Conjugate Acid Structure for Oxaziridines Bearing Primary and Secondary 2-Alkyl Groups

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Received April 28, 1977

The protonation of five representative oxaziridines is reported for inert solvents (deuteriochloroform or carbon tetrachloride) where conjugate acid formation may be effected by the addition of about 20% (v/v) TFA. Comparison of the ^1H nmr chemical shifts for neutral and conjugate acid forms suggests that oxaziridines usually undergo protonation on the *N*-atom under these conditions. For one compound studied, 2-ethyl-3-*p*-nitrophenyloxaziridine, there is a possibility that protonation occurs on the alternative *O*-atom. The relevance of these findings to the mechanism of the acid-catalysed hydrolysis of oxaziridines is discussed.

J. Heterocyclic Chem., **14**, 1393 (1977)

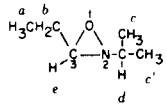
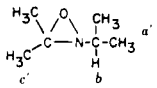
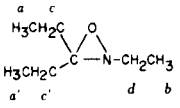
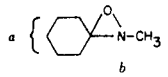
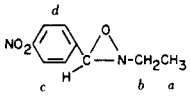
Hydrolytic cleavage of the oxaziridine ring under acidic and basic conditions is well known (2,3). Examination of the reaction products (3) suggests that more than one pathway is involved dependent not only mainly on the structure of the ring substituents, but also on the experimental conditions. With both *O*- and *N*-atoms in the ring available as basic sites, it is reasonable to suppose that the acid catalysed pathway involves reaction *via* a reactive conjugate acid intermediate. This mechanism has been validated for the decomposition of 2-*t*-butyloxaziridines (I) in strong acids, where kinetic studies (particularly solvent deuterium isotope effects) show that rapid pre-equilibrium protonation precedes either unimolecular or bimolecular (by water) ring cleavage depending on the substituent (R) (2). Further, protonation of these oxaziridines was observed to be complete in quite dilute acid, with pK_A values in the range + 0.13 to -1.81 again de-

I

R = alkyl or aryl

Table

^1H Nmr Chemical Shifts for Compounds II-VI in Either Carbon Tetrachloride or Deuteriochloroform and Their Conjugate Acids in Carbon Tetrachloride or Deuteriochloroform plus 20% TFA

	Substrate	Solvent	^1H_n	τ (a)	τ' (b)	$\Delta\tau$/ppm	*N* (c)	*O* (d)
II		Carbon tetrachloride	*a*	8.93	8.77	0.16	γ	γ
			c, *c'*	8.85, 8.73	8.47	0.38, 0.26	β	γ
			b	8.37	7.92	0.45	β	β
			d	7.85	6.49	1.36	α	β
			e	6.32	5.11	1.21	α	α
III		Carbon tetrachloride	*a*, *a'*	9.03, 8.88	8.68, 8.59	0.35, 0.29	β	γ
			c, *c'*	8.72, 8.56	8.32, 8.27	0.40, 0.29	β	β
			b	7.60	7.04	0.56	α	β
IV		Deuterio-chloroform	*a*, *a'*	9.06, 8.94	8.87, 8.78	0.19, 0.16	γ	γ
			b	8.84	8.50	0.34	β	γ
			c, *c'*	8.32	7.85	0.47	β	β
			d	7.21	6.38	0.83	α	β
V		Carbon tetrachloride	*a*	8.32 7.78	8.14 7.59	0.18 0.19	β,γ,ϵ	β,γ,ϵ
			b	7.38	6.78	0.60	α	β
VI	 (A,B isomers)	Carbon tetrachloride	B *a*	8.93	8.90	0.03	β	γ
			A *a*	8.70	8.67	0.03	β	γ
			B *b*	7.52	6.82	0.70	α	β
			A *b*	7.06	6.41	0.65	α	β
			A *c*	5.49	4.34	1.15	α	α
			B *c*	4.80	3.72	1.08	α	α
			A,B *d*	2.35-1.73	2.35-1.73	*ca* 0	γ,ϵ	γ,ϵ

(a) In the inert solvent. (b) In the inert solvent plus *ca* 20% of TFA (trifluoracetic acid). (c) Position of ^1H_n relative to the oxaziridine *N*-atom. (d) Position of ^1H_n relative to the oxaziridine *O*-atom.

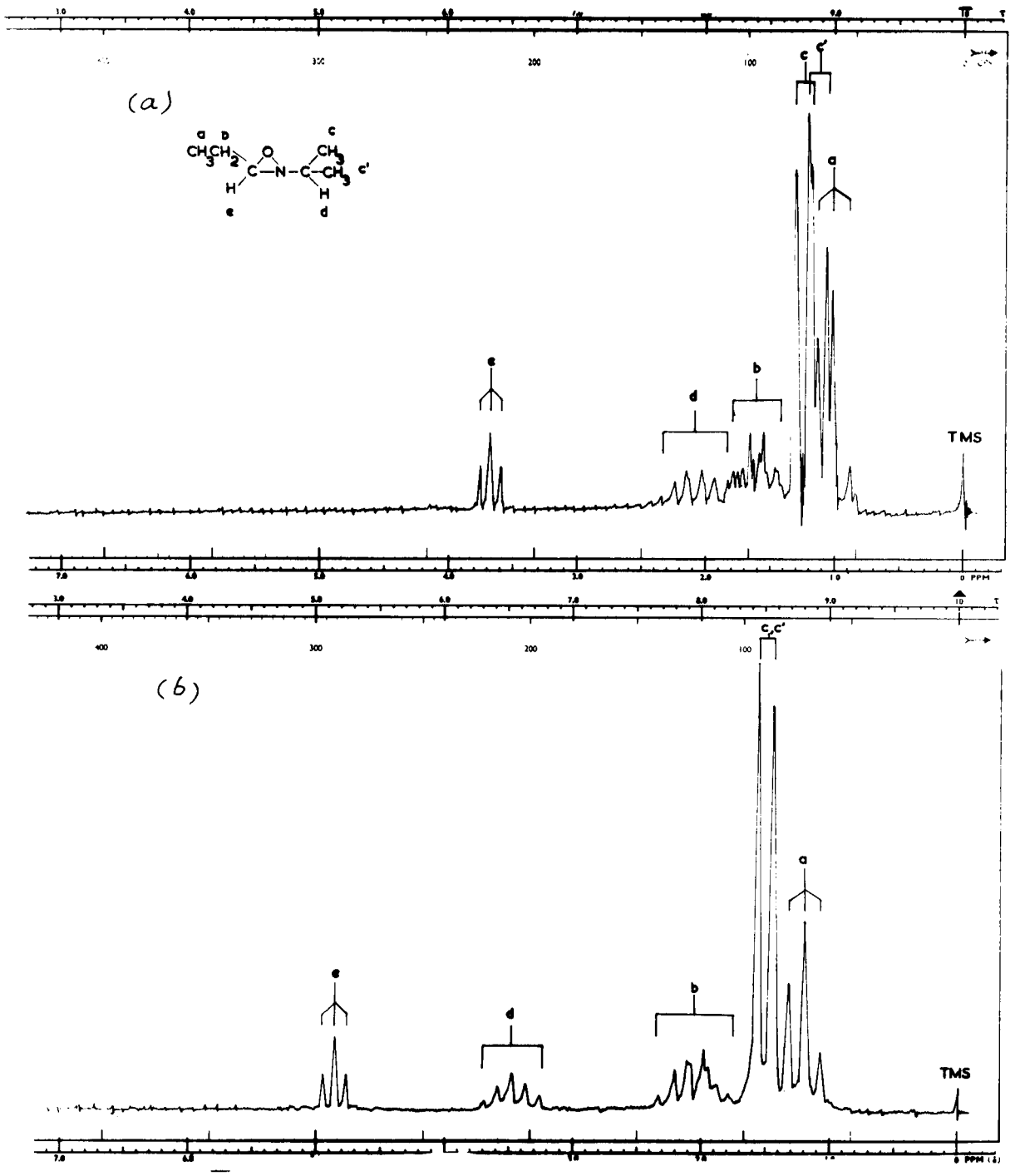


Figure 1. ^{1}H nmr spectrum of 2-isopropyl-3-ethyloxaziridine (II) in: a) carbon tetrachloride; b) carbon tetrachloride plus 20% (v/v) TFA.

pending on the substituent (R) (2). Subsequent work (4) has confirmed these findings. None of the kinetic studies with 2-*t*-butyloxaziridines unambiguously define the site of pre-equilibrium protonation, but the products were more consistent for reaction *via* an *O*-conjugate acid (2,3,4,5). This result was unexpected inasmuch as nitrogen is usually more basic than oxygen, even for compounds such as hydroxylamines (6) where both atoms are also present in the same molecule. Further, theoretical calculations for oxaziridines firmly indicate that nitrogen should be the

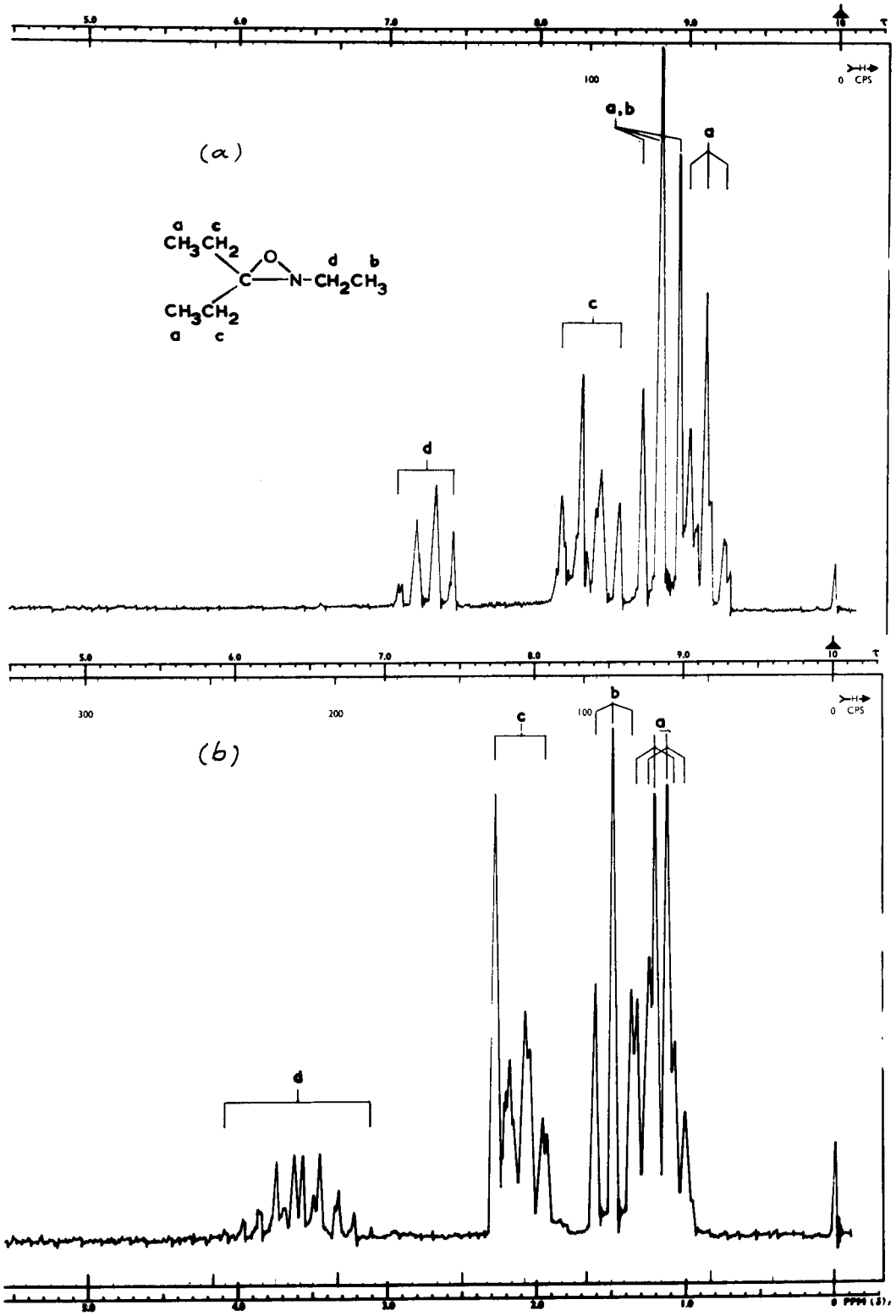


Figure 2.

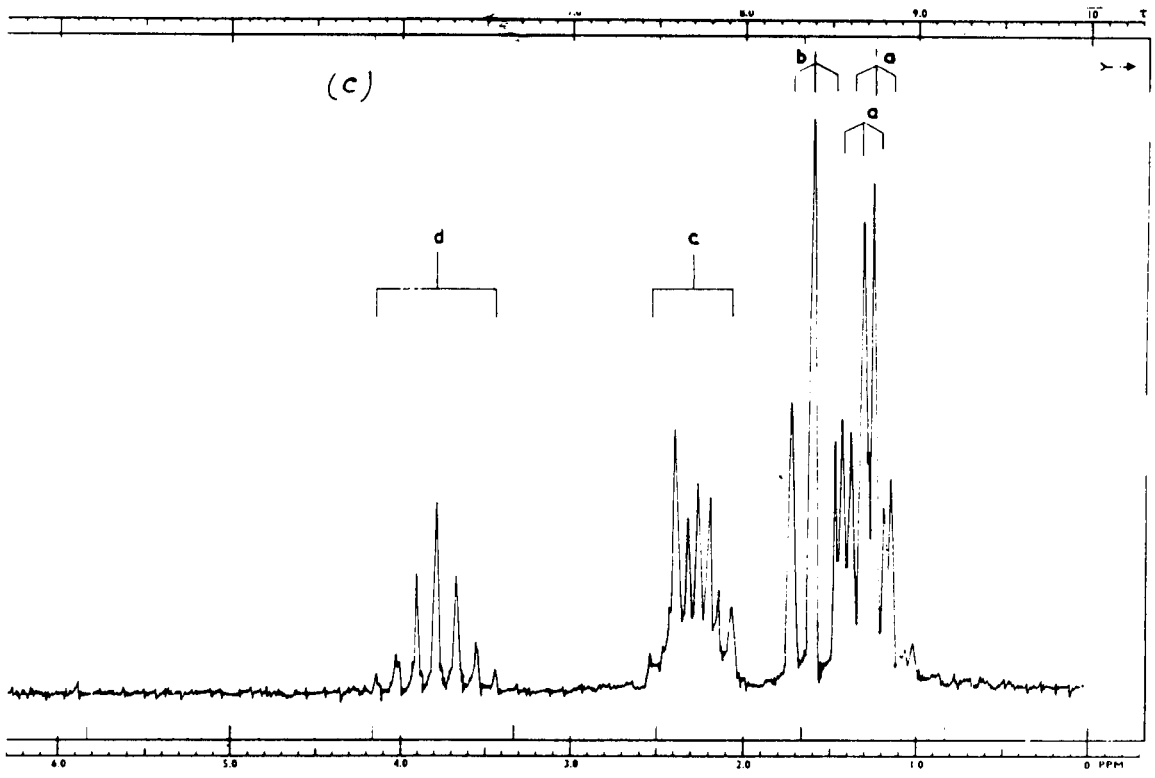


Figure 2. ^{1}H nmr spectrum of 2,3,3-triethyloxaziridine (IV) in: a) carbon tetrachloride; b) carbon tetrachloride plus 20% (v/v) TFA; c) 6*N* deuteriosulphuric acid.

more basic site, at least in the gaseous phase (7a,b). It was therefore considered (2) either that the bulky 2-*t*-butyl substituent effected a reversal of the normal (*i.e.* $N > O$) order of basicity because of steric hindrance to solvation of the *N*-conjugate acid or that *N*-conjugate acid was indeed formed, but it was stable and resistant to hydrolysis.

Direct physical examination of the conjugate acid structures of oxaziridines has not been reported hitherto, probably because their decomposition is rapid if other nucleophilic (basic) entities are also present in solution. However, the reported pK_A values from examination of the rates of hydrolysis (2) clearly suggest that protonation may be effected in inert solvents under mild conditions suitable for nmr spectroscopic investigations. This particular technique has proven definitive in determining the site of protonation of a wide range of organic substrates (8).

The nmr spectra of oxaziridines have been examined and are often complicated by the existence of diastereoisomers resulting from relatively slow inversion about the *N*-atom and by other conformational restrictions (9a,b). Both factors were manifest in the present investigation but they did not prevent satisfactory assignment of the various bands necessary to identify the site of protonation. In practice this was examined for each oxaziridine II-VI by comparative ^{1}H nmr measurements (at *ca* 43°) of the compound in an inert (carbon tetrachloride or deuteriochloroform) and an acidic solvent (usually carbon tetrachloride or deuteriochloroform to which 20% (v/v) TFA had been added). For each solvent, the chemical shifts of the various resonances were computed relative to an internal TMS standard.

The spectra for compound II (see Table) shown in Figure 1 are illustrative. Figure 1a refers to the neutral II in carbon tetrachloride from which the assignments (τ) summarised in Table are drawn. The single resonances observed for both the 3-H and 3-Et substituents suggests that either only a single diasterioisomer is present because there is no inversion about the *N*-atom or this inversion is rapid under our conditions and the spectrum is a time-averaged mean. Other deductions drawn below make the second explanation least likely. All the bands in Figure 1a show a consistent multiplicity except those associated with the 2-isopropyl substituent. Here, both the multiplet (d) for the methine H and the overlapping doublets (c and c′) observed for the two methyl groups show that the latter are not equivalent. This effect has been noted before (9b) and is also evident in the spectrum for the other oxaziridine (III) bearing a 2-isopropyl substituent: in all these examples, the non-equivalence between the two methyl groups of the 2-isopropyl substituent is of the order of 0.12-0.15 ppm. Since the 3-carbon of III is symmetrical, the most likely explanation for this effect is

that rotation about the exocyclic *C-N* is restricted. In turn, and taking into account steric considerations (9) this strongly suggests that the 3-ethyl and 2-isopropyl substituents of II have essentially the *trans* disposition to each other and that there is a considerable barrier to inversion about the *N*-atom.

The spectrum of II after addition of TFA is shown in Figure 1b and the assignments (τ') are summarised in the Table. On protonation, all the bands are shifted to lower field (relative to TMS) but there are no major changes in their multiplicities. The methyl groups of the 2-isopropyl substituent, however, appear to become equivalent. Thus the equivalence observed in Figure 1b is either due to the fact that protonation of II facilitates rotation about the exocyclic *C-N* bond, which is somehow difficult to visualize, or that protonation having changed the anisotropy in the vicinity of the three-membered ring causes the signals attributed to the methyl groups of the 2-isopropyl substituent to degenerate. Either one of these explanations is fully consistent with the observation that on protonation the corresponding 2-methyl groups of III remain non-equivalent.

Similar ^{1}H nmr data obtained for the other oxaziridines (compounds III-VI) are summarised in the Table. For compound III, both the 3-methyl substituents and the methyl groups of the 2-isopropyl substituent are non-equivalent in both neutral and conjugate acid structures, with the difference diminishing (as for II above) on protonation. Apart from the deductions about the slow rate of *C-N* bond rotation made above, this shows that *N*-inversion must be slow for III and its conjugate acid.

Assignments for compound IV were finalised by reference to 2-[α,α'-$^2H_2$-]-ethyl-3,3'-diethyloxaziridine whose spectrum was considerably simpler [τ = 9.06 (3H, tr,), 8.94 (3H, tr), 8.83 (3H, s), 8.32 (4H, qu)]. For both the deuteriated and normal isomers (Figure 2a) the nmr signals of the substrate and its conjugate acid clearly indicate the non-equivalence of all the alkyl residues. This might be due to the inherent anisotropy existent in these molecules as well as slow inversion about the nitrogen atom. A further interesting observation is that on addition of TFA to IV, the slightly distorted quartet (d) assigned to the α-methylene protons of the 2-ethyl substituent undergoes further splitting (Figure 2b) and in 6*N* deuteriosulphuric acid appears to be a well-defined septet (Figure 2c). This cannot possibly result from the formation of two diastereoisomeric conjugate acid species because of the symmetry of the 3-*C* atom, but a plausible explanation is that steric constraints to free rotation about the exocyclic *C-N* bond are imposed by protonation and the attendant solvation of the acidic hydrogen.

The ^{1}H nmr spectrum of compound VI, both in carbon tetrachloride and on addition of TFA is complicated considerably by the presence of the two diastereoisomers with the 3-*p*-nitrophenyl group *cis* and *trans*, respectively, to the 2-ethyl substituent. Both isomers, in fact, have been reported previously and shown to interconvert at room temperature (9b). The present data are in good agreement with earlier assignments, where the *trans* isomer in carbon tetrachloride was associated with the bands at τ = 5.49 (1H, s), 7.06 (2H, m), 8.70 (3H, tr), (9b). This implies that the *trans* isomer is the more stable, which also agrees with previous deductions (9b).

Site of Protonation.

The downfield shift of the bands for compound II in Figure 1b is by a varying degree clearly related to the position of the particular ^{1}H within the molecule. These positions relative to the potential *O*- and *N*-atom sites of protonation are also listed in the Table alongside the differential chemical shifts ($\Delta\tau = \tau-\tau'$) observed on addition of TFA. The largest differential shifts (1.36 and 1.21 ppm) occur for ^{1}H = (d) and (e), respectively, and the smallest (0.16 ppm) for ^{1}H = (a). Differential shifts for ^{1}H = (b), (c) and (c') are intermediate (0.26-0.45 ppm). Assuming that the deshielding effect on any particular ^{1}H induced by the addition of TFA is proportional to the proximity of the positive charge on the conjugate acid species, it is apparent that the observed differential shifts are more satisfactorily described by protonation of the *N*-, rather than the *O*-atom, of the heterocyclic ring.

A similar clear cut conclusion about the site of protonation may be drawn from assignments for compounds III-V and their conjugate acids, also listed in the Table. For all three compounds, a sensible relationship between the magnitude of the differential shift ($\Delta\tau$) and the proximity of any particular ^{1}H to the positive charge is best fitted by an *N*-protonated structure for the conjugate acid. In the case for compound III, this deduction is further supported by the observation that steric constraint to free rotation about the exocyclic *C-N* bond is imposed by protonation (*v. supra*).

The reasons for the wide range of $\Delta\tau$ values obtained for the protons α to the ring nitrogen, namely for II, while the corresponding values for the β,γ, *etc.*, protons are of the same order of magnitude, are not entirely clear. However, the high value of the relative shift observed for compound II probably reflects the possibility of a preferred conformation (unobtainable in other cases where the ring carbon is doubly substituted) being adopted by the conjugate acid of this oxaziridine, whereby the α-proton comes within the influence of the deshielding cone of the heteroatoms (*cf.* also values listed in (10)). For protons further removed from the ring this effect is clearly very attenuated or not observable.

An equivocal result is obtained by this procedure for compound VI. The differential shifts listed in the Table (particularly that for 3-methine ^{1}H) suggest formation of

an *O*-conjugate acid on addition of TFA. It is difficult to understand, however, why the 3-*p*-nitrophenyl substituent should invert the relative basicities of the *O*- and *N*-atoms, particularly in view of its equable disposition to both heteroatoms. It is possible that an *N*-conjugate acid is in fact formed, as with the other oxaziridines, but the 3-methine ^{1}H signal is shifted downfield by an inequitable degree on protonation of the substrate because the benzylic 3-*C*-atom has considerable carbonium ion character.

It is interesting to recall here the results of Crist and coworkers (10) who found that oxaziridines react with silver fluoborate giving rise to stable complexes, the ring nitrogen being the atom through which complexation with the soft Ag^+ (11) occurs. Nonetheless and still according to the same workers small concentrations of the Ag^+-ring oxygen complexes might be kinetically significant. Also (10) interaction between oxaziridines and the hard Li^+ (11) was seen to occur, all the available, albeit sparce, evidence suggesting again the involvement of the nitrogen atom as the contact point of the ligand.

Our results, also in agreement with the above work, strongly suggest that oxaziridine's conjugate acid is essentially constituted by the *N*-protonated species.

Acid-catalysed Hydrolysis of Oxaziridines.

Unfortunately, the ^{1}H nmr method for examining the site of equilibrium protonation was successful only for compounds bearing a 2-α-^{1}H atom with a relatively slow decomposition rate in TFA solutions. These limitations excluded examination of the 2-*t*-butyl compounds reported previously, for which *O*-protonation was considered to occur (2). Two observations can be made that bear on this problem. The first is that examination of the acid-catalysed hydrolysis of compounds II-VI reveals an entirely different kinetic pattern (12) to that observed for the 2-*t*-butyloxaziridines. This difference can be related to the formation of stable and unreactive *N*-conjugate acid species for compounds II-VI, the *O*-conjugate acid being the species which is kinetically significant and rationalises best the hydrolysis products (2). The second is that the present results, in particular the observation of restricted exocyclic *C-N* bond rotation for compounds II and III and the conjugate acid of IV, imply that the heterocyclic *N* is sterically congested. It follows that the presence of a 2-*t*-butyl group may well induce a reversal of the normal order ($N > O$) of atom basicities.

EXPERIMENTAL

Imines were prepared by condensation of the appropriate amine and ketone or aldehyde in the presence of base (13). They were converted to oxaziridines by oxidation with peracetic acid, following the procedure of Emmons (3). Purity was checked by microanalyses, refractive indeces and determination of 'active' oxygen content by the method of Hörner and Jürgens (14). Because of their instability, all the oxaziridines were stored in the dark at -5° and were used within a few days of preparation.

The ^{1}H nmr measurements were made at *ca.* 43° using a Varian A 60 spectrometer. The substrate (*ca* 100 mg.) was first examined in 2 ml. of either carbon tetrachloride or deuteriochloroform containing trimethylsilane (TMS). Then *ca* 20% (v/v) purified TFA was carefully added to the nmr tube. After rapid warming to ambient temperature, the ^{1}H nmr spectrum of the sample was quickly redetermined. For some compounds, the nmr spectra of the conjugate acid were also taken in neat TFA or 6*N* deuteriosulphuric acid.

For signals with a multiplicity >2, the τ values refer to the centre of the band. The accuracy of the chemical shift determinations is about $\pm$ 0.02 τ so the differential chemical shifts ($\Delta\tau$) are known to about 0.04 ppm.

Acknowledgments.

The Gulbenkian Foundation is thanked for a grant to A. M. L., and Laporte Industries Ltd. for supplying 90% hydrogen peroxide.

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