PROTONATED HETEROALIPHATIC COMPOUNDS

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I. Introduction

Protonated organic compounds play a vital role as intermediates in acid-catalyzed reactions. This review emphasizes information about the structure of these intermediates as a means toward a better understanding of such reactions. In particular, for each class of compound we will discuss the site of protonation, the conformation of the protonated compound, the electronic distribution in these positively charged species, and some of the reactions they undergo. The recent advances in this field[1a-c] have been a direct result of the development of superacid systems which, because of their high acidity and low nucleophilicity, enable the preparation of stable solutions of many protonated organic compounds. Nuclear magnetic resonance spectroscopy can be used to observe the acidic protons in the ions directly without the complications arising from proton exchange with the solvent, as generally occurs rapidly in weaker acid systems.

In our review we have perhaps overemphasized the results from nmr studies of superacid solutions of protonated organic compounds and as a consequence failed to discuss in sufficient detail many of the significant results obtained in other acid systems. Our reasons for this approach are our own interest in superacid systems and also our desire to present an as up-to-date account of the field as is compatible with brevity and readability.

We have also been somewhat selective about the classes of compounds dealt with and only discuss oxygen, nitrogen, and sulfur protonation of aliphatic compounds. This has stemmed from the fact that our interest in the direct observation of protonated heteroaliphatic molecules arose from their importance to studies of stable carbonium ions. In fact many of these ions can be considered as substituted carbonium ions. Thus protonated acetone, acetic acid, and carbonic acid correspond to dimethylhydroxycarbonium ion, dihydroxymethylcarbonium ion, and trihydroxycarbonium ion, respectively. In addition, reactions of many of these ionic species involve formation of true carbonium ions, as, for example, the dehydration of protonated alcohols to give alkylcarbonium ions. We have omitted discussion of the carbon protonation of hydrocarbons as these stand out as separate topics.

II. Experimental Methods for the Study of Protonated Compounds

The experimental methods for the study of protonated compounds in solution can be grouped into two categories. The first are methods which allow detection of these species but which give little information concerning their structure. This group includes, for example, the cryoscopic and conductometric methods, both of which have been valuable in the detection of protonated species but which have given little or no information as to the site of protonation. The second category are those methods which permit structural assignments to be made, and, in particular, allow the site of protonation to be determined. This category includes the spectroscopic methods of which nmr has probably contributed the most to our knowledge of the structure of protonated species. While infrared and Raman spectroscopy could potentially provide such information, particularly since exchange of acidic protons with solvent molecules is not a limiting factor as it is in many nmr ex-

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(1) (a) N. C. Deno, *Progr. Phys. Org. Chem.*, 2, 129 (1964); (b) H.-H. Perkampus, *Advan. Phys. Org. Chem.*, 4, 195 (1966); (c) G. A. Olah and P. von R. Schleyer, Ed., "Carbonium Ions," Interscience, New York, N.Y.: Vol. I, 1968; Vol. II, 1970; Vol. III–IV, in press.

periments, difficulties, both in obtaining and interpreting such spectra, have limited the application of these techniques. Electronic (ultraviolet and visible) spectroscopy has been of considerable benefit to the study of equilibria, particularly between the organic base and its conjugate acid, but again detailed interpretation is difficult and has been restricted to certain classes of conjugated compounds.

It is not the purpose of this review to deal in detail with the physical methods that have been used in the study of protonation, particularly since there are many excellent reviews[2] of these methods already available. Rather it is the aim to examine the more frequently used methods in relation to the type of organic substrate being protonated and, in particular, in relation to the type of acid system being employed. Since the physical method employed frequently dictates to a large extent the acid systems that can be used, it is convenient to commence with a review of the acid systems that have been developed for examination of protonated species in solution.

A. ACID SOLVENT SYSTEMS

The choice of an acid system for the observation of protonated species in solution is dependent upon a number of factors. Of prime importance is the selection of an acid system which will meet the demands of the method of observation being employed. Secondly the protonated species must be reasonably stable in the acid system. Lastly the acid system must be sufficiently acidic to protonate the organic base in question.

The ability of a given acid to donate a proton to a base is conveniently expressed by an acidity function.[3,4] In largely aqueous media, and in dilute solution with respect to the organic substrate, the hydrogen ion concentration, as given by the pH, accurately expresses the protonating ability of the medium. In more acidic solvents, where the activity coefficients (referred to dilute solution in water) of the species present become significantly different from unity, this is no longer true and various methods have been used to set up acidity functions in such media.

For an acidity function H_x, and a base having a thermodynamic equilibrium constant, K_a, the concentrations of the base C_b and that of its conjugate acid C_a are given by

$$H_x = pK_a + \log C_b/C_a \quad (1)$$

Unfortunately, no one acidity function accurately describes the protonation behavior of all organic bases in a given acid system. For present purposes, however, the acidity of acid media will be described in terms of the Hammett acidity function H_0, derived originally from the protonation of a series of primary anilines and some oxygen bases in sulfuric acid, and since extended to a large number of acid media.[5,6]

The majority of organic bases whose protonation will be discussed in this review have pK_a values which lie between 0 and −10. Table I summarizes the known basicity values of some representative aliphatic weak bases. The values given refer to the value of H_0 at half-protonation in sulfuric acid, and thus the pK_a value will only have thermodynamic significance if the base accurately obeys the H_0 acidity function. While this is known not to be true in some cases (for example, olefins[7] and amides[8]), these values do give a guide to the relative basicities of various types of organic bases, both with respect to each other and with respect to the various acid systems to be discussed.

Table I

Basicities of Some Representative Aliphatic Bases[a]

Class	*Compound*	pK_a
	Carbonyl Protonation	
Carboxylic acid	Acetic acid	−6.1
Carboxylic acid ester	Ethyl acetate	−6.5
Ketone	Acetone	−7.2
Aldehyde	Alkyl aldehydes	ca-8
Amides	Acetamide	0.0
	Ether O-Protonation	
Ethers	Diethyl ether	−3.6
Alcohols	Methanol	−2.0
	Sulfur Protonation	
Mercaptans	Methyl mercaptan	−6.8
Sulfides	Dimethyl sulfide	−5.4
	Nitrogen Bases	
Amines	Methylamine	10.6
Nitriles	Acetonitrile	−11
	Other	
Nitro	Nitromethane	−11.9
Olefin	1,1-Diphenylethylene	−5.5
Phosphines	*n*-Butylphosphine	0.0
	Dimethylphosphine	3.9
	Trimethylphosphine	8.7

[a] Values taken from extensive data tabulated by Arnett.[9]

For comparison with Table I the H_0 values for some pure protonic acids are listed in Table II. As can be seen, the majority of the classes of compound listed in Table I could be examined as their protonated form in any of the acids listed in Table II provided no further reaction of the protonated species occurred. However, for many observations it is necessary to either increase or decrease the acidity of the medium.

According to the solvent-system definition of acids and bases,[10] an acid in a particular solvent system is a compound which increases the concentration of the characteristic cation, while a base increases the concentration of the characteristic anion. The characteristic cation or anion is established, in the case of protonic solvents, by the autoprotolysis equilibrium and in the case of nonprotonic solvents by self-ionization which may or may not have any physical reality for the pure solvent. Thus, to decrease the acidity of one of the protonic solvents in Table II it is necessary to add a proton acceptor to the system. An example of this is the sulfuric acid–water system in which a range of acidities between −11 and +7 (on the H_0 scale) may be obtained by suitably adjusting the concentrations of the components. To increase the acidity it is necessary to select a compound which will increase the concentration of the characteristic cation. Thus considering the autoprotolysis equilibrium for HF (eq 2) it can be seen that a

$$2HF \rightleftharpoons H_2F^+ + F^- \quad (2)$$

(2) E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Vol. I, Academic Press, New York, N. Y., 1955; F. C. Nachod and W. D. Phillips, Ed., *ibid.*, Vol. II, 1962.
(3) F. A. Long and M. A. Paul, *Chem. Rev.*, 57, 1 (1957).
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(9) E. M. Arnett, *Progr. Phys. Org. Chem.*, 1, 223 (1963).
(10) D. W. Meek in "The Chemistry of Non-Aqueous Solvents," Vol. I, J. J. Lagowski, Ed., Academic Press, New York, N. Y., 1966, p 6.

compound which behaves as a fluoride ion acceptor will increase the concentration of the H_2F^+ ion and thereby increase the acidity of the medium. A further example of this type of behavior is provided by the oleum system, which, at least in simple terms, can be considered as being more acidic than sulfuric acid owing to the increased concentration of the $H_3SO_4^+$ ion by complexing of the SO_3 with the HSO_4^- ion giving $HS_2O_{10}^-$.[11]

$$2H_2SO_4 = H_3SO_4^+ + HSO_4^- \xrightarrow{SO_3} HS_2O_{10}^- \quad (3)$$

The effects of different fluoride ion acceptors have been compared,[12] and have been ranked according to the ability of HF solutions of these Lewis acids to dissolve electropositive metals. The strongest Lewis acid investigated was found to be SbF_5. Weaker but still to be considered as strong acids in HF were AsF_5, BF_3, and PF_5. A similar conclusion was reached by studies of the extraction of *o*- and *p*-xylenes into solutions in HF of various fluoride ion acceptors, which is a measure of the ability of the media to protonate the aromatic.[13]

Table II

H_0 Values of Some Strong Acids[11,14]

HSO_3F	−12.8	H_2SO_4	−11.0
HSO_3Cl	−12.8	HF	−10.2

A number of difficulties are encountered in obtaining direct measurements of acidity in these mixed acid systems. One is that it is difficult to find a weak enough base for measurement of the equilibrium between the base and its conjugate acid using conventional spectroscopic techniques. Nitro compounds have been used. It is not at all clearly established, however, that nitro compounds protonate according to the H_0 acidity function,[9] and thus it is doubtful whether these compounds give a true extension of the H_0 scale for acids stronger than sulfuric acid. With these reservations in mind, some evaluations of the acidity function H_0 in some mixed acid systems are given in Table III.

Fluorosulfonic acid containing SbF_5 is besides $HF–SbF_5$ probably the most acidic solvent system yet found although its acidity has not been accurately established.[11,14] A number of observations in our laboratories suggest that the acidity increases up to at least 1 mol of added SbF_5. (We estimate H_0 for 1:1 *M* $FSO_3H–SbF_5$ as −17.5 to −18.) The remarkably high acidity of 1:1 *M* $FSO_3H–SbF_5$ has resulted in its trivial naming as "magic acid." It should be noted that fluorosulfonic acid is synonymous with fluorosulfuric acid. Both names are currently used although the latter appears to be becoming the most acceptable.

Certain added solvents have little or no effect on the concentration of either the characteristic cation or anion of the solvent and can thus be used as inert diluents. Thus addition of SO_2 to FSO_3H does not affect the conductivity as would be expected if it were acting as a base, and it is thus believed not to be protonated under these conditions.[16] Similarly the Raman and ir spectra of SO_2 in HF are virtually unchanged from those of neat SO_2—again evidence that SO_2 is not behaving as a base.[15] This has important consequences in the recording of low-temperature nmr spectra in mixed acids of high acidity. By addition of SO_2 or SO_2ClF it is possible to circumvent the broadening of peaks due the high viscosity of the media at low temperature without appreciably diminishing the acidity of the system, although a slight decrease has been observed.[17]

Table III

H_0 Values of Some Mixed Acid Systems[15]

H_2SO_4 + 1.0 *M* SO_3	−12.2
H_2O + 1.0 *M* BF_3	−11.4
HF + 0.02 *M* NbF_5	−12.5
HF + 0.36 *M* NbF_5	−13.5
HF + 0.36 *M* SbF_5	−14.3
HF + 3.00 *M* SbF_5	−15.3

It is thus possible, in a particular acid system, to increase or decrease the acidity at will, or to dilute the acid without markedly effecting the overall acidity.

With these points in mind, the most important of the physical methods that have been used to study protonation will be discussed.

B. CRYOSCOPIC AND CONDUCTOMETRIC METHODS

Historically the study of protonation in strong acid systems was first investigated by the cryoscopic method in sulfuric acid.[18,19] Sulfuric acid, due to its convenient freezing point (10.371°)[20] and its large cryoscopic constant (6.12° mol^{-1} kg^{-1}),[21] is a very suitable solvent for cryoscopic measurements. Care has to be taken in such determinations either to repress, or suitably correct for, the self-ionization of the solvent. This can be achieved by carrying out the determinations in slightly aqueous acid. There is a danger, however, in that certain solutes, such as nitro compounds,[22] show nonideal behavior in slightly aqueous sulfuric acid and, in addition, solutes which are capable of dehydration will give misleading freezing point depressions in the presence of small amounts of water. An example of this latter behavior is acetic anhydride, which in 99.8% sulfuric acid gives a twofold depression of freezing point but in the absence of water gives a fourfold depression.[23] This is interpreted as due to dehydration of the acid by the anhydride, the ionization scheme being

$$(CH_3CO)_2O + H_3O^+ + H_2SO_4 = 2CH_3CO_2H_2^+ + HSO_4^- \quad (4)$$

The results of cryoscopic determinations give the ν factor, which is defined as the number of kinetically separate dis-

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(15) H. H. Hyman, L. A. Quarterman, M. Kilpatrick, and J. J. Katz, *J. Phys. Chem.*, 65, 123 (1961).
(16) R. J. Gillespie and S. Pez, personal communication; see ref 14.
(17) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 89, 4752 (1967).
(18) R. J. Gillespie in "Studies on Chemical Structure and Reactivity," J. H. Ridd, Ed., Methuen, London, 1966, p 173.
(19) R. J. Gillespie and E. A. Robinson in "Carbonium Ions," Vol. I, G. A. Olah and P. von R. Schleyer, Ed., Interscience, New York, N. Y., 1968.
(20) S. J. Bass and R. J. Gillespie, *J. Chem. Soc.*, 814 (1960).
(21) R. J. Gillespie, *ibid.*, 1851 (1954).
(22) J. R. Brayford and P. A. H. Wyatt, *ibid.*, 3453 (1955).
(23) J. Leisten, *ibid.*, 298 (1955).

solved particles that are produced by the addition to the solution of one molecule of the solute.[24]

The ν factor can be obtained for any solute in 100% sulfuric acid from expression 5 which takes into account the self-ionization of the solvent.[18] θ is the freezing point depression mea-

$$\nu = \theta/6.12m(1 + 0.002\theta - 0.098ms) - (md/m) \quad (5)$$

sured from the freezing point of the hypothetically undissociated sulfuric acid (10.625°), m is the molal concentration of the solute, md is the total molal concentration of ions and molecules arising from self-dissociation, and s is the number of moles of solvent used up in the ionization of 1 mol of the solute. Values of md for different electrolytes have been tabulated.[25]

Clearly the ν factor can be ambiguous as to the precise nature of the ionization step, and furthermore gives no information concerning the structure of the species formed. Some of this ambiguity can be removed by measurements of freezing point depressions in various cryoscopic mixtures of sulfuric acid,[26-28] and in this way certain complex modes of ionization have been distinguished. Additional data can be provided by conductivity measurements in sulfuric acid.[29,30] It has been found that 99% of the current in solutions of bases in sulfuric acid is carried by the hydrogen sulfate ions; similarly in solutions of acids in sulfuric acids, the current is carried by the $H_3SO_4^+$ ions. Thus by measurements of the conductivity of solutions in sulfuric acid the value of γ or the number of HSO_4^- or $H_3SO_4^+$ ions produced per molecule of solute can be determined.

C. SPECTROSCOPIC METHODS

Of the various spectroscopic methods available for study of protonation of weak organic bases, infrared and nmr spectroscopy have received the most attention and give the most information concerning the structure of the ions under examination. While much of the early work on protonation was conducted using ultraviolet and visible spectroscopic techniques, the accent in this area has been on the use of changes in the electronic spectra on protonation to determine relative concentrations of protonated and unprotonated substrate and thus the basicity of the compound as well as the acidity of the medium. Electronic spectra are very valuable in studies of the protonation of aromatic and heteroaromatic systems and can, on detailed interpretation, give information on the charge distribution of the protonated molecule. The majority of protonated aliphatic compounds, however, do not show absorption above 200 mμ, and as a result only a few studies have been reported.

1. Vibrational Spectroscopy

The infrared and Raman spectral techniques have provided much detailed information on the position of protonation in a number of heteroorganic compounds. These techniques are of particular value in the protonation of carbonyl compounds, a class of compound that has received considerable attention because of the intermediacy of the protonated species in many acid-catalyzed reactions.

The application of ir spectroscopy to the study of protonation is not without its pitfalls, difficulties arising both experimentally and in the assignment of bands in the spectrum. Considerable controversy, for example, was generated in the literature[31] concerning the site of protonation of amides due to an apparent increase in the carbonyl stretching frequency on protonation. Protonation on the carbonyl oxygen would be expected to lead to a decrease in this frequency, and the observed increase was attributed to N protonation. The resolution of this question, chiefly by the application of nmr spectroscopy, shows that carbonyl protonation occurs and will be discussed later. In a number of cases the ir evidence as to the site of protonation is less ambiguous. Thus the carbonyl stretching frequency of acetic acid appears at 1715 cm^{-1} in water and gradually diminishes in intensity with increase in the sulfuric acid concentration.[32,33] At the same time a new band appears at lower frequency (1600 cm^{-1}) which is Raman inactive and is assigned to an antisymmetric C–O stretching band in the carbonyl protonated species. In the carboxylate anion, which has the same symmetry, an antisymmetric C–O stretch appears at 1584 cm^{-1}.

The ir spectra of protonated heteroorganic bases all have a broad, strong band in the region 2000–3500 cm^{-1} due to the X–H stretching mode.[34] The position of this band depends on the hydrogen bonding with the anion and on the nature of the anion and thus gives little information on the nature of the atom protonated. The X–H bending mode is more characteristic of the type of atom protonated, and this has been correlated with the position of protonation in a number of organic bases.[34] A summary of X–H deformation frequencies in a number of classes of protonated molecules is given in Table IV.

Table IV

X–H and X–D Deformation Frequencies in Protonated Heteroaliphatic Compounds[34]

Class	*X*	*XH*, cm^{-1}	*XD*, cm^{-1}
Carbonyls	O	1257	983
Thiocarbonyls	S	968	730
N-Heterocycles	N	1258	944
Tertiary amines	N	1402	1062
Secondary amines	N	1585	1178
Primary amines	N	1580	1182
Amine oxides	O	1463	1084
Ethers	O	1072	820

The experimental difficulties, and their resolution, associated with spectroscopic observations in a number of highly acidic media have been discussed in detail.[35,36]

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(33) S. Hoshino, H. Hosoya, and S. Nagakura, *Can. J. Chem.*, 44, 1961 (1966).
(34) D. Cook, *ibid.*, 42, 2292 (1964).
(35) Reference 10, p 1.
(36) T. C. Waddington, Ed., "Non-Aqueous Solvent Systems," Academic Press, New York, N. Y., 1965.

2. *Nuclear Magnetic Resonance Spectroscopy*

Nuclear magnetic resonance spectroscopy offers a unique possibility for examining in detail the structure of protonated molecules in solution. Proton magnetic resonance has been used extensively in the elucidation of structure and, as well as structural information, indications of the charge density at various sites in the ion can be obtained. In addition nmr can be used, in a number of cases, to determine rates of inter- and intramolecular processes including determinations of rotational barriers in protonated molecules. Many comprehensive treatments are available on the general application and theory of nmr spectroscopy, and it will be the purpose of this section only to elaborate points which are of particular pertinence to studies of protonation behavior.

Of especial importance is the limiting factor associated with the exchange of acidic protons in the protonated molecule with the solvent. For observation of separate resonances in the nmr spectrum, the lifetime of the acidic proton on the site of protonation must be at least 10^{-1}–10^{-2} sec. The lifetime of the proton in a solvent of given acidity will be dependent on the basicity of the site protonated and also on the temperature. For a given site,[37,38] the rate of exchange of the acidic proton with the solvent will, in general, decrease with increasing acidity of the medium. The most favorable case for observing an acidic proton by nmr will thus be at low temperature and in a medium high acidity. It is for this reason that superacid systems and the use of low-temperature nmr spectroscopy has led to the direct observation of a considerable number of protonated weak bases, under conditions where the exchange rate with the solvent is low enough to observe the acidic proton directly. The use of low temperatures, both to decrease the rate of exchange and also to prevent further reaction of the ion, leads to experimental difficulties due to the viscosity of the acid system. In this regard the availability of diluents such as SO_2 and SO_2ClF which apparently have only a small effect on the acidity, enables temperatures as low as $-120°$ to be attained in media such as 1:1 *M* FSO_3H–SbF_5 ("Magic Acid").

For the FSO_3H–SbF_5, FSO_3H–SbF_5–SO_2, and FSO_3H–SbF_5–SO_2ClF acid system, normal glass sample tubes may be used. In acid systems containing HF, however, glass is unsuitable due to reaction to give silicon tetrafluoride. Sample tubes for use with HF can be made of polyethylene, polypropylene, Teflon, or Kel-F. Quartz tubes may also be used, but sealing should be avoided due to slow production of SiF_4 gas which may result in explosions.[39]

Another practical consideration in recording nmr spectra in strong acid systems is the choice of a suitable reference standard. Tetramethylsilane, the usual reference standard used in nmr work, is decomposed by sulfuric acid and other strong acids and is therefore not suitable as an internal standard.[40] Capillaries containing TMS as an external standard have proved highly suitable and can also be used with nmr spectrometers which utilize the internal lock method of field-frequency stabilization. It is most convenient to quote chemical shift values in δ (ppm from TMS), because of the fact that the highly acidic protons encountered in these systems would have negative chemical shifts on the τ scale. To convert from external TMS to internal TMS as standard, relationship 6 is used[41]

$$\delta_{TMS}^{int} = \delta_{TMS}^{ext} + 0.21 \quad (6)$$

for 1:1 *M* FSO_3H–SbF_5–SO_2 at $-60°$. δ values are negative for protons absorbing to low field of TMS, although according to current convention the sign is omitted.

Several internal standards can also be used. The H_3O^+ peak in a number of strong acid systems is invariant with concentration and temperature and appears at δ 10.05 (from internal TMS).[41] The tetramethylammonium ion (as the SbF_6^- or BF_4^- salt) is stable under strong acid conditions and absorbs at δ 4.05–4.15 (from internal TMS). Methylene chloride can be used as a standard but will react with some superacids, particularly in the presence of SO_2, to give protonated formaldehyde and a variety of other intermediates.[42]

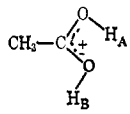
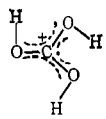
Sample preparation for nmr measurements of protonated species requires special attention due to the high concentration (5–10%) of substrate normally employed. The heat of protonation resulting from dissolving such large concentrations of precursors in the acid necessitates slow addition and cooling of both compound and acid. It is also inadvisable to allow protonated and unprotonated material to come into contact as this can result in complications such as polymerization. A suggested method for preparing samples in FSO_3H–SbF_5–SO_2 (or SO_2ClF) solution is to add a solution of the compound in SO_2 (or SO_2ClF) slowly to a FSO_3H–SbF_5–SO_2 (SO_2ClF) solution, both solutions being cooled to $-78°$ in a Dry Ice–acetone cooling bath. Rapid mixing, such as is obtained by means of a vortex-type stirrer, is also recommended for obtaining "clean" nmr spectra of the protonated organic substrate. An excess of superacid will protonate any moisture in the system to form H_3O^+, and it is, therefore, not always necessary to take extra precautions to work in an inert, dry atmosphere. Whenever such conditions are needed, however, usual vacuum line and drybox techniques should be applied.

Finally it is sometimes the case that the solvent acid peak obscures the region of the nmr spectrum of interest. This problem can be overcome by variation of the acid system, by a change in temperature or by variation in the concentration of the diluent used.

It is pertinent, in this introductory section, to review briefly some of the salient features associated with the nmr spectra of ions and in particular the features associated with the acidic protons, observed at low temperature, in superacid media. Generally, these will be protons attached to heteroatoms and will show certain distinct features. The chemical shift of protons attached to oxygen reflects the charge on the proton and the double-bond character of the oxygen. Typical shifts for such protons are presented in Table V for various classes of protonated molecules. Protons attached to sulfur occur at higher field than those on oxygen; thus in protonated thiols the SH proton is in the range δ 5.9–6.6 and in thiocarboxylic acids the range is δ 6.5–7.5. NH protons are often broadened due to the presence of the nitrogen quadrupole. The shift appears to follow the bond order of the nitrogen, protonated nitriles (δ 10.5–11.5), protonated imines (δ 9.5–10.0), and protonated amines (δ 8.0–9.0).

(37) C. MacLean, J. H. van der Waals, and E. L. Mackor, *Mol. Phys.*, 1, 247 (1958).
(38) C. MacLean and E. L. Mackor, *J. Chem. Phys.*, 34, 2207 (1961).
(39) M. Kilpatrick and J. G. Jones in ref 30, p 151.
(40) R. E. Reavill, *J. Chem. Soc.*, 519 (1964).
(41) G. A. Olah and A. M. White, unpublished results.
(42) G. A. Olah, D. H. O'Brien, and M. Calin, *J. Amer. Chem. Soc.*, 89, 3582 (1967).

Table V

Class	Ion	Shift (δ) from ext TMS	Range of chemical shifts (δ)
Aldehydes		15.1	15–17
Ketones		14.9	13–15
Carboxylic acids		13.0 (H_B) 12.3 (H_A)	12–13.5
Carbonates		10.5	9.5–11.5
Alcohols	$CH_3OH_2^+$	9.4	9.0–10.0
Ethers		9.0	8.0–9.0

Hindered rotation about the carbon–heteroatom bond often leads to the observation of *cis–trans* isomerism in the protonated molecule. A close parallel has been found between vicinal coupling constants in such ions and the corresponding coupling constants in olefins, *trans* HCXH coupling constants being larger than *cis* HCXH coupling constants. This parallelism has been used in assignment of the spectrum to particular isomers in many instances, and a number of examples of this approach will be given later. This approach has been recently criticized[48] as a result of theoretical calculations on the stability of the various isomers of protonated aldehydes and carboxylic acids. There is, however, now a considerable amount of evidence which supports the approach (for a more detailed discussion see ref 44), and there now seems to be little doubt as to its validity. The analogy with uncharged olefinic systems is less valid for four-bond allylic coupling constants, and, while in the olefinic systems *cis* allylic coupling constants are invariably larger than the *trans* coupling constants, the reverse has been found to be true in several ions.[45]

Carbon magnetic resonance has much potential application to the observation of protonated species due to the much larger chemical shifts which are encountered with carbon as compared to proton spectra.[46] In addition, a close correlation of the chemical shift with charge density has been found, and ^{13}C–H coupling constants can give information on the hybridization of the carbon atom concerned. ^{13}C resonance has, however, achieved only limited application at present due to experimental difficulties associated with low natural abundance and low sensitivity of ^{13}C. Protonated species have to be observed in relatively dilute solution, and thus, without the use of ^{13}C enrichment of the substrate, highly sensitive techniques coupled with time-averaging computer techniques for observation of spectra have to be employed. Undoubtedly this area will receive much more attention in the future, with more widespread use of the application of Fourrier transform methods to natural abundance ^{13}C nmr spectroscopy. Internuclear double resonance (indor)[47] has been used for the observation of ^{13}C spectra of simple protonated organic molecules.[45,48,49] This method entails observation of the proton spectrum while simultaneously irradiating the ^{13}C region. In cases where there is a coupling of the ^{13}C nucleus with a proton nucleus, changes in the proton spectrum will result when the irradiating frequency coincides with transition frequencies of the ^{13}C nucleus. By scanning the ^{13}C region and simultaneously monitoring a ^{13}C satellite peak in the proton spectrum, the ^{13}C spectrum can be obtained, together with the chemical shift of the ^{13}C nucleus. This method has the advantages implicit in observing direct proton resonance but has the disadvantages that a carbon–hydrogen coupling must be present and that difficulties arise in other than simple molecules.

For protonation on oxygen and nitrogen, ^{17}O and ^{14}N or ^{15}N resonance could potentially provide much information, but this field has to date received only little attention,[44] although ^{14}N shifts in protonated amides have been reported.[50]

A more extensive discussion of ^{13}C, ^{17}O, ^{14}N, ^{15}N as well as ^{1}H resonance spectra can be found in ref 44.

III. Protonated Alcohols

In sulfuric acid it has been shown by cryoscopic measurements that methyl and ethyl alcohol give stable solutions of the hydrogen sulfates.[51] Many other alcohols show similar initial behavior, but the solutions are not stable at room temperature. Alcohols form acid salts (eq 7) which in some cases can be isolated, and in solution it has been presumed that oxygen protonated species exist.[52] The first direct nmr evidence for the existence of protonated alcohols in strong acid solutions was found in 1961. The nmr spectrum of ethanol in BF_3–HF solution at −70° gave a well-resolved triplet at about δ 9.90 for the protons on oxygen coupled to the methylene protons.[38] In HSO_3F this fine structure is not observed, even at −95°, due to fast exchange.[53]

$$ROH + 2H_2SO_4 \longrightarrow RHSO_4 + H_3O^+ + HSO_4^- \qquad (7)$$

The nmr spectra of a series of aliphatic alcohols has been investigated in the stronger acid system, HSO_3F–SbF_5 using sulfur dioxide as diluent.[54,55] Methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *n*-amyl, neopentyl, *n*-hexyl, and neohexyl alcohol all give well-resolved nmr spectra at −60°, under these conditions.

$$ROH \xrightarrow[-60°]{FSO_3H\text{–}SbF_5\text{–}SO_2} ROH_2^+ \qquad (8)$$

The strength of this acid system is reflected by the fact that even at 25° solutions of primary alcohols in HSO_3F–SbF_5 show fine structure for the proton on oxygen (Figure 1). This

(43) P. Ros, *J. Chem. Phys.*, 49, 4902 (1968).
(44) G. A. Olah, J. M. Bollinger, and A. M. White, *Progr. Nucl. Magn. Resonance Spectrosc.*, in press.
(45) A. M. White and G. A. Olah, *J. Amer. Chem. Soc.*, 91, 2943 (1969).
(46) J. B. Stothers, *Quart. Rev., Chem. Soc.*, 1, 144 (1965).
(47) E. B. Baker, *J. Chem. Phys.*, 37, 911 (1962).
(48) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 90, 1884 (1968).
(49) G. A. Olah and A. M. White, *ibid.*, 91, 5801 (1969).
(50) R. E. Richards, *Trans. Faraday Soc.*, 58, 845 (1962).
(51) R. J. Gillespie and J. A. Leisten, *Quart. Rev., Chem. Soc.*, 8, 40 (1954).
(52) Reference 11, p 689.
(53) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, 43, 1045 (1965).
(54) G. A. Olah and E. Namanworth, *J. Amer. Chem. Soc.*, 88, 5327 (1966).
(55) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, 89, 3576 (1967).

Table VI

Nmr Shifts and Coupling Contents of Protonated Alcohols at −60° in HSO_3F[a]

Alcohol	*OH_2*	*H_1*	*H_2*	*H_3*	*H_4*	*H_5*	*J_{HCOH}*
$\overset{1}{C}H_3OH$	9.4 (q)[b]	4.7 (t)					3.6
$\overset{2}{C}H_3\overset{1}{C}H_2OH$	9.3 (t)	4.9 (m)	1.9 (t)				3.6
$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2OH$	9.4 (t)	4.7 (m)	1.8 (m)	0.8 (t)			3.5
$\overset{2}{C}H_3\overset{1}{C}H(OH)CH_3$	9.1 (d)	5.5 (m)	1.7 (d)				3.0
$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2OH$	9.4 (t)	5.0 (m)	2.0 (m)	1.4 (m)	1.1 (t)		3.5
$(\overset{3}{C}H_3)_2\overset{2}{C}H\overset{1}{C}H_2OH$	9.4 (t)	4.7 (m)	2.3 (m)	1.1 (d)			3.6
$\overset{4}{C}H_3\overset{3}{C}H_2\overset{1}{C}HOH\overset{2}{C}H_3$	9.1 (d)	5.4 (m)	1.6 (d)	1.9 (m)	0.9 (t)		3.0
$\overset{5}{C}H_3\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2OH$	9.3 (t)	4.9 (m)	2.3 (m) → 1.1 (H_2–H_4)			0.9	3.4
$(\overset{4}{C}H_3)_2\overset{3}{C}H\overset{2}{C}H_2\overset{1}{C}H_2OH$	9.4 (t)	4.3 (m)	1.8 (m) (H_2–H_3)		0.9 (d)		3.6
$(\overset{2}{C}H_3)_3C\overset{1}{C}H_2OH$	9.5 (t)	4.5 (t)	1.0 (s)				3.7
$\overset{6}{C}H_3\overset{5}{C}H_2\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2OH$	9.2 (t)	4.8 (m)		2.8 (m) to 0.8 (H_2–H_6)			3.5
$(\overset{3}{C}H_3)_3C\overset{2}{C}H_2\overset{1}{C}H_2OH$	9.3 (t)	4.9 (m)	1.9 (t)	0.8 (s)			3.5

[a] From TMS external capillary. [b] Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

indicates that at this relatively high temperature the exchange rate is still slow on the nmr time scale. The chemical shift data for a number of protonated alcohols are presented in Table VI, and the spectrum of protonated methanol is illustrated in Figure 1. The OH_2^+ protons of the normal alcohols appear at a lower field (δ 9.3–9.5) than the isomeric secondary alcohols (δ 9.1). This is due to a different charge distribution as confirmed by the C_1 protons appearing at higher field with the normal alcohols (δ 5.0–4.7) than the C_1 methine proton of the secondary alcohols (δ 5.4 and 5.5).

As would be expected, the proton on oxygen of protonated alcohols (δ 9.1 to 9.5) is slightly more deshielded than the proton on oxygen of protonated ethers (δ 7.8–9.0). The hydrogens on the carbon adjacent to oxygen show a significant downfield shift of about 1.5 ppm when compared to the protonated alcohol.

Aliphatic glycols in FSO_3H–SbF_5–SO_2 solution give diprotonated species at low temperatures.[56] In diprotonated diols the protons on oxygen are found at lower fields than in protonated alcohols reflecting the presence of two positive charges. This is especially true for ethylene glycol (δ 11.2) where the positive charges are adjacent. As the separation of the positive charges becomes greater with increasing chain length, the chemical shift of the protons on oxygen of protonated diols approaches that of protonated alcohols.

The reactivity of protonated alcohols[55] and protonated diols[56] in strong acids has been studied by nmr spectroscopy. Protonated methyl alcohol shows surprising stability in HSO_3F–SbF_5 and can be heated to 50° without undergoing significant decomposition. Protonated ethyl alcohol is somewhat less stable and begins to decompose at about 30°. The cleavage of protonated *n*-propyl alcohol has been followed in

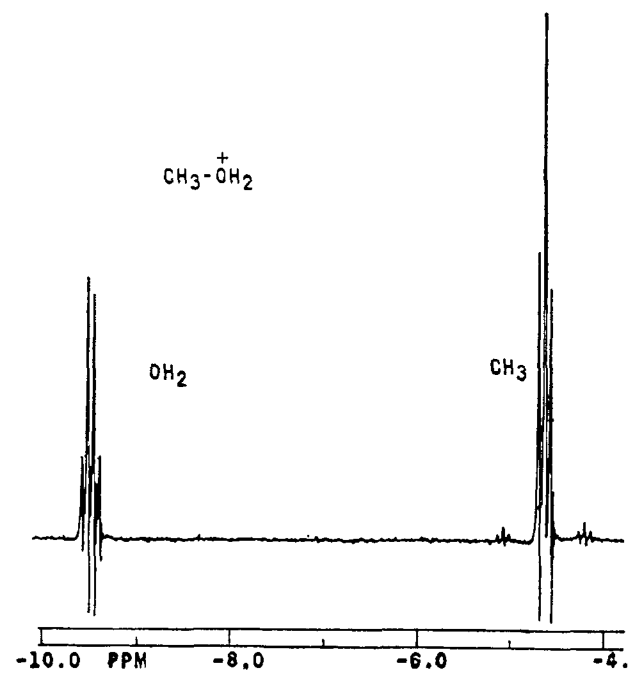


Figure 1. Pmr spectrum of protonated methyl alcohol in FSO_3H–SbF_5–SO_2 solution at −60° (according to G. A. Olah, J. Sommer, and E. Namanworth, *J. Amer. Chem. Soc.*, **89**, 3576 (1967)).

the temperature range of 5–25°, giving a mixture of trimethyl carbonium ion and isopropyldimethyl carbonium ion (eq 9).

$$CH_3CH_2CH_2OH_2 \xrightarrow[HSO_3F-SbF_5]{5-25^\circ} (CH_3)_3C^+ + (CH_3)_2CH\overset{+}{C}(CH_3)_2 + H_3O^+ \quad (9)$$

(56) G. A. Olah and J. Sommer, *J. Amer. Chem. Soc.*, 90, 927 (1968).

Higher protonated alcohols cleave to stable tertiary carbonium ions. For protonated primary and secondary alcohols, the initially formed primary and secondary carbonium ions rapidly rearrange to the more stable tertiary carbonium ions under the conditions of the reaction. For example, protonated *n*-butyl alcohol cleaves to *n*-butyl cation which rapidly rearranges to trimethylcarbonium ion (eq 10).

$$CH_3CH_2CH_2CH_2\overset{+}{O}H_2 \xrightarrow{k_1} [CH_3CH_2CH_2CH_2^+] \xrightarrow{k_2} (CH_3)_3C^+ \qquad (10)$$
$$k_2 \gg k_1$$

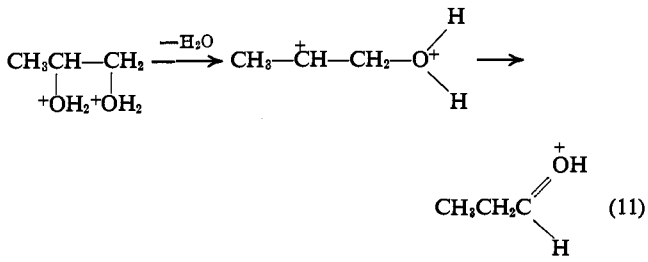
The cleavage to carbonium ions, shown to be first order, is enhanced by branching of the chain: protonated 1-pentanol is stable up to 0°, isopentyl alcohol is stable up to −30°, and neopentyl alcohol cleaves at −50°. The stability of the protonated primary alcohols also decreases as the chain length is increased. This is shown by comparison of the rate constants of the cleavage at 15° (Table VII).

Table VII

Rate of Cleavage of Protonated Normal Aliphatic Alcohols at 15°

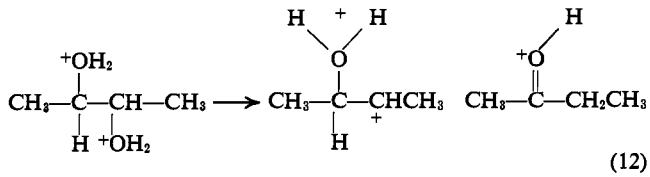
Protonated alcohol	*Rate constant* × 10^{-3} *min*$^{-1}$
n-Methyl	Stable to +50°
n-Ethyl	Stable to +30°
n-Propyl	20.5
n-Butyl	48.1
n-Pentyl	68.4
n-Hexyl	91.4

When the FSO_3H–SbF_5–SO_2 solutions of diprotonated glycols are allowed to warm up, pinacolone rearrangements, formation of allylic carbonium ions, and cyclization reactions of diprotonated glycols can be directly observed by nmr spectroscopy. Diprotonated ethylene glycol rearranges to protonated acetaldehyde in about 24 hr at room temperature. Protonated 1,2-propanediol undergoes a pinacolone rearrangement to protonated propionaldehyde probably through the initial cleavage of water from the secondary position (eq 11).

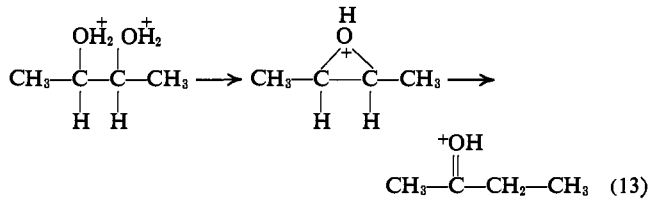


(11)

Diprotonated 2,3-butanediol rearranges to protonated methyl ethyl ketone either through a direct hydride shift (eq 12) or through a bridged intermediate (eq 13).

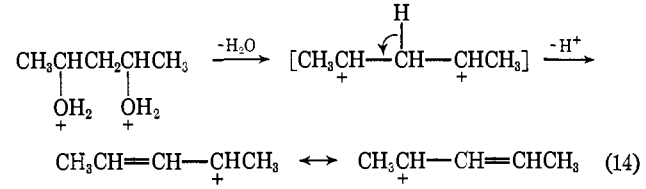


(12)



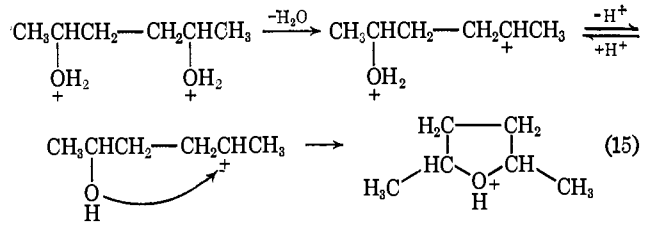
(13)

Diprotonated 2,4-pentanediol loses water and rearranges to form a stable allylic carbonium ion (eq 14). Diprotonated 2,5-



(14)

hexanediol, above about −30°, rearranges to a mixture of protonated *cis*- and *trans*-δ,δ′-dimethyltetrahydrofurans (eq 15). This would seem to indicate that there are either significant amounts of the monoprotonated form present or that the carbonium ion formed can easily lose a proton before ring formation takes place.



(15)

IV. Protonated Thiols

Aliphatic thiols are completely protonated in FSO_3H–SbF_5 diluted with SO_2 at −60°[57] (see Figure 2).

$$RSH \xrightarrow[-60°]{FSO_3H\text{-}SbF_5\text{-}SO_2} RSH_2^+\ SbF_5\text{–}FSO_3^- \qquad (16)$$

The resonance for the proton on sulfur is at considerably higher field (δ 5.9–6.6) than the corresponding proton on oxygen in protonated alcohols (δ 9.1–9.5) reflecting the larger size of the sulfur atom compared to oxygen. Table VIII summarizes the nmr data for a series of protonated aliphatic thiols. The protonated thiols are considerably more stable than protonated alcohols. Protonated *t*-butyl thiol shows no appreciable decomposition at −60° in HSO_3F–SbF_5–SO_2, while tertiary alcohols could not be observed under the same conditions and even secondary alcohols decompose at a significant rate. Protonated thiols decompose at higher temperatures to give protonated hydrogen sulfide (singlet, δ 6.60) and stable carbonium ions. For example, protonated *t*-butyl thiol slowly cleaves to trimethylcarbonium ion and protonated hydrogen sulfide (eq 17) when the temperature is increased to −30°

$$(CH_3)_3CSH_2^+ \xrightarrow{-30°} (CH_3)_3C^+ + H_3S^+ \qquad (17)$$

($t_{1/2} \sim 15$ min). Protonated *t*-amyl thiol also cleaves at this temperature to the dimethylethylcarbonium ion (eq 18).

(57) G. A. Olah, D. H. O'Brien, and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, 89, 2996 (1967).

Table VIII

Nmr Chemical Shifts and Coupling Constants of Protonated Thiols at −60° in HSO_3F–SbF_5–SO_2

Thiol	δ, ppm[a,b] H_1	H_2	H_3	H_4	SH_2^+	J_{H-H^+}, cps
HSH					6.60 (1)	...
$\overset{1}{C}H_3SH$	2.95 (3)[b]				6.45 (4)	8.0
$\overset{2}{C}H_3\overset{1}{C}H_2SH$	3.37 (6)	1.48 (3)			6.22 (cm)	8.0
$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2SH$	3.40 (cm)	1.98 (cm)	1.00 (3)		6.37 (cm)	8.0
$\overset{2}{C}H_3\overset{1}{>}CHSH$, CH_3	3.98 (cm)	1.73 (2)			5.93 (2)	7.5
$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2SH$	3.47 (6)	1.70 (cm)	1.70 (cm)	0.90 (3)	6.45 (3)	7.6
$\overset{2}{C}H_3\overset{2}{>}\overset{1}{C}HCH_2SH$, CH_3	3.32 (cm)	2.25 (cm)	1.03 (cm)		6.40 (3)	8.0
$\overset{3}{C}H_3\overset{2b}{C}H_2\overset{1}{C}HSH$, $\overset{2a}{C}H_3$	4.08 (6)	a 1.82 (2) b 2.10 (cm)	1.15 (3)		6.35 (2)	7.0
$(CH_3)_3CSH$	...	1.75 (1)			6.42 (1)	...
$\overset{3}{C}H_3\overset{2b}{C}H_2CSH$, CH_3, $\overset{2a}{C}H_3$	...	a 1.75 (1) b 1.97 (cm)	1.07 (3)		6.32 (1)	...

[a] From external capillary of TMS. [b] Multiplicity of peaks shown in parentheses; cm = complex multiplet.

$$CH_3CH_2-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-SH_2^+ \xrightarrow{-30°} CH_3CH_2-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}{}^+ + H_3S^+ \qquad (18)$$

Protonated secondary thiols are stable at even higher temperatures. Protonated isopropyl thiol cleaves slowly at 0° in FSO_3H–SbF_5 (1:1 *M*) solution. No well-identified carbonium ions were found in the nmr spectra due to the instability of the isopropyl cation under these conditions. Protonated *sec*-butyl thiol cleaves to trimethylcarbonium ion at this temperature.

$$CH_3CH_2\underset{CH_3}{\overset{|}{C}}HSH_2^+ \xrightarrow{0°} [CH_3CH_2\overset{+}{C}HCH_3] \longrightarrow (CH_3)_3C^+ \qquad (19)$$

Protonated primary thiols are stable at much higher temperatures. Protonated *n*-butyl thiol slowly cleaves to trimethylcarbonium ion only at +25°.

$$CH_3CH_2CH_2CH_2SH_2^+ \xrightarrow{+25°} [CH_3CH_2CH_2\overset{+}{C}H_2] \longrightarrow (CH_3)_3C^+ \qquad (20)$$

V. Protonated Ethers

The proton acceptor properties of both aliphatic and aromatic ethers have been studied extensively by a wide variety of techniques. The results of these investigations have been reviewed.[51,58,59] It is well known that ethers form low-melting solid complexes with acids in which the proton is attached to the basic site, the oxygen atom.[59] In solution, cryoscopic,[60] infrared,[61-65] conductance[66,67] and solubility measurements[68]

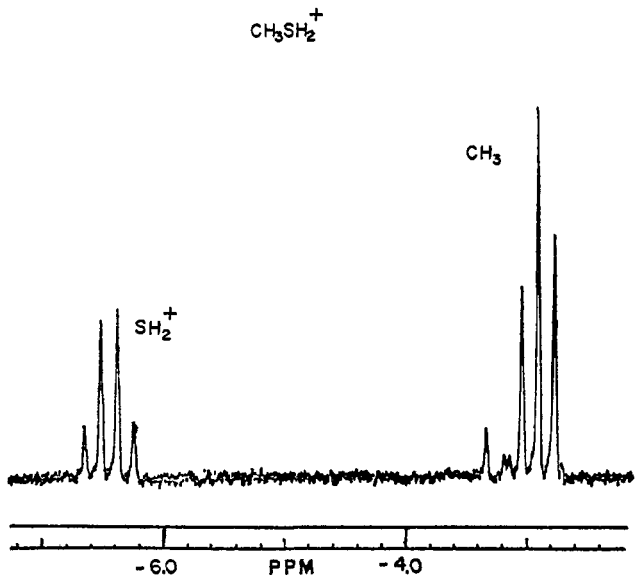


Figure 2. Pmr spectrum of protonated methyl mercaptan in HSO_3F–SbF_5–SO_2 solution at 60°.

(58) R. L. Burwell, *Chem. Rev.*, **54**, 615 (1954).
(59) W. Gerrard and E. D. Macklen, *Chem. Rev.*, **59**, 1105 (1959).
(60) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, p 47.
(61) P. Grange, J. Lascombe, and M. L. Josien, *Spectrochim. Acta*, **16**, 981 (1960).
(62) R. M. Adams and J. J. Katz, *J. Mol. Spectrosc.*, **1**, 306 (1957).
(63) J. Arnold, J. E. Bertie, and D. J. Millen, *Proc. Chem. Soc.*, 121 (1961).
(64) P. Grange and J. Lascombe, *J. Chim. Phys.*, **60**, 1119 (1963).
(65) C. Quivoron and J. Neel, *C. R. Acad. Sci.*, **259**, 1845 (1964).
(66) V. A. Plotnikov and M. L. Kaplan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 256 (1948); *Chem. Abstr.*, **42**, 7151*f* (1948).
(67) G. Jander and K. Kraffczyk, *Z. Anorg. Allg. Chem.*, **282**, 121 (1955).
(68) M. V. Ionin and V. G. Shverina, *Zh. Obshch. Khim.*, **35**, 209 (1965).

indicate that a 1:1 complex is formed between the ether and the acid. Recent investigations in strong acid systems have confirmed these earlier findings.

$$R{-}O{-}R + H{-}Y \rightleftharpoons R{-}\overset{\overset{H}{|}}{\overset{+}{O}}{-}R + Y^- \qquad (21)$$

A. ALIPHATIC ETHERS

Until recently the basicity of saturated aliphatic ethers had not been compared quantitatively to the protonation equilibria of other organic bases. The difficulty was caused primarily by the inability of saturated aliphatic ethers to give significant spectral changes in the ultraviolet and thereby act as Hammett indicators and be amenable to calculation of base strength on the familiar Hammett pH–H_0 scale.[8,69] This difficulty has been overcome in a series of recent investigations by a combination of the usual Hammett acidity calculations with solvent extraction and analysis by gas chromatography.[70–75] The method involves the distribution of the ether between a nonpolar, inert organic solvent and an aqueous phase containing a variable amount of sulfuric acid. The distribution of the ether between the phases was measured from low sulfuric acid concentration where the ether is essentially unprotonated to high acid concentration where the ether is essentially completely protonated. The distribution constants were determined by means of gas chromatographic analysis of the inert phase. The reliability of the method has been tested by comparison with results obtained using the H_0–indicator method[70] and by comparing the order of basicities with the order determined from the effect of various aliphatic ethers on the O–D stretching frequency of deuteriomethanol.[71] Some representative pK_a's for the conjugate acids of several aliphatic ethers are presented in Table IX. Earlier investigations had concluded that the basicity of aliphatic ethers would be primarily controlled by steric effects and that an increase in the size of the alkyl groups would result in base weakening.[76,77] However, inspection of Table I shows that no single factor controls the order of basicity, but rather it appears to be a delicate balance between steric, inductive, and solvation effects.[74] In the series of methyl ethers studied, an increase in the size of the other alkyl group causes a trend toward greater basicity. In this series the steric effect is relatively constant and the base-strengthening inductive effect predominates. As the size of both alkyl groups is increased, steric factors become more important. The line between inductive and steric control of basicity is crossed when the groups become as big as about *n*-propyl and decreasing basicity is observed. This decrease in basicity has been ascribed to steric hindrance due to "F-strain" and to solvation of the oxonium ion.[74] The much greater basicity of cyclic aliphatic ethers has been explained as primarily caused by substantial relief of internal strain upon protonation.[75]

Table IX

Dissociation Constants of Conjugate Acids of Some Aliphatic Ethers

Ether			
R_1	R_2	pK_a	*Lit. ref*
CH_3	CH_3	−3.83	71, 74
CH_3	CH_3CH_2	−3.82	74
CH_3	$CH(CH_3)_2$	−3.47	74
CH_3	$CH_3CH_2CH_2CH_2$	−3.50	74
CH_3	$C(CH_3)_3$	−2.89	74
CH_3CH_2	CH_3CH_2	−3.59	71, 74
CH_3CH_2	$CH_3CH_2CH_2CH_2$	−4.12	74
CH_3CH_2	$C(CH_3)_3$	−2.84	74
		−2.08	71, 74
		−2.79	71, 74
		−2.02	75
CH_3	C_6H_5	−6.54	70–73

A recent investigation of the nmr and infrared spectra of oxonium salts in methylene chloride has led to the identification of the resonance due to the proton on oxygen. These solutions of hexachloroantimonates were found to form both "free" complexes in which the proton is bonded to only one oxygen (**1**) and complexes in which the proton is shared be-

$$(C_2H_5)_2\overset{+}{O}H\ SbCl_6^- \qquad (C_2H_5)_2\overset{+}{O}H\cdots O(C_2H_5)_2\ SbCl_6^-$$
1 **2**
δ 9.34 δ 3.58

tween two ether molecules (**2**).[81] The infrared spectrum was studied and used to confirm the existence of the "free" complex and the bridged species. The proton on oxygen resonances were singlets, indicating that the proton is rapidly exchanging under the conditions of the experiment. Investigations using the extremely strong acid system, HSO_3F–SbF_5–SO_2 at low temperatures leads to comparable values for the chemical shift of the proton on oxygen for a variety of aliphatic ethers of δ 7.88–9.03 (Table X). Because of the stronger acid system and the low temperature, however, the exchange rate is slowed sufficiently so that the expected splitting of the proton on oxygen by the adjacent hydrogens is observed[82] (Figure 3).

(69) L. P. Hammett, ref 60, Chapter IX.
(70) E. M. Arnett and C. Y. Wu, *Chem. Ind. (London)*, 1488 (1959).
(71) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, 82, 4999 (1960).
(72) E. M. Arnett and C. Y. Wu, *ibid.*, 82, 5660 (1960).
(73) E. M. Arnett, C. Y. Wu, J. N. Anderson, and R. D. Bushick, *ibid.*, 84, 1674 (1962).
(74) E. M. Arnett and C. Y. Wu, *ibid.*, 84, 1680 (1962).
(75) E. M. Arnett and C. Y. Wu, *ibid.*, 84, 1684 (1962).
(76) J. Hine and M. Hine, *ibid.*, 74, 5266 (1952).
(77) P. D. Bartlett and J. D. McCollum, *ibid.*, 78, 1441 (1956).
(78) J. T. Edward, *Chem. Ind. (London)*, 489 (1963).
(79) T. Higuchi, C. H. Barnstein, H. Glassemi, and W. E. Perez, *Anal. Chem.*, 34, 400 (1962).
(80) J. T. Edward, J. B. Leane, and I. C. Wang, *Can. J. Chem.*, 40, 1521 (1962).
(81) F. Klages, J. E. Gordon, and H. A. Jung, *Chem. Ber.*, 98, 3748 (1965).
(82) G. A. Olah and D. H. O'Brien, *J. Am. Chem. Soc.*, 89, 1725 (1967).

Table X

Nmr Chemical Shifts and Coupling Constants of Protonated Ethers at −60° in $HSO_3F–SbF_5–SO_2$ (ppm)[a]

Ether	H_1	H_2	H_3	H_4	OH^+	J_{H-OH^+}, *cps*
$(\overset{1}{C}H_3)_2O$	4.49 (2)				9.03 (7)	3.4
$(\overset{2}{C}H_3\overset{1}{C}H_2)_2O$	4.73 (8)	1.53 (3)			8.61 (5)	3.6
$(\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2)_2O$	4.63 (6)	1.90 (6)	0.92 (3)		8.60 (5)	3.8
$((\overset{2}{C}H_3)_2\overset{1}{C}H)_2O$	5.18 (m)	1.55 (2)			7.88 (3)	4.1
$(\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2)_2O$	4.52 (6)	~1.60 (m)	~1.60 (m)	~0.90 (m)	8.56 (5)	3.8
$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1a}{C}H_2O\overset{1b}{C}H_3$	a 4.73 (6) b 4.37 (2)	~1.66 (m)	~1.66 (m)	0.90 (3)	8.86 (6)	3.7
$\overset{3}{C}H_3\overset{2a}{C}H_2\overset{1a}{C}H(\overset{2b}{C}H_3)O\overset{1b}{C}H_3$	a 4.96 (m) b 4.30 (2)	a 1.97 (m) b 1.61 (2)	0.97 (3)		8.47 (5)	3.8

[a] From external capillary of TMS; figures in parentheses represent multiplicity of peaks; m = multiplet.

The cleavage of protonated ethers in strong acid systems has not been studied extensively. Kinetic investigation of the cleavage of ethers in 99.6% sulfuric acid using cryoscopic methods showed that cleavage takes place by unimolecular fission of the conjugate acid of the ether to form the most stable carbonium ion and an alcohol. The carbonium ion and alcohol formed rapidly unite with hydrogen sulfate ion. The overall rate in sulfuric acid, however, appears to be dependent upon the concentration of sulfur trioxide. To reconcile these observations, the mechanism of eq 22–24 has been proposed.[83]

$$R{-}O{-}R' + H_2SO_4 \rightleftharpoons R{-}\overset{+}{O}(H){-}R' + HSO_4^- \quad (22)$$

$$R{-}\overset{+}{O}(H){-}R' + SO_3 \rightleftharpoons R{-}\overset{+}{O}(SO_3H){-}R' \quad (23)$$

$$R{-}\overset{+}{O}(SO_3H){-}R' \xrightarrow{RDS} R^+ + R'HSO_4;\quad R^+ \xrightarrow{HSO_4^-} RHSO_4 \quad (24)$$

Inductive and resonance effects seem to be more important in the alkyl chain of the potential carbonium ion than in the other alkyl group.

In a solution of $HSO_3F–SbF_5$, *n*-butyl methyl ether does not show any significant change, either cleavage or rapid exchange, as indicated by the nmr spectrum up to +40°. At this temperature, *n*-butyl methyl ether cleaves and a sharp singlet appears at δ 4.0. This can be attributed to the rearrangement of the *n*-butyl cation, formed in the cleavage, to trimethylcarbonium ion (eq 25).

$$CH_3\overset{+}{O}(H)CH_2CH_2CH_2CH_3 \longrightarrow CH_3\overset{+}{O}H_2 + [CH_3CH_2CH_2CH_2]^+ \longrightarrow (CH_3)_3C^+ \quad (25)$$

Ethers in which one of the groups is secondary begin to show appreciable cleavage at −30°. Protonated *sec*-butyl methyl ether cleaves cleanly at −30° to protonated methanol and trimethylcarbonium ion. Ethers in which one of the alkyl groups is tertiary cleave rapidly even at −70°.

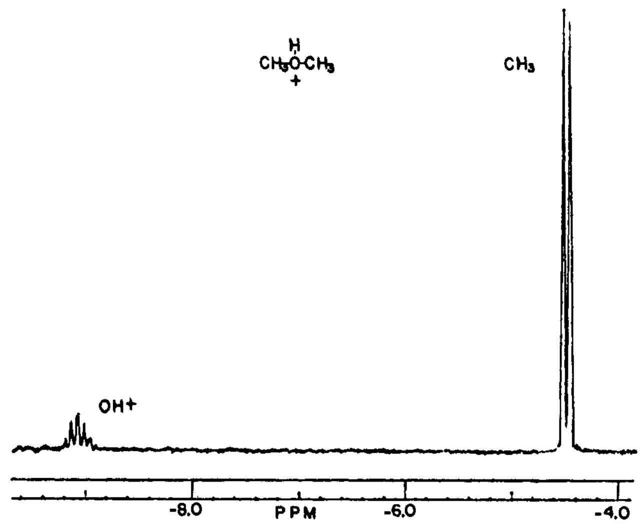


Figure 3. Pmr spectrum of protonated dimethyl ether in $FSO_3H–SbF_5–SO_2$ solution.

It was found possible to measure the kinetics of cleavage of protonated *sec*-butyl methyl ether by following the disappearance of the methoxy doublet in the nmr spectrum with simultaneous formation of protonated methanol and trimethylcarbonium ion. Kinetic data are summarized in Table XI. The cleavage shows pseudo-first-order kinetics. Presumably the rate-determining step is the formation of methylethylcarbonium ion followed by rapid rearrangement to the more stable trimethylcarbonium ion ($k_1 \ll k_2$) (eq 26).

$$CH_3CH_2CH(CH_3)\overset{+}{O}(H)CH_3 \xrightarrow{k_1} CH_3\overset{+}{O}H_2 + CH_3CH_2\overset{+}{C}HCH_3 \xrightarrow{k_2} (CH_3)_3C^+ \quad (26)$$

B. PROTONATED ALKYL PHENYL ETHERS

Recently, a lively controversy has developed concerning the site of protonation of phenols and aromatic ethers. Three

(83) D. Jaques and J. A. Leisten, *J. Chem. Soc.*, 4963 (1961).

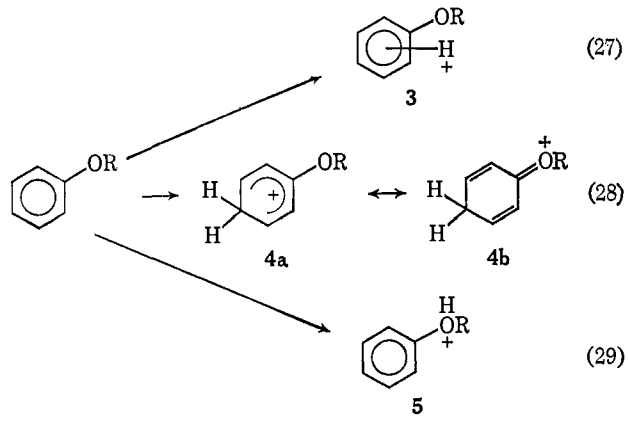
Table XI

Kinetics of Cleavage of $CH_3CH_2\overset{+}{C}HOCH_3$

Temp, °C	*k*, $sec^{-1} \times 10^4$
−29.0	3.64
	3.68
	5.11
	Av 4.14 ± 0.64
−17.5	10.9
	8.22
	7.57
	9.65
	Av 9.08 ± 1.2

E_a = 8.5 ± 3 kcal

possible protonated species can be envisioned: a π complex of the proton with the aromatic ring (**3**); a σ complex of the proton with one of the ring carbons (**4**); and protonation of the oxygen to form **5**. The evidence has pointed toward the existence in solution of either **4** or **5** and has been based primarily on ultraviolet and nmr data. Table XII[72,84-92] summarizes the protonation behavior of a number of phenols and alkyl phenyl ethers in strong acid systems. When one considers the wide differences in temperature, acid system, and structure of the substrate, differences in the site of protonation are not unexpected. For example, a number of alkyl phenyl ethers and phenols were found to undergo exclusive oxygen protonation at 0° in 30–90% aqueous sulfuric acid.[72] These results were based on the disappearance of the n–π^* transition at about 270 mμ. Similar spectral changes have been found when aniline is protonated[93] and in both cases may be attributed to the removal of the nonbonded electrons on the heteroatom from the resonance system upon protonation. However, under apparently comparable conditions (uv, 25°, 100% sulfuric acid; nmr, −64°, HSO_3F), phenol and anisole give exclusive carbon protonation.[84,85] These conclusions were based on ultraviolet evidence and the integrated intensity of the proton resonances in the nmr spectrum. The lack of the peak at about 270 mμ in the previous work[72] and the lack of the expected band at about 350 mμ for anisole and phenol similar to that found for protonated phloroglucinol were attributed to the substantial contribution of the quinoid structure of the carbon-protonated species (**4b**).[84] This apparently contradictory behavior of phenol and alkyl phenyl ethers upon protonation was clarified recently when it was pointed out that the conjugate acid of anisole might be expected to change from primarily the O-protonated species to the C-protonated species in going from 60% sulfuric acid to 100% sulfuric acid.[94] The oxygen protonated form would be expected to be more stabilized by hydrogen bonding to water than the carbon protonated form. Thus the decrease in the amount of water upon increasing the sulfuric acid concentration would be expected to favor carbon protonation.



The subtle interplay of several factors seems to determine whether oxygen or carbon protonation is observed. Examination of Table I for general trends shows that oxygen protonation is observed for unsubstituted phenols and unsubstituted alkyl phenyl ethers usually at relatively low temperatures. Substitution of electron-releasing groups on the aromatic ring causes carbon protonation to predominate. The strength of the acid system and the temperature-dependent rate of exchange of the proton on oxygen compared to the rate of exchange on carbon is important. This is especially true for nmr investigations because differences in these exchange rates will determine which type of protonation will be *observed* experimentally. It has been stated that, generally, oxygen-protonated cations exchange their protons much more readily than carbon-protonated cations.[86]

Observation of both oxygen-protonated and carbon-protonated species in the same solution bears out these subtle differences.[86] The lack of oxygen protonation in the ring-substituted phenols and alkyl phenyl ethers can be explained by substantial inductive increase of carbon basicity while the oxygen basicity remains relatively constant. For example, anisole displays both oxygen protonation and carbon protonation in HF or HF–BF_3 from 0 to −80° but 2,5- and 3,5-dimethylanisole show only carbon protonation down to −80°.[86] For protonated anisole, the strong temperature dependence of the mode of protonation is shown by the change of the ratio of C-protonated to O-protonated species from 1.5 at −80° to over 50 at 0°.[86]

VI. Protonated Sulfides

Protonated aliphatic sulfides have been studied at low temperatures by nmr spectroscopy in strong acid systems.[57] They

$$RSR \xrightarrow[-60°]{FSO_3H\text{–}SbF_5\text{–}SO_2} R\text{—}\overset{+}{\underset{H}{S}}\text{—}R \quad SbF_5FSO_3^- \qquad (30)$$

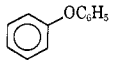
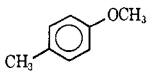
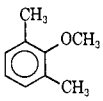
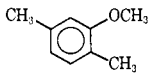
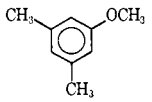
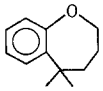
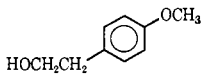
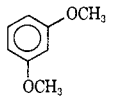
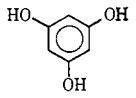
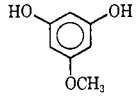
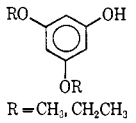
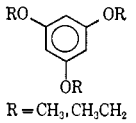
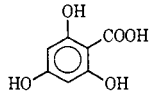
show well-resolved nmr spectra, the proton on sulfur being observed at about 6 ppm (Table XIII).

Recently, the nmr spectrum of protonated thiane-3,3,5,5-d_4 has been studied in FSO_3H–SO_2 in order to determine the con-

(84) T. Birchall, A. N. Bourns, R. J. Gillespie, and P. J. Smith, *Can. J. Chem.*, **42**, 1433 (1964).
(85) T. Birchall and R. J. Gillespie, *ibid.*, **42**, 502 (1964).
(86) D. M. Brouwser, E. L. Mackor, and C. Maclean, *Rec. Trav. Chim. Pays-Bas*, **85**, 109 (1966).
(87) D. M. Brouwer, E. L. Mackor, and C. Maclean, *ibid.*, **85**, 114 (1966).
(88) C. MacLean and E. L. Mackor, *Discuss. Faraday Soc.*, **34**, 196 (1962).
(88a) G. A. Olah, E. Namanworth, M. B. Comisarow, and B. Ramsey, *J. Amer. Chem. Soc.*, **89**, 5259 (1967).
(89) W. M. Schubert and R. H. Quacchia, *ibid.*, **84**, 3778 (1962).
(90) W. M. Schubert and R. H. Quacchia, *ibid.*, **85**, 1278 (1963).
(91) A. J. Kresge, G. W. Barry, K. R. Charles, and Y. Chiang, *ibid.*, **84**, 4343 (1962).
(92) A. J. Kresge and Y. Chiang, *Proc. Chem. Soc. London*, 81 (1961).
(93) G. W. Wheland, "Resonance in Organic Chemistry," Wiley, New York, N. Y., 1955, p 289.
(94) A. J. Kresge and L. E. Hakka, *J. Amer. Chem. Soc.*, **88**, 3868 (1966).

Table XII

Protonation of Phenols and Alkyl Phenyl Ethers. Oxygen *vs.* Carbon Protonation

Compound	Acid system[a]	Temp, °C	Exptl method	Position of protonation	Lit. ref
	1	0	Uv	O	72
	2	−64	Nmr, uv	C	84
	2	−67	Nmr, uv	C	84
	1	0	Uv	O	72
	2	−64	Nmr, uv	C	84–86
	3	−10	Nmr	C	
	3	−40 to −80		O, C	86–88
	4	...	Nmr	C	
	2	−85	Nmr	C	84
	3	−100	Nmr	O	86
	3	−100	Nmr	O	86
	4	−20	Nmr	C	86
	4	−20	Nmr	C	86
	4	−78	Nmr	C	87
	1	0	Uv	O	72
	5	−60	Nmr	O[b]	88
	4	−70	Nmr	C	86
	6	25	Nmr, uv	C	84, 89–91
	2	−80	Nmr	C	84
	2	25	Uv	C	89
	6	25	Nmr, uv	C	91
	6	25	Nmr, uv	C	89–91
	4	−80	Nmr	C	86
	6	25	H^3 exchange	C	92
	2	−63	Nmr	C	84
	6	−55	Nmr	C	84

[a] Acid systems: 1, H_2SO_4 (aqueous, 30–90%); 2, HSO_3F; 3, HF + BF_3; 4, HF; 5, HSO_3F–SbF_5–SO_2; 6, $HClO_4$ (aqueous, 40–75%). [b] Di-O-protonated species observed.

formational position of the proton on sulfur in this six-membered ring and to study the ring inversion process.[95] The proton on sulfur resides exclusively in the axial position.

The protonated sulfides are more stable to cleavage than the corresponding protonated ethers and also more stable than the protonated thiols. Protonated methyl *t*-butyl ether is completely cleaved to trimethylcarbonium ion and protonated methanol even at −70°. Protonated methyl *t*-butyl sulfide is

(95) J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Amer. Chem. Soc.*, 89, 5921 (1967).

Table XIII

Nmr Chemical Shifts and Coupling Constants of Protonated Sulfides at −60° in HSO_3F–SbF_5–SO_2

Sulfide	δ, ppm[a] *H_1*	*H_2*	*H_3*	*H_4*	*SH^+*	*J_{H-SH^+}, cps*
$(\overset{1}{C}H_3)_2S$	3.08 (2)[b]				6.52 (7)	8.0
$(\overset{2}{C}H_3\overset{1}{C}H_2)_2S$	3.57 (cm)	1.67			6.23 (5)	8.0
$(\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2)_2S$	3.33 (cm)	2.00 (cm)	1.07 (3)		6.18 (5)	8.1
$((\overset{2a}{C}H_3)(\overset{2b}{C}H_3)>CH)_2S$	3.98 (6)	a 1.62 (2) b 1.57 (2)			5.80 (3)	7.5
$(\overset{2}{C}H_3)_2\overset{1a}{C}HS\overset{1b}{C}H_3$	a 3.89 (cm) b 2.90 (2)	1.63 (2)			6.07 (cm)	8.0
$(\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2)_2S$	3.33 (cm)	~1.70 (cm)	~1.70 (cm)	1.00 (cm)	6.13 (5)	8.0
$(\overset{3}{C}H_3\overset{2a}{C}H_2\overset{1}{C}H(\overset{2b}{C}H_3))_2S$	3.70 (cm)	a 2.00 (cm) b 1.71 (cm)	1.10 (3)		5.73 (cm)	7.7
$((\overset{2}{C}H_3)_3C-)_2S$		1.83 (1)			5.83 (1)	...
$((CH_3)_3C-)S\overset{1}{C}H_3$	2.87 (2)	1.67 (1)			6.00 (4)	8.0
$(CH_3)_3CS\overset{1}{C}H(\overset{2a}{C}H_3)(\overset{2b}{C}H_3)$	4.05 (cm)	a 1.62 (2) b 1.73 (1)			6.25 (2)	7.0

[a] From external capillary of TMS. [b] Multiplicity of peaks shown in parentheses; cm = complex multiplet.

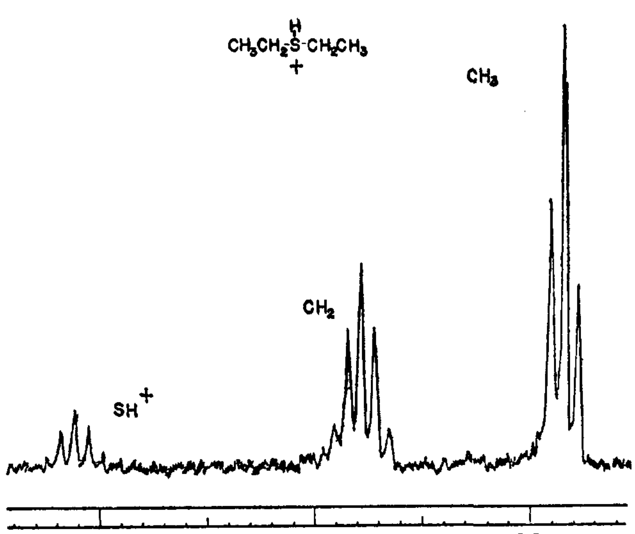


Figure 4. Pmr spectrum of protonated diethyl sulfide in FSO_3H–SbF_5–SO_2 solution at −60°.

completely stable at −60°. When the temperature is increased to −15°, protonated methyl *t*-butyl sulfide very slowly cleaves to trimethylcarbonium ion and protonated methyl thiol.

$$(CH_3)_3C-\overset{H}{\underset{+}{S}}-CH_3 \xrightarrow{-15°} (CH_3)_3C^+ + CH_3SH_2^+ \quad (31)$$

Protonated di-*t*-butyl sulfide shows very little cleavage at −60°. At 35° it cleaves slowly ($t_{1/2}$ ~1 hr) to trimethylcarbonium ion and protonated hydrogen sulfide, the latter giving a peak at δ 6.60.

$$(CH_3)_3C-\overset{H}{\underset{+}{S}}-C(CH_3)_3 \xrightarrow{-35°} (CH_3)_3C^+ + (CH_3)_3CSH_2^+$$

$$\downarrow$$

$$(CH_3)_3C^+ + H_3S^+$$

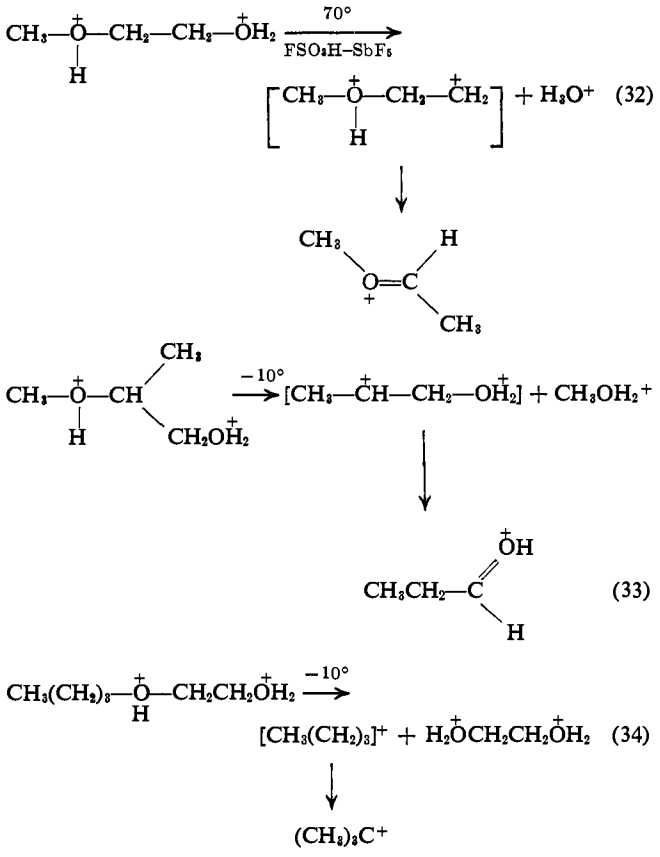
Protonated secondary sulfides show extraordinary stability toward the strongly acidic medium. Protonated isopropyl sulfide shows no appreciable cleavage up to +70° in a solution of FSO_3H-SbF_5 (1:1).

VII. Diprotonated Alkoxy Alcohols

Aliphatic alkoxy alcohols have been studied in FSO_3H–SbF_5–SO_2 solution by nmr and were found to be diprotonated.[96] The spectra show the alkoxy proton at about 11 ppm and the hydroxyl protons at about 10 ppm, slightly deshielded from the corresponding protons in the protonated ethers and alcohols, respectively. Cleavage of these dications *via* three different pathways was reported, and while the mechanism of these reactions has not been studied, the mode of cleavage observed

(96) G. A. Olah and J. Sommer, *J. Amer. Chem. Soc.*, 90, 4323 (1968).

apparently reflects the stability of the leaving groups and on their ability to undergo rapid conversion to a stable ion. These three cleavage pathways are illustrated by the examples in eq 32–34. Ions in brackets are presumed to be intermediates although they were not observed.



(32)

(33)

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VIII. Protonated Aldehydes and Ketones

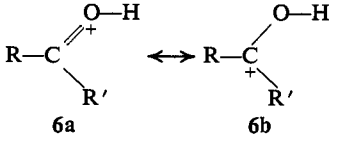
Extensive kinetic and spectral evidence indicates that in acidic media nucleophilic attack at the carbonyl carbon takes place with prior protonation at the carbonyl oxygen.[97] In relatively weak acid systems (dilute, aqueous sulfuric acid to <90% sulfuric acid) ultraviolet data have been used to study the equilibrium between acetone and its conjugate acid.[98] These data show a shift of the n–π^* transition (275 mμ) to shorter wavelength with increasing acid concentration. This shift was attributed to protonation. However, at higher acid concentrations, the self-condensation of acetone to mesityl oxide and phorone makes the interpretation of the ultraviolet data more difficult. The surprisingly high basicity of acetone (pK_{BH^+} = 1.58)[98] reported in this investigation led to the reinvestigation of the protonation of a number of aliphatic ketones in sulfuric acid.[99] This work demonstrates that the shift of the band at about 275 mμ at low acid concentrations is due to a medium effect rather than protonation. Increase in the acid strength above about 65% sulfuric acid results in the complete disappearance of this peak because of protonation of the oxygen. The pK_{BH^+} values based on these spectrophotometric results[99] lead to more reasonable values for acetone and other aliphatic ketones of about −7.0. The basicity of variously substituted benzaldehydes and acetophenones in sulfuric acid[100,101] and perchloric acid[102] have been determined from ultraviolet data. These basicity values have been correlated with σ_+,[101] σ_m, and variations of the carbonyl stretching frequency.[101,103]

In comparing the ultraviolet and infrared data to the more recent application of nuclear magnetic resonance to the protonation of carbonyls in strong acid systems, it can be seen that the ultraviolet and infrared data can be interpreted in terms of bond order and hybridization of the carbonyl carbon–oxygen bond, but little structural information results. On the other hand, nuclear magnetic resonance yields quite definite structural information but care must be taken in relating chemical shift and coupling data directly to bond-order and hybridization considerations, especially since other factors such as the effect of protonation on the magnetic anisotropy of the carbonyl bond and the conformation about the α-carbon–carbonyl carbon must be taken into account.

Combined with the earlier ultraviolet and infrared studies, nuclear magnetic resonance leads to a more detailed knowledge of the structure of protonated carbonyls in strong acid solution and demonstrates for the first time the existence of isomers of the protonated species.

A summary of the nmr data for a representative group of protonated aldehydes and ketones is presented in Table XIV.[42,58,104–108] When one allows for the wide variety of acid systems and solvents used and the differences in concentration and temperature, the close correspondence of the chemical shifts for the proton on oxygen for a particular carbonyl is quite remarkable. These values generally agree within 1 ppm. Examination of data from only one source, where conditions of acid system, temperature, and concentration are usually more constant, shows that the agreement is much better than this.

The extent of the contribution of the resonance forms of protonated carbonyls (**6a,b**) has been discussed on the basis of the nmr data.[42,58,104–110] These arguments have been based on the large deshielding of the proton on oxygen, the size of the coupling between the proton on oxygen and the aldehydic hydrogen for protonated aldehydes, the existence of isomers for protonated carbonyls, and the appearace of allylic-like coupling between the proton on oxygen and the hydrogens on the α carbon. These data strongly indicate that there is substantial double-bond character in the carbonyl carbon–oxygen bond for protonated carbonyls. These data have been treated in only a qualitative manner, however, and until a more quantitative



(35)

6a **6b**

(97) S. Patai, Ed., "The Chemistry of the Carbonyl Group," Interscience, New York, N. Y., 1966, Chapter 9.
(98) S. Nagakura, A. Minegishi, and K. Stanfield, *J. Amer. Chem. Soc.*, 79, 1033 (1957).
(99) H. J. Campbell and J. T. Edward, *Can. J. Chem.*, 38, 2109 (1960).
(100) K. Yates and R. Stewart, *ibid.*, 37, 664 (1959).
(101) R. Stewart and K. Yates, *J. Amer. Chem. Soc.*, 80, 6355 (1958).
(102) K. Yates and H. Wai, *Can. J. Chem.*, 43, 2131 (1965).
(103) M. Liler, *Spectrochim. Acta, Part A*, 23, 139 (1967).
(104) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, 86, 696 (1967).
(105) D. M. Brouwer, *ibid.*, 86, 879 (1967).
(106) M. Brookhart, G. C. Levy, and S. Winstein, *J. Amer. Chem. Soc.*, 89, 1735 (1967).
(107) G. A. Olah, M. Calin, and D. H. O'Brien, *ibid.*, 89, 3585 (1967).
(108) G. A. Olah and M. Calin, *ibid.*, 90, 938 (1968).
(109) D. M. Brouwer, *Chem. Commun.*, 515 (1967).
(110) G. A. Olah and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, 88, 3310 (1966).

Table XIV

Characteristic Chemical Shifts and Coupling Constants of Protonated Aldehydes and Ketones[a]

Aldehyde: $R-\overset{2}{C}H=\overset{+}{\underset{1}{O}}H$

R	H_1	$J_{1,2}$	H_2	*Acid system*[b]	*Temp, °C*	*Lit. ref*
H	16.73	8.7 (*syn*)	−10.18	1	−60	42
		21.1 (*anti*)				
CH_3	15.11	9.0	10.10	1	−60	42
(H_1, H_2 *syn*)	16.01	8.1	10.00	2	−82	104
	15.47	8.5	10.02	3	−20	105
	14.78	8.5	9.77	1	−52	106
CH_3	15.47	19.5	*c*	1	−60	42
(H_1, H_2 *anti*)	15.74	19	*c*	3	−20	105
	15.14	18.5	*c*	1	−52	106
CH_3CH_2	15.03	8.8	−10.15	1	−60	42
(H_1, H_2 *syn*)	16.04	8.1	9.97	2	−80	104
	15.12	9	...	1	−65	106
$(CH_3)_2CH$	15.22	8.8	10.25	1	−60	42
$(CH_3)_3C$	15.30	9.0	10.17	1	−60	42

Ketone: $R-\overset{}{C}(R')=\overset{+}{\underset{1}{O}}H$

R	*R'*	H_1 *syn to R*	H_1 *syn to R'*	*Acid system*[b]	*Temp, °C*	*Lit. ref*
CH_3	CH_3	14.93	...	1	−60	107
		14.24	...	1	−59	106
		14.68	...	3	−20	105
		14.45	...	4	+25	53
CH_3	CH_3CH_2	14.26	13.91	1	−60	107
		14.03	13.65	1	−60	106
		14.67	14.40	3	−20	105
CH_3	$CH_3CH_2CH_2$	14.30	14.16	1	−60	
CH_3	$CH(CH_3)_2$	14.41	13.95	1	−60	107
		14.69	14.34	3	−20	105
CH_3	$C(CH_3)_3$	14.23	...	1	−60	107
		14.72	...	3	−20	105
CH_3	CH_3CH_2	14.06	...	1	−60	107
		14.43	...	3	−20	105
$CH(CH_3)_2$	$CH(CH_3)_2$	13.86		1	−60	107
$C(CH_3)_3$	$C(CH_3)_3$	13.51		1	−60	107
CH_3	C_6H_5	13.03	...	1	−52	106
		13.46	...	5	−82	53

[a] Chemical shifts in ppm relative to TMS; coupling constants in Hz. [b] Acid systems: 1, HSO_3F–SbF_5–SO_2; 2, HF–BF_3; 3, HF–SbF_5; 4, HSO_3F–SbF_5; 5, HSO_3F. [c] Exact chemical shift not observed; probably obscured by predominating *syn* isomer.

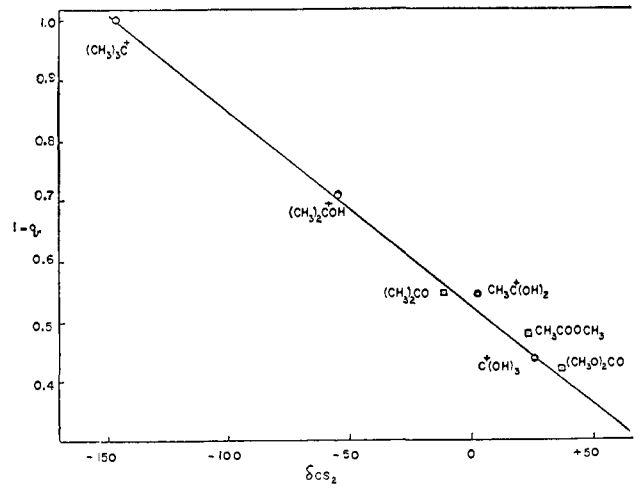


Figure 5. Correlation of π-electron densities (q_r) with ^{13}C chemical shifts.

relationship can be developed, it should be repeated that care should be taken in relating chemical shift data directly to hybridization and bond order considerations.

Evidence for the charge distribution in aldehydes and ketones has also been obtained using ^{13}C spectroscopy. A correlation between calculated π-electron density (using a Hückel molecular orbital approach) and ^{13}C chemical shift has been reported and is shown in Figure 5.[48] The ^{13}C shifts in protonated formaldehyde, protonated acetaldehyde, and protonated acetone show that the effect of successively replacing the hydrogens in protonated formaldehyde by methyl groups is to cause an upfield shift of 15 ppm.[49] This is a slightly greater effect than in alkanes and indicates that the charge on the sp^2 carbon in these three ions is very similar and that the methyl group is not exerting any special stabilizing effect on the ion—any inductive or hyperconjugative effects being similar to those in alkanes. The ^{13}C resonances of the methyl groups in protonated acetaldehyde and protonated acetone are almost identical with those in their uncharged precursors.[49] This observation, coupled with information from the proton spectra of these ions, indicates that the positive charge in these ions is distributed between the sp^2 carbon, the methyl and aldehydic protons, and the hydroxyl group, the methyl carbon having a charge close to that in the uncharged precursor. A similar charge distribution has recently been calculated theoretically.[48] These calculated charge densities are shown below for acetaldehyde and protonated acetaldehyde together with the

assumed bond lengths and angles in the isomers depicted (Figure 6).

In connection with the evaluation of the charge distribution in protonated aldehydes and ketones the nmr spectra of protonated benzaldehyde and protonated acetophenone are quite revealing. It has been found that whereas in protonated acetophenone the two *ortho* protons in the phenyl ring are equivalent at temperatures as low as −90° in FSO_3H–SbF_5–SO_2 solution, protonated benzaldehyde under the same conditions shows nonequivalence of both *ortho* and *meta* protons. Collapse of the two *ortho* multiplets due to the two protons becoming equivalent occurs at −30°. Barring accidental equivalence in the case of protonated acetophenone, this result requires that the barrier to rotation about the C–phenyl bond be substantially higher in the case of protonated benzaldehyde. While this could possibly be due to the bulk of the methyl group as compared to hydrogen, it can also be taken to indicate a greater contribution of resonance structures placing the positive charge on the phenyl ring in the case of protonated benzaldehyde, and thus that the methyl group in protonated acetophenone is exerting a stabilizing effect on the ion. This can be shown in a different manner from the ^{19}F chemical shifts in *meta*- and *para*-substituted fluorobenzenes in which the substituent can be protonated. These shifts can be related to the electronic effects of the substituents, and substituent constants (both resonance and inductive) have been obtained for a wide variety of substituents.[111] This approach has been applied in superacid solution in which the substituent is protonated, and some of these results are given in Table XV.[41] In the case of the protonated *m*- and *p*-fluorobenzaldehyde and -acetophenone, it can be seen that the substitution of methyl for hydrogen reduces significantly both the inductive (σ_I) and resonance ($\sigma_R°$) interaction of the cationic center

Table XV

^{19}F Nmr Shifts for *m*- and *p*-Fluorophenyl Derivatives Attached to a Positively Charged Center

Substituent	ϕ_m	ϕ_p	$\Delta\phi_p - \phi_m$	σ_I	$\sigma_R°$	$(\sigma_I + \sigma_R°)$
$-\overset{+}{C}(CH_3)_2$	6.35	52.39	46.0	0.98	1.56	2.54
$-C(=\overset{+}{O}H)CH_3$	11.03	45.13	34.1	1.64	1.16	2.80
$-\overset{+}{C}H(OH)$	6.71	40.61	33.9	1.03	1.15	2.18
$-\overset{+}{N}(OH)=O$	8.60	39.60	31.0	1.30	1.05	2.35
$-\overset{+}{C}(CH_3)(OH)_2$	4.63	32.43	27.8	0.74	0.94	1.68
$\overset{+}{C}(OH)_3$	4.90	24.92	20.0	0.77	0.67	1.44
$-\overset{+}{N}\equiv N$	10.19	32.00	11.8	1.52	0.40	1.92
$-\overset{+}{N}H_3$	5.01	3.75	−1.3	0.79	−0.04	0.75

(111) R. W. Taft, *et al.*, *J. Amer. Chem. Soc.*, **85**, 709, 3146 (1963).

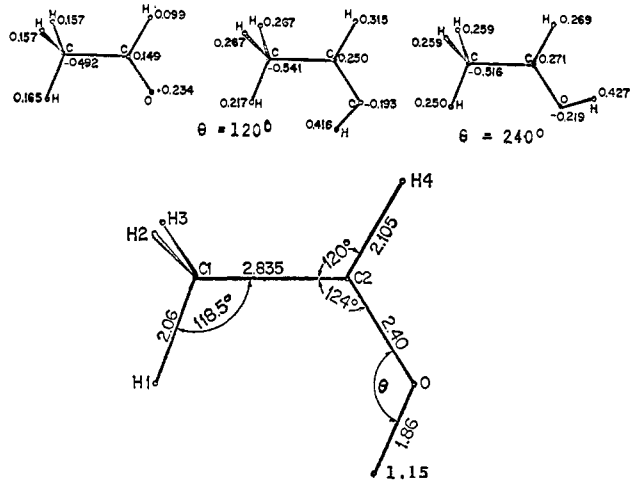
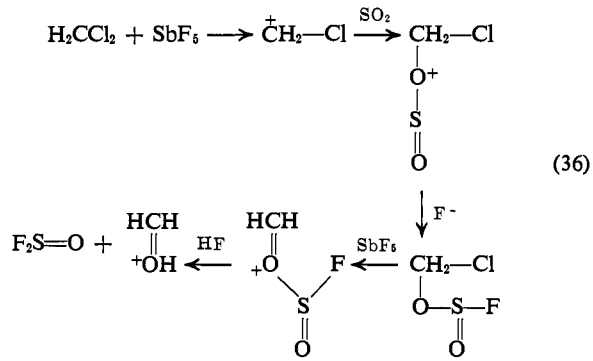


Figure 6. Gross atomic charges for acetaldehyde and protonated acetaldehyde.

with the phenyl ring showing that methyl is behaving as an electron donor with respect to hydrogen.

Protonated formaldehyde is the simplest heteroatom containing organic species that has been studied and can be generated by passing formaldehyde from the pyrolysis of paraformaldehyde over a stirred solution of FSO_3H–SbF_5 in SO_2 at −76° or by reaction of methylene chloride with FSO_3H–SbF_5 diluted with SO_2 at −100°. The proposed mechanism[112] for this latter reaction is shown in eq 36.



(36)

The proton and ^{13}C spectrum of the ^{13}C-enriched ion have been studied in some detail,[45] and the signs and magnitudes of all the coupling constants have been obtained and are given in Table XVI.

The assignment of H_1 and H_2 given is consistent both with the magnitudes of the vicinal coupling constants and those of the two direct carbon–hydrogen coupling constants. The large, positive geminal proton–proton coupling constant compares

Table XVI

^1H and ^{13}C Nmr Data for Protonated Formaldehyde

		δ values		*Coupling constant, Hz*
H^1, H_3, $^{13}C=O^+$, H_2	$\delta(H_1)$	9.820	J_{12}	+21.7
	$\delta(H_2)$	9.940	J_{13}	+9.0
	$\delta(H_3)$	16.70	J_{23}	+19.0
(FSO_3H–SbF_5–SO_2, −60°)	$\delta(^{13}C)$	−29.2	$J_1(^{13}C)$	+198.4
			$J_2(^{13}C)$	+209.8
			$J_3(^{13}C)$	−8.7

(112) G. A. Olah, J. M. Bollinger, and J. Brinich, *ibid.*, 90, 2587 (1968).

with a value of +42 in formaldehyde itself, and the decrease of this value on protonation has been discussed in terms of the molecular orbital approach to the calculation of coupling constants.[45] The *cis* and *trans* vicinal coupling constants of 4.0 and 21.7 Hz compare with 11.4 and 19.1 Hz found in ethylene.

The nuclear magnetic resonance spectra of protonated acetaldehyde and methyl ethyl ketone have been reported by a number of investigators.[42,104-107] These spectra are representative of the nmr evidence which can lead to conclusions concerning the structure of protonated carbonyls and are reproduced in Figures 7 and 8. The complex resonances between δ 14 and 17 can be assigned to the proton on oxygen. For protonated aldehydes, where the integrated intensity of the proton on oxygen and the carbonyl hydrogen is 1:1, proof that these low-field resonances are caused by the proton on oxygen and not the carbonyl hydrogen was obtained from the spectrum of protonated acetaldehyde-d_4.

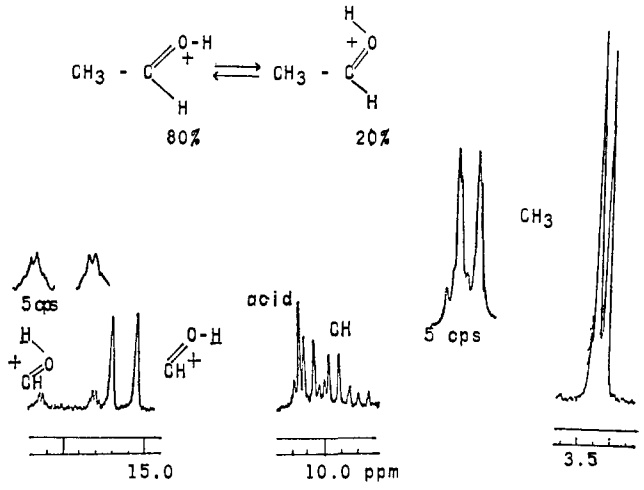
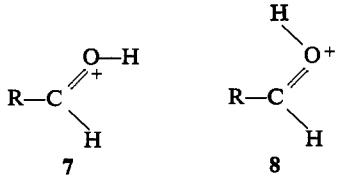


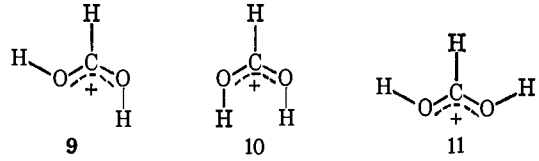
Figure 7. Nmr spectrum of protonated acetaldehyde (HSO_3F–SbF_5–SO_2; −60°).

The multiplicity of the low-field resonances leaves little doubt that more than one isomer exists for protonated acetaldehyde and for protonated ketones in which the alkyl groups are not the same. For protonated acetaldehyde (Figure 7) a doublet appears centered at about 15.47 ppm coupled to the carbonyl hydrogen ($J_{HC=\overset{+}{O}H}$ = 8.5 Hz) for the isomer in greater abundance. Slightly downfield from this doublet is another doublet showing fine structure with a larger coupling to the carbonyl hydrogen ($J_{HC=\overset{+}{O}H}$ = 19.5 Hz). These proton on oxygen resonances have been assigned to the *syn* (or *cis*)



(**7**) and *anti* (or *trans*) (**8**) arrangement of the proton on oxygen to the carbonyl hydrogen. The magnitudes of these coupling constants are comparable with analogous *cis* and *trans* coupling constants found for uncharged, isoelectronic alkenes.[118]

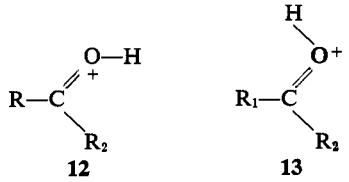
Nonempirical molecular orbital calculations have been carried out[48] to determine the relative stabilities of the two isomers of protonated acetaldehyde. Configuration **7** (R = CH_3) was found to be less stable than **8** (R = CH_3) by 1.4 kcal/mol in reverse order to that observed on the basis of the assignments given above. For protonated formic acid the most stable system was found to be **9**, followed by **10**, which is 1.5 kcal/



mol higher in energy. The other possible structure, **11**, was found to be another 6.0 kcal/mol higher in energy. These latter two structures are again in the reverse order of stabilities to those found on the basis of the assigned structures.

Three explanations for these discrepancies have been presented and discussed: first, that the calculations are too inaccurate; second, that the assignments made experimentally are incorrect; and third, that the difference lies in the fact that the calculations are for an isolated ion while experimental observations have been made in solution. No firm conclusion has been reached as to which of these explanations is the correct one though the body of experimental evidence obtained seems to have such a high degree of consistency as to rule out the possibility of the assignments made experimentally being incorrect.

For ketones in which the alkyl groups are different ($R_1 \neq R_2$), two proton on oxygen resonances appear (**12**, **13**). Pro-



tonated methyl ethyl ketone (Figure 8) shows the resonance for the proton on oxygen of the isomer with the proton on oxygen *syn* to the methyl group at approximately 14.30 ppm and for the isomer with the proton on oxygen *syn* to the ethyl group at 13.99 ppm. The explanation given[114] for the appearance to two OH resonances in the case of protonated unsymmetrical benzo-

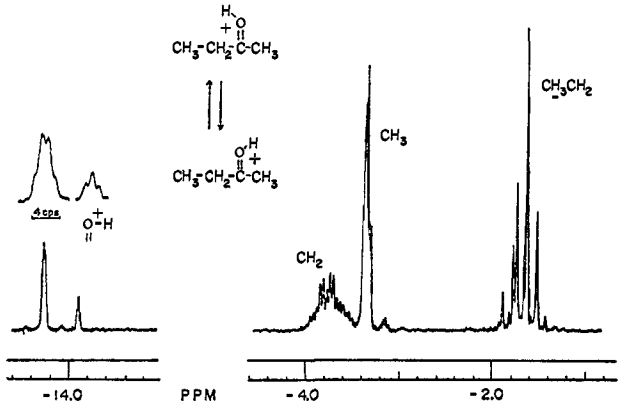


Figure 8. Nmr spectrum of protonated methyl ethyl ketone (HSO_3F–SbF_5–SO_2; −60°).

(113) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, 83, 231 (1961).

(114) T. J. Sekuur and P. Kranenburg, *Tetrahedron Lett.*, 4793 (1966).

phenones is probably incorrect—an equilibrium between **12** and **13** is more consistent with the spectra obtained. It will be noted that for the isomer in greater abundance (**13**, R_1 = CH_3; R_2 = CH_2CH_3) the proton on oxygen appears at lower field than for the isomer in which the proton on oxygen is *syn* to the larger ethyl group (**12**, R_1 = CH_3; R_2 = CH_2CH_3). For the protonated ketones studied, the proton on oxygen of the isomer in greatest abundance was found consistently at lower field. For acetaldehyde, the only aldehyde for which isomerism was observed when protonated, the opposite was true. The chemical shift of the proton on oxygen of protonated carbonyls perhaps reflects changes in the carbon–oxygen bond anisotropy upon protonation and any steric deshielding experienced by the proton on oxygen caused by the *syn* alkyl group.

Closer examination of some of the proton on oxygen resonances leads to evidence which further supports the isomer assignment. The proton on oxygen resonance for the *anti* isomer of protonated acetaldehyde (**8**, R = CH_3, and Figure 7) centered at 15.47 ppm is further split into a doublet of quartets. For protonated methyl ethyl ketone, the proton on oxygen resonance *syn* to the methyl is a quartet and the proton on oxygen *syn* to the ethyl is a triplet (Figure 8). These couplings are small, on the order of 0.8–1.2 Hz. Similar couplings were found for the other protonated ketones[107] and have been assigned to long-range, allylic-like coupling of the proton on oxygen with the hydrogens on the α-carbon. Similar coupling for the *syn* isomer of protonated acetaldehyde in which the proton on oxygen is *trans* to the methyl (**7**, R = CH_3, and Figure 7) was too small to be resolved and is probably less than 0.3 Hz.[42] In isoelectronic olefinic systems *cis* allylic coupling is usually larger than *trans* allylic coupling.[115] Thus, observation of allylic-like couplings in protonated carbonyls further justifies the isomer assignment and the double-bond character of the carbon–oxygen bond. The appearance of these small allylic couplings in other protonated organic compounds such as esters, acids, and amides has been found to be of value in determining the structure of the protonated species; however, cases have been found in which the magnitude of the *syn* and *anti* allylic coupling constants are reversed and caution should be exercised[45] in drawing conclusions from these four-bond couplings. The exceptions usually are ions in which the methyl group is attached directly to a heteroatom as in methoxycarbonium ion, $CH_3OCH_2^+$.

The isomer in greater abundance, as determined by integration of the proton on oxygen resonances, is the isomer which would have been predicted from simple steric considerations, with the proton on oxygen *syn* to the smaller group. For protonated aldehydes, the increase in steric requirements in going from methyl (acetaldehyde) to ethyl (propionaldehyde) is apparently great enough not to allow observation of the isomer with the proton on oxygen *syn* to the ethyl. For protonated ketones this trend is also observed. Only one isomer is observed for protonated methyl *t*-butyl ketone in which the proton on oxygen is *syn* to the methyl group.[107] Qualitative isomer distributions for some protonated carbonyls are presented in Table XVII.

Attempts have been made to measure the energy of activation for the *syn–anti* conversion, and it has been estimated that the barrier to rotation for the proton on oxygen about the carbonyl carbon–oxygen bond has a minimum value of about 17 kcal/mol.[105] Attempts to obtain precise values have not yielded conclusive results. As the temperature is raised to about +35°, the proton on oxygen resonances begin to broaden. However, before a sharp singlet is formed, indicating free rotation about the carbonyl carbon–oxygen bond, intermolecular proton exchange with the acid system also becomes rapid.[104,105]

Table XVII

Isomer Distribution for Protonated Aldehydes and Ketones, $R_1—C—(R_2)=\overset{+}{O}H$

R_1	R_2	*syn* to R_1, %	*syn* to R_2, %	Temp, °C	Lit. ref
CH_3	H	~20	~80	−20	105
		~18	~82	−56	106
		20	80	−60	42
c-C_3H_5	H	~25	~75	−50	106
$CH_3CH_2CH_2$	H	~100	~0	−60, −65	42, 106
CH_3CH_2	CH_3	~33	~67	−20	105
		~20	~80	−60	106
		19.4	80.6	−60	107
$(CH_3)_2CH$	CH_3	~16	~84	−20	105
		15.4	84.6	−60	107
$(CH_3)_3C$	CH_3	~6	~94	−20	105
		~100	~0	−60	107

It is possible that the lowest barrier to interconversion of isomers in protonated acetaldehyde is not rotation about the C–O bond but motion of the hydroxyl proton through the plane. Nonempirical molecular orbital calculations[48] have been done which suggest the latter alternative. In protonated aldehydes a rotation about the C–O bond is rather difficult and has an energy barrier of 25–30 kcal/mol. A rotation through the plane, however, requires only 17–18 kcal/mol. In protonated formic acid the C–O bond is not as strong as in aldehydes, and a rotation around the C–O bond requires only 15 kcal/mol, while the motion through the plane still requires 17 kcal/mol. The experimental barrier in the case of protonated formic acid has been found to be 15.3 kcal in HF–SbF_5.[116] The C–O bond order dependence of the calculated barriers to rotation and motion of the hydroxyl proton through the plane is illustrated in Figure 9.

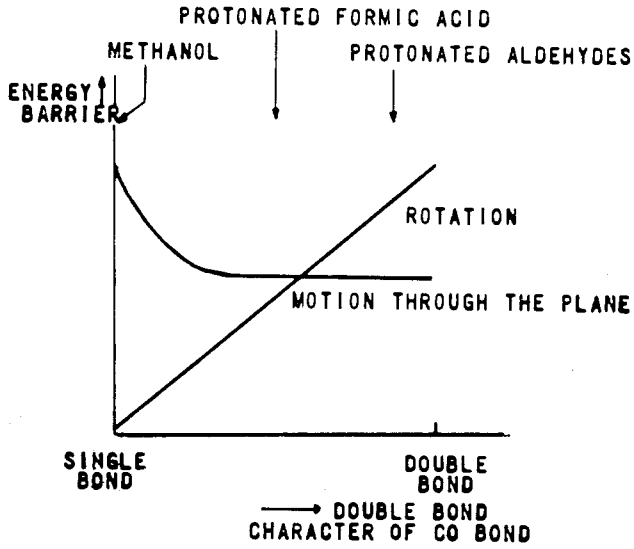


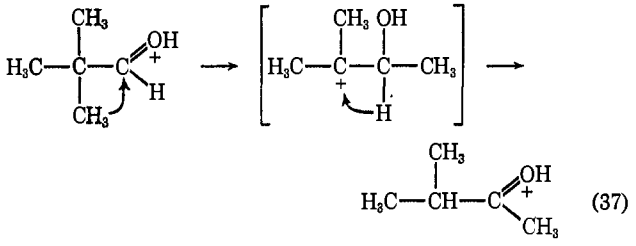
Figure 9. Schematic comparison of energy barriers for rotation and motion through the plane (according to P. Ros, *J. Chem. Phys.*, **49**, 4902 (1968)).

(115) (a) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); (b) *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).

(116) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, 87, 1313 (1968).

Analysis of the nmr spectra of protonated carbonyls leads to evidence for changes in the conformation about the α-carbon–carbonyl carbon bond. The coupling between the α-hydrogens in *syn* protonated acetaldehyde (5) and the carbonyl hydrogen (J_{CH_3-CH} = 3.4 Hz[42,104–106]) and the lack of this coupling in the other aldehydes indicate subtle changes in the preferred conformation about this bond. For protonated aldehydes other than acetaldehyde where only the *syn* isomer is observed, a measurable increase in the *trans* allylic coupling is found.[42] This indicates a change in the preferred conformation as alkyl substitution is made at the α-carbon. The conformation about the α-carbon–carbonyl carbon bond for protonated carbonyls has been discussed,[104,105] the conclusions being based largely on analogy with the conformations found for unprotonated carbonyls.[117] However, until these small variations in coupling constants are examined in more detail in relation to structural variations, the conformation about this bond for protonated carbonyls will be in doubt.

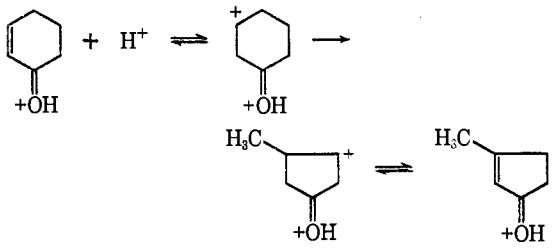
Little work has been done concerning the reactivity of protonated carbonyls in strong acid systems. The cleavage of the carbonyl carbon–α-carbon bond is difficult, and the protonated species is apparently relatively stable in excess strong acid even to high temperatures. It has been found for aldehydes that if the α-alkyl group is tertiary, rapid rearrangement takes place. Protonated pivaldehyde undergoes rapid rearrangement even at −70° to protonated methyl isopropyl ketone probably through a tertiary carbonium ion (eq 37).[42] Similar



(37)

reactions in dilute aqueous acid systems have been known for some time.[118,119] Undoubtedly rearrangements of even secondary and primary alkyl groups of protonated aldehydes making use of strong acid systems at higher temperatures, and longer reaction times are possible.

Protonated cyclohex-2-enone is converted[120] to 3-methylcyclopent-2-enone in HF–SbF_5 solution at 50°. The proposed mechanism is shown in eq 38.



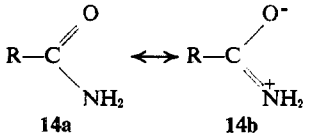
(38)

(117) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, 87, 2864 (1965).
(118) S. Daniloff and E. Venus-Danilova, *Ber.*, 59, 377 (1926).
(119) H. Hopff, C. D. Nenitzescu, D. A. Isacescu, and I. P. Cantuniari, *ibid.*, 69, 2244 (1936).
(120) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, 87, 1295 (1968).

IX. Protonated Amides and Thioamides

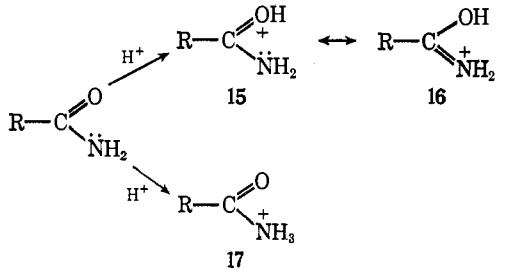
A. GENERAL

Because of the fundamental importance of the peptide link in biological systems, the nature of the species obtained from amides in acid systems has been extensively studied. It has been shown that there is substantial double-bond character in the carbon–nitrogen bond in amides.[121–123] The barrier to free rotation about this bond has been estimated at 12 ± 3 kcal/mol for N,N-diethylacetamide from nmr spectroscopy.[122] This indicates that there is appreciable contribution from the resonance form **14b** in amides, and from this point of view it is reasonable to assume that proton addition will occur



14a **14b**

at the oxygen. Further, proton addition at oxygen does not destroy this resonance interaction with the free pair of electrons on nitrogen (**15**, **16**) and satisfactorily explains restricted rotation in protonated amides as well as for amides themselves. If protonation occurs at nitrogen, free rotation would



15 **16** **17**

be expected about the carbon–nitrogen bond. Similar arguments have been used for the preferred site of protonation in thioamides, ureas, and thioureas. Cryoscopic measurements have shown that amides[124,125] and thioamides[126] are monoprotonated in strong acid systems such as sulfuric acid.

Oxygen protonation of amides and ureas and sulfur protonation of thioamides and thioureas has been challenged by several investigators during the last decade.[127–130] The principle evidence favoring oxygen protonation has been based on nmr spectroscopy while the evidence for nitrogen protonation was provided by infrared spectroscopy and some basicity measurements of substituted aromatic amides using ultraviolet measurements.[103,130] These conflicting arguments have been summarized through 1961 in an excellent review,[31] and it is concluded that the weight of the experimental evidence favors oxygen protonation. Since this review appeared, improved experimental techniques have substantiated this view. In this section we will not attempt to review the older data in detail and

(121) W. D. Phillips, *J. Chem. Phys.*, 23, 1363 (1955).
(122) H. S. Gutowsky and C. H. Holm, *ibid.*, 25, 1228 (1956).
(123) V. J. Kowalewski and D. G. deKowalewski, *ibid.*, 32, 1272 (1960).
(124) J. L. O'Brien and C. Niemann, *J. Amer. Chem. Soc.*, 79, 1386 (1957).
(125) G. Fraenkel and C. Franconi, *ibid.*, 82, 4478 (1960).
(126) J. Sandstrom, *Acta Chem. Scand.*, 16, (2), 1616 (1962).
(127) E. Spinner, *Spectrochim. Acta*, 15, 95 (1959).
(128) E. Spinner, *J. Phys. Chem.*, 64, 275 (1960).
(129) M. Davies and L. Hopkins, *Trans. Faraday Soc.*, 53, 1563 (1957).
(130) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, 38, 1518 (1960).

will only stress those earlier investigations which will give perspective concerning this controversy.

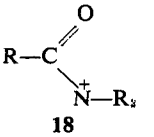
B. THE SITE OF PROTONATION

In retrospect, the argument (sometimes somewhat heated) concerning the preferred site of protonation of amides and thioamides resulted from a complete dependence on one experimental method and the failure of that method to give conclusive evidence concerning the site of protonation. One is reminded of the similar controversy concerning the site of protonation of phenols and alkyl phenyl ethers, and, like the protonation of phenols and alkyl phenyl ethers, there now appears to be evidence for the simultaneous existence of both oxygen and nitrogen protonated amides in strong acid systems.

1. Infrared Evidence

The principal evidence in favor of nitrogen protonation is provided by infrared spectroscopy. For the acid salts of acetamide,[127] urea,[127,129] and thiourea,[127] the infrared shows the presence of additional vibrations in the N–H region, ascribed to the presence of NH_3^+, the apparent displacement of the carbonyl stretching frequency to higher values, and the absence of a definite O–H (or S–H) vibration. For example, acetamide hydrochloride shows a vibration at about 1715 cm^{-1} compared to the band at 1675 cm^{-1} in the spectra of acetamide. This shift was attributed to the increase in the double-bond character of the carbonyl carbon–oxygen bond upon protonation of the nitrogen atom.[127] Comparable shifts have been found for other protonated amides. Such evidence for nitrogen protonation is difficult to contradict if it can indeed be proven that the assigned bands are due to carbonyl stretching.

Considerable doubt has been cast on these assignments and the interpretation that follows them by recent infrared studies. A comparison of the spectra of dicyclohexylurea and ^{18}O-labeled dicyclohexylurea showed that the expected isotopic shift to lower frequency caused the band at 1628 cm^{-1} to shift to 1611 cm^{-1}.[131] This evidence indicates that the band at about 1680 cm^{-1}, usually associated with carbonyl stretching in amides and ureas, may be misassigned. The infrared spectra of N-acyltrialkylammonium halides (**18**) further indicates the in-



18

correct assignment of the carbonyl stretching frequency in the earlier work. Structurally these salts would be similar to protonated amides if protonation occurred at the nitrogen. These compounds show a strong band at about 1810 cm^{-1} assigned to the carbonyl stretching vibration[132] and no band in the vicinity of 1700 cm^{-1}. The infrared spectra of amide complexes with boron halides indicates that coordination occurs at oxygen rather than nitrogen.[133]

In the earlier work[127,129] it was assumed that thiourea and thioacetamide also protonate on nitrogen. This conclusion was based on the presence of a band at 2350 cm^{-1} in both acetamide hydrochloride and thioacetamide hydrochloride, assigned to the NH_3^+ group. These conclusions have been reexamined.[134-137] The ultraviolet spectra of thioacetamide shows the disappearance of the n–π^* transition in concentrated sulfuric acid solution indicating protonation of the sulfur.[136] The N–H band assignments which were thought to be characteristic of the NH_3^+ are reinterpreted in light of this new evidence.[136]

2. Nuclear Magnetic Resonance Evidence

The nmr evidence concerning the site of protonation of amides, ureas, thioamides, and thioureas has been consistently interpreted in terms of oxygen protonation. While the interpretation of the infrared data in favor of nitrogen protonation resulted from incorrect band assignment, the early nmr work suffered from the inability to directly observe the proton on either oxygen or nitrogen. This was caused by the weakness of the acid system used resulting in rapid exchange rates and the quadrupole broadening caused by the nitrogen atom.

It was recognized early that for the protonation of amides four limiting cases were possible and would be significant in the interpretation of the nmr spectra.[125] (1) Nitrogen protonation with slow proton exchange. This would lead to free rotation about the carbon–nitrogen bond. For protonated N,N-dimethylamides, the nitrogen methyl groups would be expected to be a doublet caused by the splitting by the proton on nitrogen. (2) Nitrogen protonation with rapid exchange. This would lead to a singlet for two methyls on nitrogen if we can assume free rotation about the carbon–nitrogen bond. (3) Oxygen protonation with slow exchange. This should show a resonance for the proton on oxygen. It should be borne in mind that the bond order of the carbon–nitrogen bond could lead to magnetically nonequivalent alkyl groups on nitrogen, and correct interpretation may depend upon determining whether the multiplicity is due to spin–spin splitting (case 1) or magnetic nonequivalence (case 3). (4) Oxygen protonation with fast exchange would yield no definite OH resonance. In all the cases listed, significant shifts of the resonances compared to the unprotonated amides is to be expected because of the presence of the positive charge.

The nmr of N-methylacetamide in dilute aqueous acid solutions led to the conclusion that both the nitrogen-protonated and oxygen-protonated species are present.[125,138] Comparison of the exchange rates indicates that the amount of nitrogen protonated species is small compared to the oxygen-protonated species.

The chemical shifts of protonated amides in strong acid systems are summarized in Table XVIII.[125,139,140] The initial investigations of the nmr of amides in strong acids can best be described by case 4. This work was done in 100% sulfuric acid at 29°. Compared to the acid systems discussed in this review, such conditions of temperature and acid strength would be expected to lead to fast exchange. For example, the spectra of N,N-dimethylformamide in 100% sulfuric acid resembles that of

(131) R. Stewart and L. J. Muenster, *Can. J. Chem.*, 39, 401 (1961).
(132) D. Cook, *ibid.*, 40, 2362 (1962).
(133) W. Gerrard, M. F. Lappert, H. Pyszora, and J. W. Wallis, *J. Chem. Soc.*, 2144 (1960).
(134) M. J. Janssen, *Rec. Trav. Chim. Pays-Bas*, 79, 454 (1960).
(135) M. J. Janssen, *ibid.*, 79, 464 (1960).
(136) M. J. Janssen, *Spectrochim. Acta*, 17, 475 (1961).
(137) W. Kutzelnigg and R. Mecke, *ibid.*, 17, 530 (1961).
(138) A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem Soc.*, 81, 62 (1959).
(139) R. J. Gillespie and T. Birchall, *Can. J. Chem.*, 41, 148 (1963).
(140) T. Birchall and R. J. Gillespie, *ibid.*, 41, 2642 (1963).

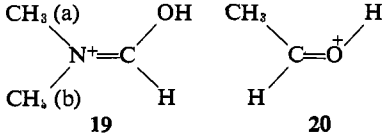
Table XVIII

Pmr Chemical Shifts for Some Protonated Amides and Thioamides[a]

Amide (thio)	*Acid system[b]*	*Temp, °C*	$=\overset{+}{O}H$ $(=\overset{+}{S}H)$	*NH*	*NCH_3*		*Lit. ref*
$HCONH_2$	1	−84.5	10.72	8.28	...		139
$HCONHCH_3$	2	29	...	...	4.11	4.03	125
	1	−85	10.49	8.58	3.33		139, 140
$HCON(CH_3)_2$	1	29	...	...	4.18	4.11	125
	2	−80	9.98	...	3.53	3.43	139
CH_3CONH_2	2	−80	10.40	8.30	...	...	139
$CH_3CONHCH_3$	1	29	...	...	3.70	2.71	125
	2	−85	10.15	8.27	3.25		140
$CH_3CON(CH_3)_2$	1	29	...	...	4.13		125
	2	−79	9.80	...	3.45		139
$C_6H_5CONH_2$	2	−86	10.34	8.72	...	...	140
CH_3CSNH_2	2	−81	5.72	9.25	...	...	140

[a] Chemical shifts in ppm relative to TMS. [b] Acid systems: 1, 100% H_2SO_4; 2, 100% HSO_3F.

the unprotonated amide.[125] The chemical shift difference between the N-methyl groups is about the same (0.14 ppm for the amide and 0.12 for the protonated amide) and is field dependent indicating that the methyls are magnetically nonequivalent. The methyl groups are further split into doublets by coupling to the formyl hydrogen. The magnitude of these couplings (1.0 and 1.5 Hz) and the absence of this coupling in protonated N,N-dimethylformamide-1-*d* indicates that this coupling is not caused by a proton on nitrogen. It is interesting to compare these small couplings with the long-range allylic couplings found for protonated aldehydes (**20**) (see p 579). The



19 **20**

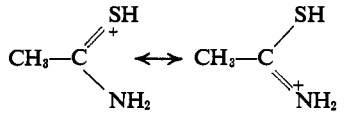
$J_{CH_3(a)-CH} = 1.5$ Hz $J_{CH_3-OH^+} = 1.2$ Hz
$J_{CH_3(b)-CH} = 1.0$ Hz

coupling of the formyl hydrogen with the methyl group has been found to be 0.8 and 0.5 Hz for unprotonated N,N-dimethylformamide.[128] The presence of allylic coupling in protonated aldehydes and ketones has been interpreted as indicating substantial contribution from **6b**. In protonated amides, the increase in this allylic coupling compared to the unprotonated amide indicates a substantial contribution of **16** where the positive charge resides on nitrogen.

Similar nmr evidence has been given for the sulfur protonation of N,N-dimethylthiobenzamide.[137]

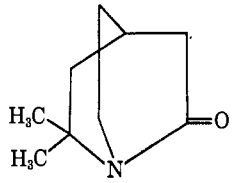
While the earlier work was unable to find the resonance for the proton on oxygen because of fast exchange, the use of stronger acid systems and lower temperatures has confirmed the oxygen protonation of amides and their thio analogs.[139,140] Acetamide, N,N-dimethylacetamide, formamide, and N,N-dimethylformamide were examined in fluorosulfonic acid at temperatures ranging from +25 to −92°. For protonated acetamide, at −80°, three resonances appear at δ 10.72, 8.30, and 2.67 and are assigned to the proton on oxygen, the protons on nitrogen, and the methyl protons. Integration of the areas of these peaks yields a ratio of 1.07:2.10:3.00. The other protonated amides give similar results, consistent only with oxygen protonation. The proton on oxygen is consistently at about 10. It is of interest to compare this value with the value for the proton on oxygen for protonated carbonyls and protonated esters. For protonated carbonyls, the proton on oxygen appears at δ 14–16, and for protonated esters, where there is considerable delocalization of the positive charge toward the alcoholic oxygen, the proton on oxygen appears at about 12. The appearance of the proton on oxygen in protonated amides at an even more shielded position of about δ 10 further strengthens the argument that there is considerable contribution from resonance form **16** where the positive charge resides on nitrogen.

The spectra of protonated thioacetamide and thioacetanilide in fluorosulfonic acid at low temperatures has been observed.[140] The proton on sulfur appears at δ 5.72. This is slightly shielded when compared to the proton on sulfur resonance for protonated thiols and sulfides[97] and, like the protonated amides, indicates delocalization as in **22** toward the nitrogen atom (10). Protonation of ureas is discussed further in a later section.



21 **22**

The one reported exception to O-protonation of amides,[141] is 2,2-dimethyl-6-oxoquinuclidene (**23**). In this example structural features enhance the basicity of the nitrogen atom compared with that of a noraml amide and prevent resonance stabilization of the O-protonated form.



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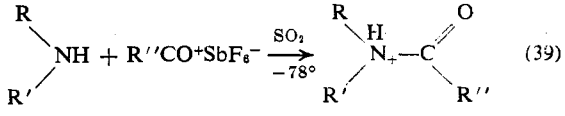
It has also been found possible to obtain N-protonated amides by reaction of oxocarbonium ions (acylium ions) with amines, in sulfur dioxide solution at low temperature (eq 39).



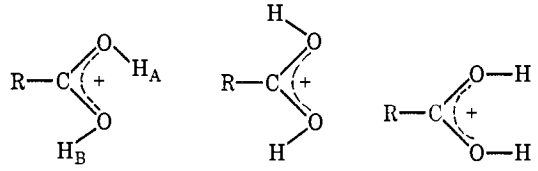
(39)

(141) H. Pracejus, *Chem. Ber.*, **92**, 988 (1959).

At higher temperatures rearrangement to the O-protonated amide occurs, this rearrangement being irreversible. The result shows that whereas the O-protonated amide is thermodynamically the most stable ion, the energy barrier for the interconversion from N to O protonation is high enough for direct observation of the former at low temperatures.[142]

X. Protonated Carboxylic Acids, Esters, and Anhydrides

In sulfuric acid, aliphatic carboxylic acids behave as simple bases being half-protonated in approximately 70% aqueous acid. Uv, ir, Raman, and nmr spectroscopy[82,83,53,143] show that protonation on the carbonyl group occurs. Formic acid is decomposed in sulfuric acid. However, it can be observed in its protonated form, and is stable as such, in fluorosulfonic acid–antimony pentafluoride solution[144] and in hydrogen fluoride–boron trifluoride solution.[145] The nmr spectrum of formic acid, at low temperatures, in these acid systems shows the presence of two conformers, **24** (R = H) predominating over **25** (R = H) by a factor of about 2:1. A third possible conformer, **26** (R = H), is not observed.



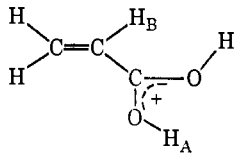
24 **25** **26**

Evidence for these structures derives from the fact that the coupling between the methine and hydroxyl protons is larger (15 Hz) for a *trans* relationship than for a *cis* relationship (3.5 Hz). Thus in isomer **24** (R = H) the methine proton is a doublet of doublets (15 and 3.5 Hz), while in isomer **25** (R = H) the methine proton is a triplet (3.5 Hz). The hydroxyl protons occur at lower field than in protonated alcohols and ethers but are more shielded than those in protonated ketones and aldehydes (see Table XIXa).

In protonated acetic acid under the same conditions[106] the isomer **25** (R = CH_3) is present to the extent of only about 5%, and in all other carboxylic acids studied only isomer **24** is found. The configurational equilibrium energy barriers in protonated formic and acetic acid have been determined[116] and are given in Table XIXb. Some disagreement exists in the literature as to the predominant isomer present in protonated pivalic acid. In $HF–BF_3$ solution at −75°, only a single OH absorption has been reported.[146] This was attributed to the large bulk of the tertiary butyl group causing the hydroxyl protons to adopt an all-*trans* configuration (**26**) (R = $C(CH_3)_3$). Since no other carboxylic acid has been found to exist in this conformation and since in $FSO_3H–SbF_5$ solution, at −60°, two OH absorptions are found,[144] there is no reason to believe that protonated pivalic acid exists in other than conformer **24** (R = $C(CH_3)_3$) and that the result obtained in $HF–BF_3$ is a result of the rotation about the C=OH$^+$ bonds not being "frozen out" on the nmr time scale. This explanation has been given to account for the observation of a single OH resonance in protonated benzoic acid[58,147] in all strong acid systems in which it has been studied. Delocalization of charge into the phenyl ring would be expected to diminish the C=OH bond order with a consequent decrease in the barrier to rotation. A similar effect is found in some protonated unsaturated carboxylic acids in which charge delocalization can also occur.

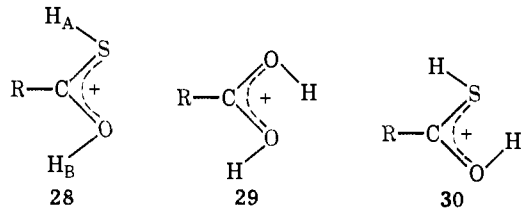
On the basis of the coupling constants in protonated formic acid[144,145] and also the $J_{^{13}COH}$ coupling constants in protonated formic, acetic, and propionic acids,[147] the "inner" proton (H_A in structure **24**) has been assigned to the highest field resonance. This assignment is in agreement with the model for the anisotropy of the carbonyl group recently proposed[148] on the assumption that similar effects are valid for the protonated group.

No measurable four-bond coupling has been detected between the alkyl group protons and the hydroxyl protons in saturated carboxylic acids although four-bond couplings have been observed in two of the protonated unsaturated carboxylic acids that have been studied in $FSO_3H–SbF_5–SO_2$ solution.[149] The highest field OH resonance (H_A in **27**) is coupled by 1.5 Hz to H_B in acrylic and crotonic acid. The magnitude of this



27

four-bond coupling reflects the favorable planar *W*-coupling path between these two protons[115] and is a further example of the fact that coupling through protonated carbonyl oxygen is similar in magnitude and spatial requirements to sp^2 carbon atoms. A similar effect is found in protonated thioformic acid in which, in 4:1 *M* $FSO_3H–SbF_5$, three isomers, **28–30** (R = H), have been detected.[150] In isomer **28**, a 3.5-Hz coupling between H_A and H_B is found. This coupling is not present in either of the other two isomers.



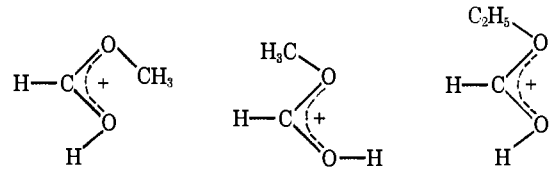
28 **29** **30**

The predominant isomer in protonated thioformic acid is **29** (60%), **28** and **30** being present to the extent of 30 and 10%, respectively. In protonated thioacetic acid the isomer ratio is 3:1:1 for **29**, **28**, and **30** (R = H), and in protonated thiopropionic acid a 7:1:2 isomer ratio is observed. The decrease in the amount of isomer **28** observed with increasing the size of the R group is consistent with the observations in the protonated carboxylic acid series, although in the latter the decrease is much more marked. A plausible explanation for this difference is that, in the isomer, interaction between the lone pairs on

(142) G. A. Olah and P. J. Szilagyi, unpublished results.
(143) R. Stewart and K. Yates, *J. Amer. Chem. Soc.*, **82**, 4059 (1960).
(144) G. A. Olah and A. M. White, *ibid.*, 89, 3591 (1967).
(145) H. Hogeveen, A. F. Bickel, C. W. Hilbers, E. L. Mackor, and C. MacLean, *Rec. Trav. Chim. Pays-Bas*, **86**, 687 (1967); *Chem. Commun.*, 898 (1966).
(146) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, **86**, 809 (1967).
(147) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 7072 (1967).
(148) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *ibid.*, 89, 5067 (1967).
(149) G. A. Olah and M. Calin, *ibid.*, 90, 405 (1968).
(150) G. A. Olah, A. Ku, and A. M. White, *J. Org. Chem.*, 34, 1827 (1969).

the two heteroatoms is a controlling factor and that sulfur–oxygen interaction is less than that between oxygen–oxygen. The actual ratios observed reflect the steric requirements of the group R, the protons on oxygen and sulfur, and the lone pairs of these atoms, and it is evident from the only small free-energy difference between the isomers that the difference between these steric requirements is small. Variations in the solvent (*e.g.*, FSO_3H–SbF_5 and HF–BF_3) has little effect on the relative isomer abundances indicating that solvation of the ions is not influencing the stability of one or more of these isomers.

The protonation of esters in both sulfuric[151] acid and mixed acid systems[53,152] follows the same pattern as the carboxylic acids. Protonation is on the carbonyl oxygen, and in FSO_3H–SbF_5–SO_2 solution at low temperature different rotational isomers can be identified in some cases.[152] Thus methyl formate, in FSO_3H–SbF_5 solution, has an nmr spectrum showing the presence of two isomers. These isomers can be assigned[45] to **31** and **32**, **31** being the predominant isomer by a



31, 90% **32**, 10% **33**

ratio of about 9:1. In protonated ethyl formate the *syn–syn* isomer, **33**, has also been detected.[152]

In sulfuric acid the protonation is complicated by cleavage of the esters at ambient temperatures,[153,154] and in the mixed acid systems cleavage[152] can be observed by raising the temperature from the low temperatures at which protonation is usually observed.

The cleavage of esters under highly acidic conditions occurs *via* unimolecular cleavage of the protonated ester, involving either alkyl–oxygen or acyl–oxygen scission.[154] Evidence for this has come from labeling experiments, from kinetic studies, and more recently by nmr spectroscopy.

In sulfuric acid the methyl and ethyl esters of both benzoic and acetic acid hydrolyze to the corresponding acids *via* acyl oxygen fission in the rate-determining step (the $A_{Ac}1$ mechanism). For the isopropyl and *t*-butyl esters alkyl–oxygen fission occurs (the $A_{Al}1$ mechanism).[154,155]

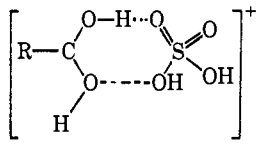
$$R'C\overset{+}{O}OHR \longrightarrow R'\overset{+}{C}O + ROH \qquad A_{Ac}1 \qquad (40)$$
$$H_2O \longrightarrow R'CO_2H$$

$$R'C\overset{+}{O}OHR \longrightarrow R'CO_2H + R^+ \qquad A_{Al}1 \qquad (41)$$
$$H_2O \longrightarrow ROH$$

At higher acidities (*e.g.*, in oleum or in other mixed acid systems) it is possible to cleave carboxylic acids in a manner analogous to the rate-determining step of the $A_{Ac}1$ mechanism, the resulting species being an oxocarbonium ion (acylium ion) and protonated water (eq 42).

$$RCOOH_2^+ \longrightarrow R\overset{+}{C}O + H_2O^+ \qquad (42)$$

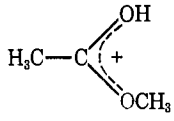
The latter reaction has been studied both under equilibrium conditions (in oleum)[156] and under kinetic conditions (in FSO_3H–SbF_5[144] and in HF–BF_3).[157] Thus acetic acid is half-ionized to the methyl oxocarbonium ion in 15% oleum at 35° as determined by observation of the changes in the position of the methyl resonance with increasing acidity.[156] In both HF–BF_3[157] and FSO_3H–SbF_5[144] protonated acetic acid alone can be observed at low temperature and then, by raising the temperature to between −30 and 0°, the kinetics of the cleavage reaction can be followed by nmr, the methyl signals of the protonated acid and the methyl oxocarbonium ion being separated by about 1 ppm. In FSO_3H–SbF_5 the protonated acid is completely converted to the oxocarbonium ion while in the HF–BF_3 acid system the reaction goes to between 40 and 70% completion, indicating the greater acidity of the former acid system over the latter and suggesting that the HF–BF_3 system is of comparable acidity to 15% oleum. While the rate constants for cleavage of acetic acid to the methyl oxocarbonium ion in FSO_3H–SbF_5 and in HF–BF_3 agree well with each other for a series of carboxylic acids, the rate constant in oleum has been estimated to be faster by a factor of 10^4–10^5. It has been suggested that this difference is due to a bimolecular mechanism (eq 43) operating in the case of the oleum system.[157]



$$\longrightarrow RCO^+ + HSO_4^- + H_3O^+ \qquad (43)$$

A significant steric factor has been found to operate in the cleavage of carboxylic acids in sulfuric acid–oleum systems. Thus 2,4,6-trimethylbenzoic acid is completely ionized to the corresponding oxocarbonium ion in 100% sulfuric acid, while it is necessary to use oleum to ionize benzoic acid.[158] It has been shown that it is the *ortho* methyl groups which cause the added stability of the oxocarbonium ion with respect to hydrolysis back to the carboxylic acid.

As has been described earlier, carboxylic acid esters show a more complex behavior than the acids, under strong acid conditions, due to the two possible modes of cleavage. In FSO_3H–SbF_5 and in HF–BF_3 solution it is possible to distinguish between the two modes of cleavage by nmr.[152,157] Thus at +30° in this acid system, methyl acetate cleaves *via* acyl–oxygen fission, and the products, the methyl oxocarbonium ion and protonated methanol, are stable under these conditions and can be identified by nmr (eq 44).



$$\longrightarrow CH_3CO^+ + CH_3OH_2^+ \qquad (44)$$

sec-Butyl acetate under the same conditions but at −30° cleaves *via* alkyl–oxygen fission, and the nmr spectrum shows the presence of protonated acetic acid and the *t*-butyl cation, the latter from rearrangement of the first formed methyl ethyl carbonium ion (eq 45). Since the protonated acid goes to the

(151) G. Fraenkel, *J. Chem. Phys.*, **34**, 1466 (1961).
(152) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).
(153) A. Bradley and M. E. Hill, *ibid.*, 77, 1575 (1955).
(154) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953.
(155) J. Leisten, *J. Chem. Soc.*, 1572 (1956).
(156) N. C. Deno, C. U. Pittman, and M. J. Wisotsky, *J. Amer. Chem. Soc.*, **86**, 4370 (1964).
(157) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, **86**, 816 (1967).
(158) H. P. Treffers and L. P. Hammett, *J. Amer. Chem. Soc.*, 59, 1708 1937).

Table XIXa

Pmr Chemical Shifts (in ppm)[a] of Protonated Acids in 1:1 *M* FSO_3H–SbF_5

	Protonated acid (J, cps)[b]			
	OH	*CH_3*	*CH_2*	*CH*
HCO_2H (58)	13.40, d (3.5)			9.70, t (3.5)
(57)	13.57, d (3.5) 13.02, d (15.0)			9.30, d of d (15.0 and 3.5)
CH_3CO_2H	13.03 12.33	3.18		
$CH_3CH_2CO_2H$	12.73 12.43	1.95, t (7.0)	3.67, q (7.0)	
$CH_3(CH_3)_2CO_2H$	12.75 12.42	1.30, t (7.0)	2.15, sx (7.0) 3.32, t (7.0)	
$CH_3(CH_2)_3CO_2H$	12.98 12.65	1.5–2.7, m	3.58, t (6.5)	
$(CH_3)_2CHCO_2H$	12.67 12.40	1.75, d (7.0)		3.52, sp (7.0)
$(CH_3)_2CHCH_2CO_2H$	13.13 12.75	1.67, d (6.0)	3.45, d (6.0)	2.83, m
$(CH_3)_3CCO_2H$	12.60 12.42	2.11		

[a] Referred to external TMS. [b] Multiplicity: d, doublet; t, triplet; q, quartet; m, multiplet; p, pentuplet; sx, sextet; sp, septet.

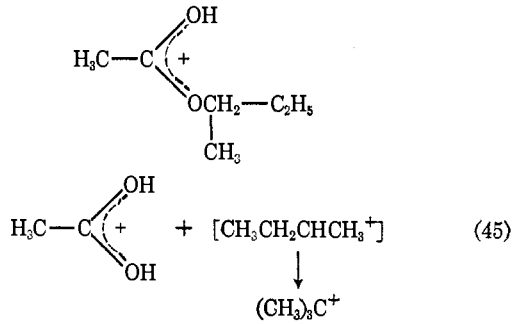
Table XIXb

Activation Parameters of Configurational Equilibration[116]

Protonated acid[a]	*E_a, kcal mol^{-1}*	*Log A, sec^{-1}*	*Solvent*
Acetic acid	13.5 ± 0.6	14.4 ± 0.7	HF–BF_3[b]
Acetic acid	12.6 ± 0.6	13.2 ± 0.6	$HFSO_3$–SbF_5–SO_2[c]
Acetic acid	11.2 ± 0.2	12.0 ± 0.2	HF–SbF_5[d]
Formic acid	15.3 ± 0.9	15.7 ± 0.9	HF–SbF_5[d]

[a] 1 *M* solution. [b] BF_3 pressure 1 atm at −80°. [c] Molar ratio 7:3:9, respectively. [d] Excess SbF_5 0.5 mol l.$^{-1}$.

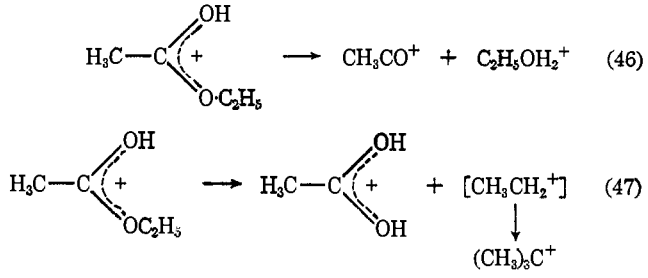
oxocarbonium ion only very slowly under these conditions, its observation is proof of alkyl–oxygen cleavage.



(45)

Esters of tertiary alcohols were found to cleave so rapidly that only the protonated acid and tertiary carbonium ions could be observed on dissolution of the ester in FSO_3H–SbF_5 at −80°.

Ethyl acetate provided an intermediate case. In the same acid system alkyl–oxygen cleavage was observed (eq 47); however, in weaker acid media such as 4:1 *M* FSO_3H–SbF_5 acyl–



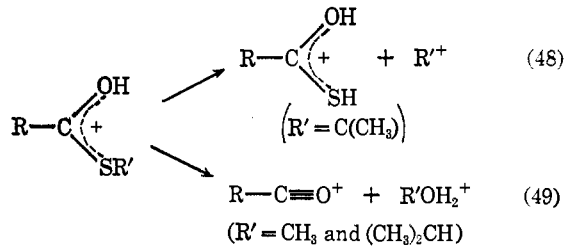
(46)

(47)

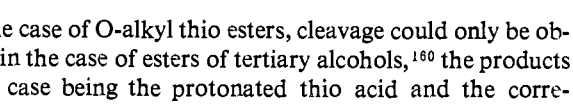
oxygen cleavage was observed[152] (eq 46). The reason for this mechanism dependence on acidity is not fully understood; however, it is probably significant that in the lower acidity conditions the cleavage does not go to completion.[159]

Methyl formate is stable at room temperature in FSO_3H–SbF_5 solution. At higher temperatures in FSO_3H–SbF_5 protonated methanol and carbon monoxide are formed, protonated carbon monoxide HCO^+ being a possible intermediate in this decomposition. In 100% H_2SO_4, methyl sulfate and formyl sulfate are the formed products.[151] Secondary and tertiary esters of formic acid cleave in FSO_3H–SbF_5 solution to give protonated formic acid and the carbonium ion product of the corresponding protonated alcohol. Protonated formic acid itself decomposes at elevated temperatures in superacids to give carbon monoxide and the hydronium ion.

Cleavage of protonated S-alkyl thio esters has been studied in FSO_3H–SbF_5–SO_2 solution.[150] Primary and secondary S-alkyl thioacetates were found to cleave *via* acyl–sulfur fission (eq 49) while alkyl–sulfur fission was found for tertiary S-alkyl thioacetates (eq 78).

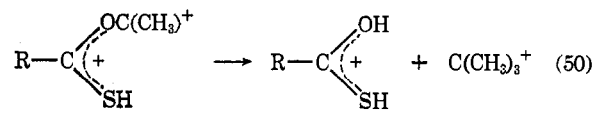


(48)



(49)

In the case of O-alkyl thio esters, cleavage could only be observed in the case of esters of tertiary alcohols,[160] the products in this case being the protonated thio acid and the corresponding carbonium ion (eq 50). Esters of primary and sec-



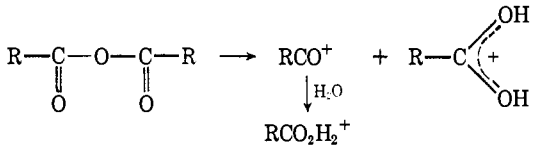
(50)

(159) For a discussion see G. A. Olah and A. M. White in "Carbonium Ions," Vol. IV, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, in press.

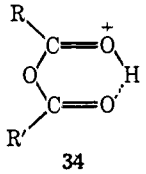
(160) G. A. Olah and A. Ku, *J. Org. Chem.* 35, 331 (1970).

ondary alcohols proved to be stable to high temperature, reflecting the stability of oxocarbonium ions as compared to their sulfur analogs.

Anhydrides of carboxylic acids behave as esters of tertiary alcohols in FSO_3H–SbF_5 solution in that cleavage is immediate on dissolution at −80° leading to one molecule of the protonated acid and one of the oxocarbonium ion in equal proportions.[17] The same behavior is found in 100% sulfuric acid and in oleum solution, while in slightly aqueous acid, the oxocarbonium ion reacts with water present leading to two molecules of the protonated acid being observed.[161]

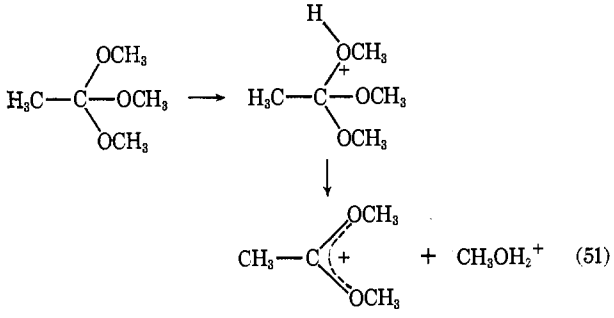


Under certain conditions protonated anhydrides can be observed without cleavage.[142] Reaction of oxocarbonium ions salts with carboxylic acids in sulfur dioxide solution leads to formation of a monoprotonated anhydride (**34**). The nmr spectrum indicates that rapid intermolecular exchange of the proton between the two carbonyl groups occurs, this exchange being favored by strong hydrogen bonding (**34**). Both symmetrical and unsymmetrical protonated anhydrides have been generated in this manner.



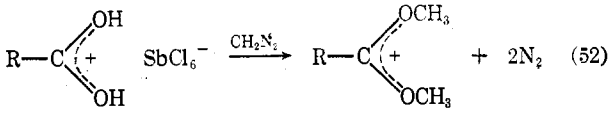
34

Ortho esters of carboxylic acid cleave at −80° in FSO_3H–SbF_5 solution to dialkoxy carbonium ions and protonated alcohols.[41]



(51)

Protonated carboxylic acids and esters have been isolated as stable complexes, either as their hexachloroantimonates or hexafluoroantimonates.[162] No detailed study of the properties of these solid complexes has, however, been reported, although the reaction of these salts with diazomethane to give dimethoxycarbonium ions has been described (eq 52).

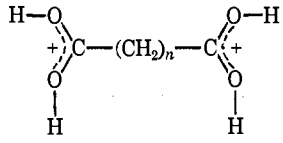


(52)

(161) E. A. Robinson and S. A. A. Quadin, *Can. J. Chem.*, **45**, 2391 (1967).
(162) F. Klages and E. Zarnge, *Ber.*, **92**, 1828 (1959).

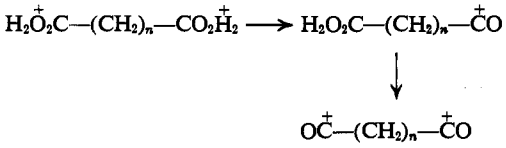
XI. Protonated Dicarboxylic Acids and Anhydrides

The protonation of saturated dicarboxylic acids in sulfuric acid has been investigated by cryoscopy.[163] Succinic acid and higher members of the series were found to be only partially ionized as diacid bases. Malonic acid was only monoprotonated under these conditions while oxalic acid underwent decomposition. Adipic acid has been investigated in oleum by nmr,[164] and a downfield shift of the methylene protons in 17% oleum was found which was tentively attributed to diprotonation. In FSO_3H–SbF_5, oxalic acid and higher members of the series were found to be diprotonated,[17] the nmr spectra showing that the protonated acids had a structure analogous to the monocarboxylic acids.



35

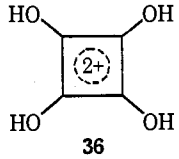
On raising the temperatures of solutions of protonated dicarboxylic acids, cleavage, again analogous to the monocarboxylic acids, was observed (eq 53).



(53)

Malonic acid did not cleave under these conditions while succinic acid cleaved to the extent of *ca.* 50% showing that an equilibrium is reached betwen the diprotonated acid and the monooxocarbonium ion. The first ionization of glutaric acid went to completion under these conditions; however, the second ionization to form a dioxocarbonium ion went only the extent of *ca.* 50%. Other dicarboxylic acids were converted completely to the dioxocarbonium ions.[17]

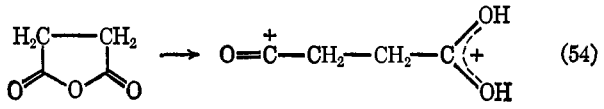
1,2-Dihydroxycyclobutenedione ("squaric acid") was found to be diprotonated.[17] The nmr evidence was taken to indicate that there was no significant contribution of the cyclobutenium dication (a potential Hückeloid aromatic structure) to the stability of the molecule (**36**).



36

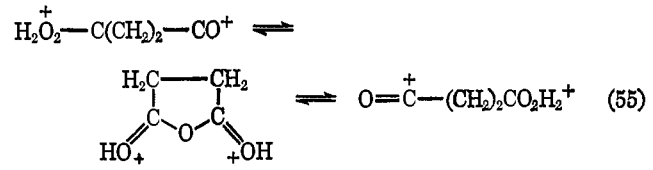
The cyclic anhydrides derived from dicarboxylic acids have been shown, by cryoscopic measurements, to undergo incomplete protonation in sulfuric acid.[51] Thus succinic anhydride[165] gives an *i* factor of 1.5, and an *i* factor of 1.8 for 1,8-naphthalic anhydride[166] has been obtained. In FSO_3H–SbF_5 solution, at −80°, cleavage of cyclic anhydrides has been found to be immediate, giving the monooxocarbonium ions.[17]

(163) L. A. Wiles, *J. Chem. Soc.*, 996 (1953).
(164) C. U. Pittman, Ph.D. Thesis, The Pennsylvania State University, University Park, Pa., 1964.
(165) G. Oddo and A. Casalino, *Gazzetta*, **47**, 232 (1917).
(166) M. S. Newman and N. C. Deno, *J. Amer. Chem. Soc.*, **73**, 3651 (1951).



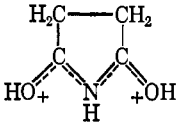
(54)

The ion derived from succinic anhydride gave a temperature-dependent nmr spectrum which was interpreted as being a result of an intramolecular rearrangement through a cyclic intermediate corresponding to the diprotonated anhydride[17] (eq 55). In contrast to this result, succinimide has been found



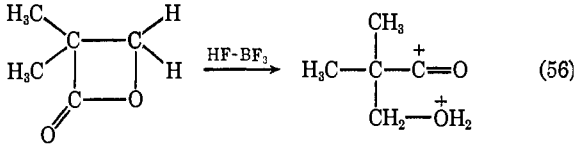
(55)

to exist in FSO_3H–SbF_5 solution as the diprotonated cyclic structure,[167] the replacement of the bridging ether oxygen by an NH allowing the molecule to accommodate the dipositive charge better in the cyclic structure (**37**). Other imides show similar behavior.[167]



37

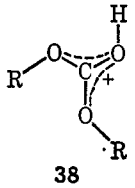
2,2-Dimethyl-β-propiolactone in HF–BF_3 at −80° has been reported to give the oxocarbonium ion (eq 56).[168]



(56)

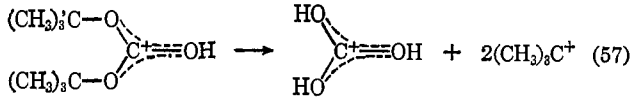
XII. Protonated Carbonic Acid and Derivatives

Dialkyl carbonates have been studied in FSO_3H–SbF_5 solution and have been shown to be protonated on the carbonyl group giving the dialkoxyhydroxy carbonium ion (**38**).[4]



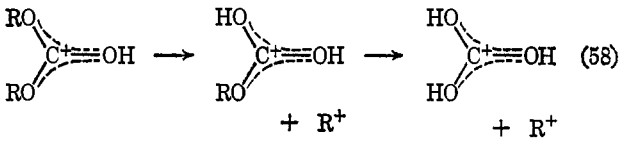
38

Di-*t*-butyl carbonate cleaves immediately at −80°, with alkyl–oxygen fission, giving the *t*-butyl cation and protonated carbonic acid. The structure of the latter has been established from the ^{13}C nmr spectrum of the central carbon atom which shows a 3.5-Hz quartet being coupled to three equivalent hydroxyl protons.



(57)

Diisopropyl and diethyl carbonate cleave at higher temperature, also *via* alkyl–oxygen cleavage, with initial formation of protonated alkyl hydrogen carbonates. The latter can also be formed by protonation of their sodium salts.



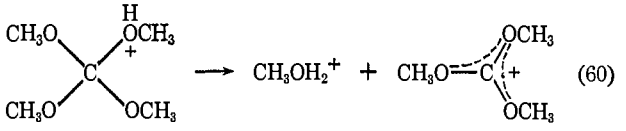
(58)

Dimethyl and diethyl carbonates have also been observed by nmr in H_2SO_4 solution, in which they are also protonated,[169] although under these conditions fast exchange precludes observation of the hydroxyl proton.

Protonated carbonic acid can also be obtained by dissolving inorganic carbonates and hydrogen carbonates in FSO_3H–SbF_5 at −80°. It is stable in solution to about 0°, at which temperature it decomposes to the hydronium ion and carbon dioxide[48] (eq 59).

$$K_2CO_3 \xrightarrow{H^+} H_3CO_3^+$$
$$H_3CO_3^+ \longrightarrow H_3O^+ + CO_2 \qquad (59)$$

Ortho esters of carbonic acid cleave at −80° in FSO_3H–SbF_5 solution giving trialkoxy carbonium ions and protonated alcohols,[41] analogous to the cleavage of ortho esters of carboxylic acids under the same conditions (eq 60).

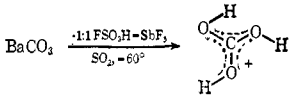
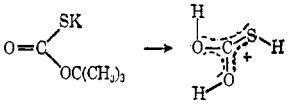
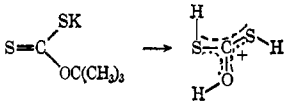
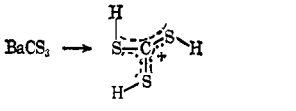


(60)

The trimethoxycarbonium ion has been prepared by isolating protonated dimethyl carbonate as a stable complex (with $SbCl_6^-$) and treating it with diazomethane.[170]

The thio analogs of protonated carbonic acid have been prepared in FSO_3H–SbF_5–SO_2 solution, and their method of preparation and the chemical shifts of the OH and SH protons are given in Table XX.[150] The increasing deshielding of both the

Table XX

Equation	*OH*	*SH*
	11.55	...
	11.99	6.73
	12.56	7.19
	...	7.66

(167) G. A. Olah and R. Schlosberg, *J. Amer. Chem. Soc.*, 90, 6464 (1968).

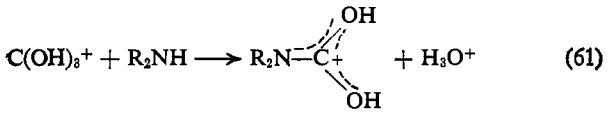
(168) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, 87, 1303 (1968).

(169) B. G. Ramsey and R. W. Taft, *J. Amer. Chem. Soc.*, 88, 3058 (1966).

(170) F. Klages and H. Mearesch, *Ber.*, 85, 863 (1952); see also H. Meerwein in "Methoden der Organischen Chemie" (Houben-Weyl), Vol. VI/3, Georg Thieme, Stuttgart, 1965, p 325.

OH and SH protons as the number of thiol groups in the ion is increased is consistent with the lesser ability of sulfur as compared to oxygen to delocalize the positive charge on the central carbon atom. Preparation of the ions containing both OH and SH groups also lead to formation of both protonated carbonic acid and protonated trithiocarbonic acid and it was proposed that protonated carbon dioxide, carbonyl sulfide, and/or carbon disulfide were intermediates in this interconversion.

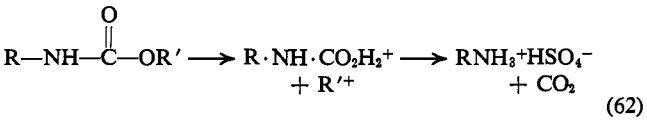
Protonated carbonic acid was shown to behave as an electrophile and with amines under suitable conditions gave carbamic acids, which were observed, protonated, in FSO_3H–SbF_5 solution.[48]



(61)

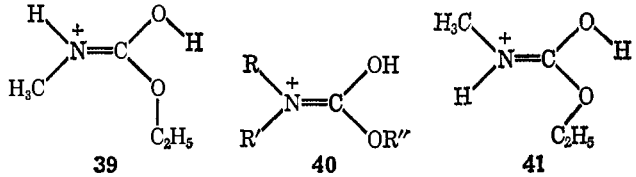
XIII. Protonated Carbamic Acid and Derivatives

In oleum solution, alkyl carbamates cleave *via* alkyl–oxygen fission giving protonated carbamic acids. The latter are unstable under these conditions and lose carbon dioxide giving the corresponding amine.[171]



(62)

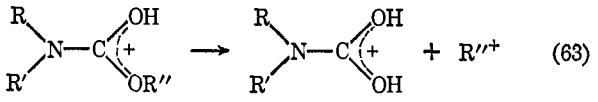
In FSO_3H–SbF_5 solution, at −60°, alkyl carbamates can be observed in their protonated form by nmr, protonation occurring on the carbonyl group (**40**).[172]



39 **40** **41**

Hindered rotation about the C=N bond results in the observation of *cis* and *trans* isomers in ethyl N-methylcarbamate (**40, 41**). In addition, the hydroxyl proton in one of the isomers is coupled to the NH proton (J = 2.8 Hz) suggesting that in this isomer these protons bear a W relation to each other as in protonated thiol acids.[150] The isomer in which this coupling is observed would thus correspond to **41**. It is unlikely, but not proven, that in this isomer rotation about the C–OH bond is "frozen out" on the nmr time scale. If "free rotation" occurs, the observed coupling of 2.8 Hz will be the weighted average of the coupling constants in the various rotamers. The second isomer, which shows no detectable four-bond coupling, will thus have structure **39**.

Carbamic acid esters of both primary and secondary alcohols cleave *via* alkyl–oxygen scission in FSO_3H–SbF_5 solution, protonated carbamic acids being stable under these conditions. The resultant spectra show the latter to be carboxyl protonated (eq 63).

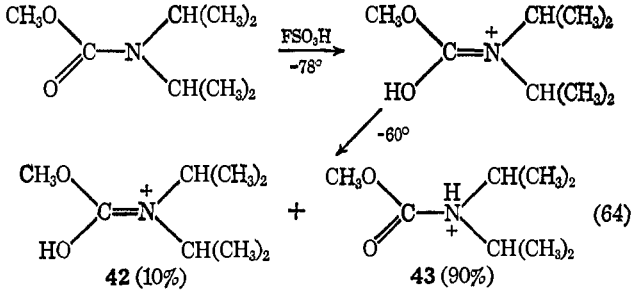


(63)

Mono-N-substituted carbamic acids, like the esters, show hindered rotation about the C=N bond and coupling of one of the hydroxyl protons to the NH proton. This coupling is not observed in protonated carbamic acid itself.

In contrast to the usual observation of O-protonation of carbamate esters, N,N-diisopropylcarbamate esters (methyl and ethyl) have been shown to be N-protonated in FSO_3H and 98% H_2SO_4 solution.[173] It has, in this case, been found possible to observe[174] rearrangement from O-protonated N,N-diisopropylcarbamate esters to the N-protonated ions. Protonation of the methyl and ethyl esters in fluorosulfonic acid alone, or diluted with either sulfur dioxide of sulfuryl chlorofluoride at −78°, gives the O-protonated carbamate ester (**42**). At −60°, rearrangement to the N-protonated ester (**43**) occurs, the rate being highly dependent on the solvent composition. This rearrangement is irreversible. At equilibrium a mixture of N- and O-protonated ions is observed, the mixture composition being 90% N-protonated and 10% O-protonated. This composition was independent of the solvent used. Carbonyl protonation is thus favored kinetically under these conditions, even though this leads to the thermodynamically least stable ion ($\Delta G°$ = 1.3 kcal).

This small free energy difference between the O- and N-protonated carbamates suggests to us that caution should be exercised in extrapolating these results to other solvents. The different acidity function behavior of amides (O-protonation) and amines (N-protonation) has been interpreted in terms of differing hydration requirements of the two types of cations, solvation by water molecules in aqueous sulfuric acid being more important in the case of O-protonated amides.[175] It is thus quite possible that in aqueous acid solvation of the O-protonated N,N-diisopropylcarbamate ester reverses the thermodynamic stabilities of the O- and N-protonated species from the stabilities observed in 98% sulfuric acid and in fluorosulfuric acid. The similar acidity function dependence[178] of ethyl N,N-dimethylcarbamate (which is O-protonated in FSO_3H solution) and ethyl N,N-diisopropylcarbamate may thus be a result of a reversal of the thermodynamic stabilities of the O- and N-protonated forms of the latter ester.



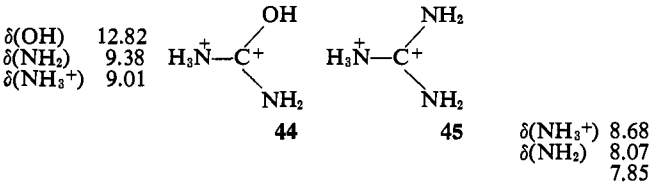
42 (10%) **43** (90%)

(64)

In contrast to monoprotonation of carbamic acid being observed in FSO_3H–SbF_5–SO_2 solution, urea and guanidine

(171) T. I. Bieber, *J. Amer. Chem. Soc.*, 75, 1409 (1953).
(172) G. A. Olah and M. Calin, *ibid.*, 90, 401 (1968).
(173) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *Chem. Commun.*, 1362 (1968).
(174) G. A. Olah, J. A. Olah, and A. M. White, unpublished results.
(175) (a) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 275 (1968); (b) R. B. Homer and R. B. Moodie, *ibid.*, 4377 (1963).

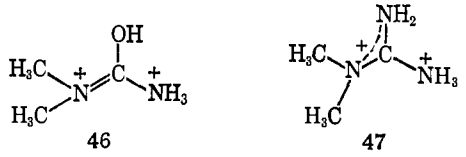
under the same conditions are diprotonated.[176] Nmr parameters for the diprotonated species (**44** and **45**) are summarized below.



44 45

Cryoscopic measurements (on tetraethylurea) in 100% sulfuric acid also show that diprotonation occurs in this acid system.[140] Guanidine, in spite of its first pK_a being higher (13.6) than that of urea, adds only 1.3 protons in sulfuric acid.[177] This is apparently due to the high stability of the guanidinium ion due to resonance stabilization of the charge. The position of the first protonation of urea and its derivatives has been the subject of some discussion;[127] however, ir, uv, and nmr data on crystalline salts of protonated urea[131,137,178,179] have indicated that the first protonation is on the carbonyl group, as would be expected by analogy with the guanidinium ion, and also with protonated carbonic and carbamic acids.

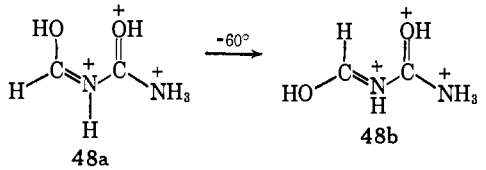
Both 1,1-dimethylurea and tetramethylurea, when diprotonated in FSO_3H–SbF_5–SO_2 solution, show two nmr signals for the imino methyl groups.[176] For this nonequivalence to be observed there must be restricted rotation about the C=N bond. A lower limit for the ΔG for rotation of 20 kcal was found indicating that the predominant contribution to the structure is from the immonium form (**46**). In diprotonated 1,-



46 47

1-dimethylguanidine (**47**) this barrier to rotation was found to be 15 kcal. This value demonstrates the greater extent of charge delocalization and hence lower C–N bond order in the diprotonated guanidines as compared to diprotonated ureas. In diprotonated guanidine itself this barrier leads to two NH resonances being observed in the nmr spectra in addition to the peak due to the ammonium protons.[176]

An interesting rearrangement has been observed for formylurea which is triprotonated in FSO_3H–SbF_5–SO_2 solution.[41] On preparation of the ion at −78° the nmr spectrum shows the conformation to be **48a**. At −50° the ion rearranges (half-life about 1 hr) completely to **48b**. This rearrangement is ir-



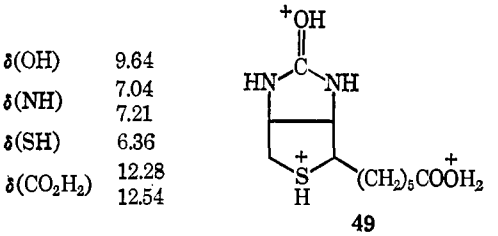
48a 48b

reversible. Apparently the mechanism of the triprotonation leads the least stable geometrical isomer being formed presumably due to hydrogen bonding in the mono- and diprotonated intermediates.

The first protonation of thiourea is on sulfur,[88,137] and there is evidence that it is diprotonated in 100% sulfuric acid and in fluorosulfonic acid.[140] In FSO_3H–SbF_5 both thiourea and selenourea have been shown to be diprotonated.

Biotin, a biologically important compound related to urea, has been shown to be protonated, without further structural changes, in FSO_3H–SbF_5.[176] It is of interest that the urea base in the molecule in this example is only monoprotonated, although the molecule as a whole is triply protonated. The sites of protonation, all of which can be clearly distinguished by nmr, are the carbonyl group, the sulfide group, and the carboxylic acid function (**49**). The nmr spectrum also shows that protonation of the sulfur occurs *trans* to the valeric acid side chain.

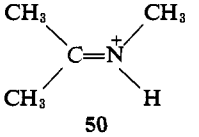
At higher temperatures, the protonated acid group is dehydrated to the oxocarbonium ion, without any other changes in the molecule.



49

XIV. Protonated Imines

Imines have been protonated in FSO_3H–SbF_5, FSO_3H, and D_2SO_4–SbF_5 solution.[180] By analogy with ketones and aldehydes, protonated ketimines should show hindered rotation about the C=N bond on the nmr time scale. This has been found to be true, and, for example, in protonated N-propylidinemethylimine, up to at least −20° in FSO_3H–SbF_5 solution, the C-methyl groups are found to be nonequivalent (**50**).



50

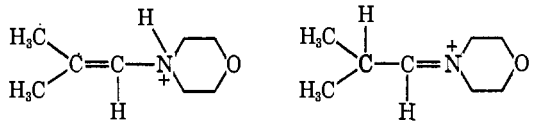
Although the barriers to rotation in carbonyl compounds and the analogous imines have not been determined, one would predict that because of the greater ability of NR_2 over OR to stabilize an adjacent positively charged center (see discussion of protonated ureas and guanidines) that the barrier in imines would be higher for rotation about the C=X bond and that the contribution of the amino carbonium ion resonance structure in protonated imines is minor.

XV. Protonated Enamines

The site of protonation in enamines has not been completely resolved.[181–185] Enamines are strong bases, their basicity being

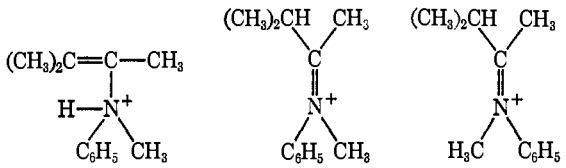
(176) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 41, 2642 (1963).
(177) G. Williams and M. L. Hardy, *J. Chem. Soc.*, 2560 (1953).
(178) C. Holstead, A. H. Lamberton, and P. A. H. Wyatt, *ibid.*, 3341 (1953).
(179) C. R. Redpath and J. A. S. Smith, *Trans. Faraday Soc.*, 58, 462 (1962).
(180) G. A. Olah and P. Kreinbuhl, *J. Amer. Chem. Soc.*, 89, 4756 (1967).
(181) E. J. Stamhuis, W. Maas, and H. Wynberg, *J. Org. Chem.*, 30, 2160 (1965).
(182) E. J. Stamhuis and W. Maas, *ibid.*, 30, 2156 (1965).
(183) W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *ibid.*, 32, 1111 (1967).
(184) J. Elguero, R., Jacquier, and G. Tarrago, *Tetrahedron Lett.*, 4719 (1965).
(185) J. Elguero, R. Jacquier, and G. Tarrago, *ibid.*, 1112 (1966).

comparable to amines.[182] The protonated molecules have been observed by nmr in dilute hydrochloric acid solution, and it was shown that the site of protonation is apparently acidity dependent.[184,185] Thus 1-N-morpholine-1-isobutylene in 6 *N* HCl solution shows initially two doublets at δ 1.3 and 1.9. The former shows a 2-Hz coupling and is attributed to the N-protonated species (**51a**) and the latter a 7-Hz coupling due to the C-protonated species (**51b**).



51a **51b**

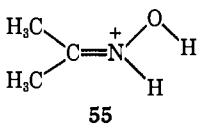
Under these conditions hydrolysis to isobutyraldehyde occurs and results in the appearance of a new doublet in the nmr spectrum on allowing the solution to stand. At acidities less than 6 *N* HCl, only the N-protonated form was observed. The N-methylanilino enamine of isopropyl methyl ketone in 12 *N* HCl initially shows three species, the N-protonated species **52** and the two geometrical isomers of the C-protonated species **53** and **54**. The former disappears after 5 min at ambient temperatures, while the latter are stable for several hours, hydrolysis to the ketone eventually occurring.



52 **53** **54**

XVI. Protonated Ketoximes

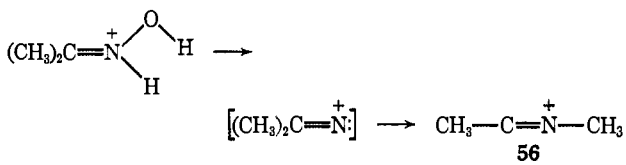
Nitrogen protonation of acetone and acetophenone oximes has been observed in FSO_3H–SbF_5–SO_2 solution.[186] The nmr spectra of protonated acetone oxime (**55**) has two methyl signals showing restricted rotation about the C=N bond as expected. Both are coupled to the NH proton.



55

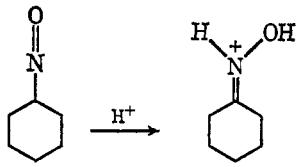
$\delta(CH_3)$	2.20
	2.26
δ(OH)	11.1
δ(NH)	12.0

On heating a solution of this ion to 100° for 30 min, conversion to N-methylacetonitrilium ion (**56**) was observed *via* a Beckmann rearrangement.



56

Protonated cyclohexanone oxime (**57**) has been observed on dissolution of nitrosocyclohexane in FSO_3H–SbF_5–SO_2 solution.[187]



57

XVII. Protonated Nitriles

Nmr studies of nitriles in sulfuric acid–oleum solution have shown that they are very weak bases.[188] By observing the chemical shift of the alkyl group, half-protonation of acetonitrile was shown to occur in 100% sulfuric acid while 30% oleum was necessary to protonate chloroacetonitrile. In slightly aqueous sulfuric acid and at 35°, the protonated nitriles slowly hydrated with formation of protonated amides.

Hydrogen cyanide, acetonitrile, and other alkyl nitriles have been examined in FSO_3H–SbF_5 solution at low temperature. Under these conditions the NH^+ proton appears as a very broad resonance at *ca.* 10 ppm. ^{13}C chemical shifts and the $J_{^{13}C-H}$ coupling constant in protonated HCN show that the nitrile carbon is still sp hybridized and that the protonated nitrile is therefore a linear species. This is also indicated by the ^{15}N–H coupling constants in protonated $HC^{15}N$.[186]

Hydrogen cyanide has also been observed in HF solution by nmr. It was found that if 2 mol of HF was added, the resulting ion was protonated difluoromethylamine.[189]

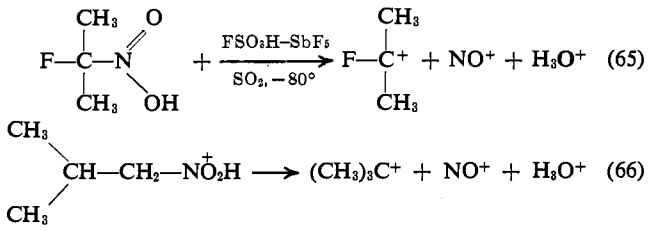
$$H{-}C{\equiv}N \xrightarrow{3HF} HF_2C{-}\overset{+}{N}H_3\ HF_2^-$$

XVIII. Protonated Nitro Compounds

Cryoscopic measurements in sulfuric acid solution have shown that mononitro compounds behave as weak bases.[190,191] Nitromethane is 20% ionized and nitrobenzene 40% ionized in 100% sulfuric acid. The low basicity of nitro compounds has been employed in spectroscopic determinations of the acidity of strong acid solutions (see "acid systems"). A number of nitro compounds have been protonated in FSO_3H–SbF_5 in HF–BF_3 and HF–SbF_5 solutions,[187,192] and under these conditions protonation on oxygen can be clearly demonstrated by nmr, the OH proton appearing at *ca.* δ 16. It is of interest that the spectra of protonated nitrobenzenes are temperature dependent.[187] Thus at low temperatures, the *ortho* protons in protonated 3,5-dichloro-4-methylnitrobenzene are nonequivalent due to restricted rotation about the C–N bond. At higher temperatures rotation about this bond is fast enough to result in *ortho* protons becoming magnetically equivalent. The barrier to rotation (ΔG = 7 kcal/mol) shows the importance of charge delocalization by the aromatic nucleus in the protonated species. This is also shown by studies of the ^{19}F resonance spectra of protonated *m*- and *p*-fluoronitrobenzenes (see p 577 and Table XV).

Nitroalkanes have been shown to cleave in FSO_3H–SbF_5 solution, leading to formation of carbonium,[187] nitrosonium, and hydronium ions. Thus 2-fluoro-2-nitropropane gives the fluorodimethyl carbonium ion (eq 65), and 1-nitro-2-methylpropane gives the *t*-butyl cation (eq 66).

(186) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, 90, 4666 (1968).
(187) G. A. Olah and T. E. Kiovsky, *ibid.*, 90, 6461 (1968).
(188) N. C. Deno, R. W. Gaugler, and M. J. Wisotsky, *J. Org. Chem.*, 31, 1967 (1966).
(189) R. J. Gillespie, personal communication.
(190) R. J. Gillespie and C. Solomons, *J. Chem. Soc.*, 1796 (1957).
(191) R. J. Gillespie, *ibid.*, 2542 (1950).
(192) H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, 86, 1320 (1967).



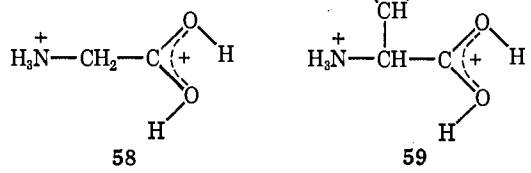
(65)

(66)

XIX. Protonated Amino Acids

Cryoscopic studies of L-leucine in 100% sulfuric acid indicated partial diprotonation of the base. Subsequently further studies of amino acids in the same media indicated that the extent of diprotonation in increased as the amino group is further removed from the carboxyl group (ν 2.2 for L-leucine, 2.7 for D-alanine, and 3.9 for aminocaproic acid).[193]

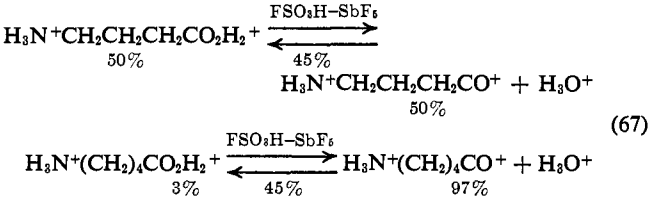
The first protonation site of amino acids is on the amino group, and the monoprotonated amino acids (in CF_3COOH and CF_3COOD) have been studied by proton nmr spectroscopy (at 220 MHz)[194] and by ^{13}C spectroscopy.[195] In fluorosulfonic acid–antimony pentafluoride solution protonation of both the amino group and the carboxyl function occurs, and in addition other basic sites in the molecule can also be protonated.[196] Such polyprotonated amino acids have been studied by nmr spectroscopy. Glycine, for example, has in FSO_3H–SbF_5 solution, a spectrum which shows the ion to have structure **58**. Leucine and valine both show similar protonation behavior. In the latter case nonequivalence of the methyl resonances is observed due to asymmetry at the α-carbon (**59**).



58

59

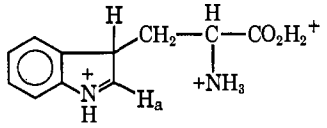
Dehydration to give an amino oxocarbonium ion is not observed in the case of the diprotonated α-amino acids. This is expected in view of the stability of diprotonated malonic acid (see dicarboxylic acids). Increasing the separation of the cationic centers facilitates the dehydration reaction, leading to the formation of γ- and α-aminooxocarbonium ions (eq 67).



(67)

Other amino acids studied under these conditions were L-alanine, L-leucine, L-isoleucine, L-cystine, and L-methionine. In the case of L-cystine, no protonation of the disulfide linkage was observed, while in the case of L-methionine an SH proton was observed at δ 6.52.

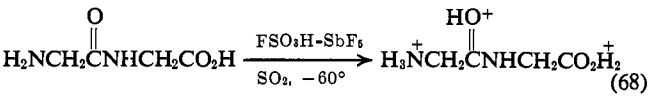
Diaminocarboxylic and monoaminodicarboxylic acids such as L-lysine, aspartic acid, and glutamic acid are triprotonated, and amino acids with a guanidine group, such as arginine and homoarginine, were tetraprotonated, the guanidine function being itself diprotonated as discussed previously. Asparagine and glutamine are α-amino acids containing amide groups on the side chain, and triprotonation of these was found, the amide group being O-protonated. Investigation of α-amino acids containing phenyl substituents was complicated by the reactivity of the ring; however, under suitable conditions diprotonated phenylalanine, triprotonated L-tyrosine, diprotonated L-3,5-dibromotyrosine, and 3-5-diiodotyrosine could be observed. The heterocyclic amino acids L-proline, L-hydroxyproline, L-histidine, and L-tryptophan were studied. In the latter case protonation at the 3 position of the indole ring was found (**60**). Protonation generates a second asymmetric



60

center in this molecule, and this gives rise to two doublets being observed for H_a.

Some simple peptides were also investigated; glycylglycine, glycylglycylglycine, and glycylglycylglycylglycine were found to be tri-, tetra-, and pentaprotonated, respectively (eq 68).



(68)

No cleavage of peptide linkages was observed under these conditions.

In this context, anhydrous HF has been found to be a good solvent for proteins, and many can be recovered from solution with essentially full retention of biological activity (for a review, see ref 197). This is also true of some enzymes, chlorophyll, vitamin B_{12}, and carbohydrates. The solubility of compounds of biological importance in hydrogen fluoride has been reviewed recently.[197] It is clear that the solubility of these compounds must be a result of polyprotonation, and this coupled with nmr spectrometers equipped with superconducting magnets may provide a new tool in the elucidation of protein structures.

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