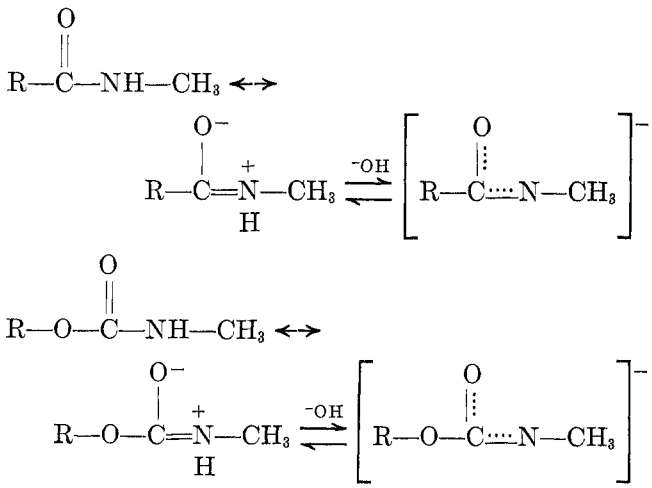
$$\frac{\text{rate}}{RH} = \frac{1}{\tau} = k_{H^+}[H_3O^+] \quad (7)$$

while under basic conditions, where hydronium ion concentration is considered insignificant, the expression is

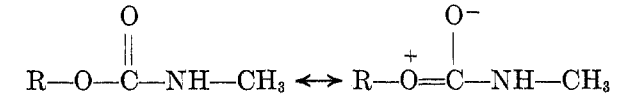
$$\frac{\text{rate}}{RH} = \frac{1}{\tau} = k_{-OH}[\bar{O}H] \quad (8)$$

The acid- and base-catalyzed rate constants and the activation energies of proton exchange of *N*-methylpropionamide (reference compound) and ethyl *N*-methylcarbamate are listed in Table I. Under basic conditions there is no significant difference in the amide and carbamate ester rate constants, while there is a larger difference under acid conditions. Under basic conditions both can donate their proton through similar intermediates (Scheme I). In both cases the carbonyl

Scheme I



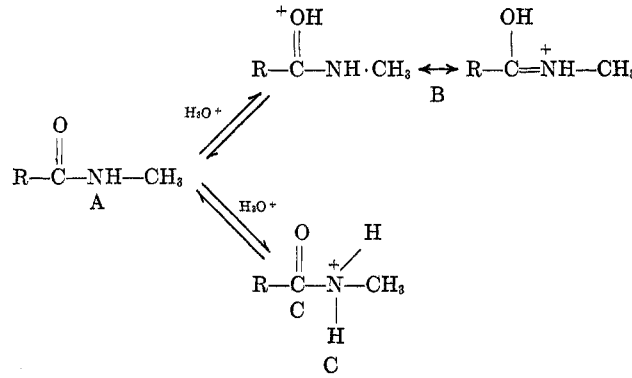
and nitrogen atoms can participate significantly to stabilize the transient negatively charged intermediates. From the data it appears that ester oxygen resonance with the carbamate carbonyl is not a significant factor during base-catalyzed proton exchange. Such reso-



nance would be expected to retard nitrogen carbonyl resonance interaction resulting in a smaller base-catalyzed rate constant (k_{-OH}) than found with the amide.

In the presence of acid (H_3O^+) the carbamate ester has a significantly higher rate constant (k_{H^+}) than the amide (Table I). It has been postulated[17] that under acid conditions amides exchange protons through intermediate C which is in equilibrium with A (Scheme II).

Scheme II



A similar intermediate seems likely to be involved with carbamates. Carbamates can probably be protonated to intermediates E, F, and possibly G (Scheme III). The protonated ester oxygen form G is probably not a significant factor in proton exchange because, in at least strong acid (SbF_5–FSO_3H–SO_2), carbamate esters exhibit only carbonyl protonation.[19] Species E, the carbamate carbonyl protonated form, is significantly different from the similar amide form, B, in that E has an additional stabilizing resonance contributor—the ester oxygen carbonyl resonance. Significant participation of the ester oxygen in resonance with the carbonyl would promote basicity of the nitrogen atom facilitating formation of F and E. The significantly larger protolysis rate constant (k_{H^+}) for the carbamate ester is evidence that carbamate esters possess a significant amount of ester oxygen carbonyl electronic delocalization in an acid medium. In the presence of acid the

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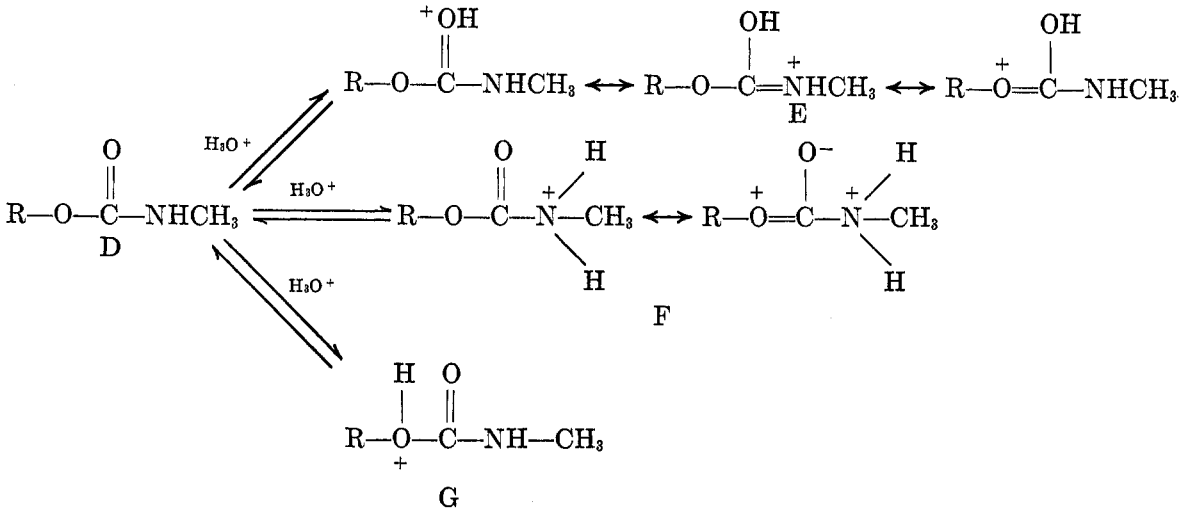
Scheme III



energy of activation of the carbamate ester is lower (8.56 ± 0.55 kcal mol^{-1}) compared to the amide (10.66 ± 0.46 kcal mol^{-1}) offering some further evidence that carbamate esters exchange protons with greater facility than amides.

Summary and Conclusion

From the data, carbamate esters and amides, in the presence of H_3O^+, exchange protons through similar intermediates, but the rates of exchange are significantly different with carbamates exchanging faster than amides. This difference seems best explained as being due to differences in resonance and inductive influences by the two types of neighboring groups on the nitrogen basicities. Under the conditions of this study the carbamate nitrogen thus appears to be more basic than the amide nitrogen. These same influences appear to be of less consequence during base-catalyzed exchange as evidenced by identical rate constants for the amide and carbamate ester.

The Observation of Positive Temperature Coefficients in the Bromine Nuclear Quadrupole Resonance Spectra of the Diethylammonium Salts of Hexabromoantimony(III) and Hexabromobismuth(III)

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The halogen nuclear quadrupole resonance spectra of hexahalometallate ions are of interest because numerous possible variations in the metal halogen bond are detectable simply by changing the metal, while most other factors remain essentially constant.[1,2] The present work was initiated in an attempt to extend the series of MX_6^{n-} ions for which nqr data are known to Sb(III) and Bi(III). It was found that strong ^{79}Br and ^{81}Br resonances could be recorded in $[(C_2H_5)_2NH_2]_3SbBr_6$ and $[(C_2H_5)_2NH_2]_3BiBr_6$. In addition, it was of interest to determine the temperature dependence of the halogen resonance frequencies for the purpose of comparison with other MX_6^{n-} ions.

Experimental Section

Synthesis. The antimony (bismuth) salt was prepared by adding 5 g of $Sb_2O_3(Bi_2O_3)$ to 20 ml of hot concentrated HBr or HCl. After the $Sb_2O_3(Bi_2O_3)$ had dissolved, a stoichiometric amount of diethylamine was added dropwise to the hot solution, and upon cooling, the well-formed colorless crystals of the compound were filtered off and dried over KOH. Other compounds mentioned in this paper were synthesized and analyzed in a similar manner. Carbon and hydrogen analyses were carried out by Galbraith Labs., Knoxville, Tenn. *Anal.* Calcd for $[(C_2H_5)_2NH_2]_3SbBr_6$: C, 17.49; H, 4.42; Sb, 14.78. Found: C, 17.75; H, 4.56; Sb, 14.96; mp 169–170°. Calcd for $[(C_2H_5)_2NH_2]_3BiBr_6$: C, 15.83; H, 3.95. Found: C, 15.84; H, 3.79; mp 194–195°.

Spectral Measurements. The nqr spectra were recorded using a Wilks Scientific NQR-1A spectrometer. Frequency measurements were made by zero-beating an external CW signal generator with the oscillator spectrum on a Tektronix 1L20 spectrum analyzer. The signal generator frequency was then measured precisely with a Monsanto 150A electronic counter. Using superregenerative techniques, two closely spaced reso-

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