VALENCE TAUTOMERISM OF 3-AZIDOPYRAZINE-1-OXIDE

Misa V. Jovanovic

Department of Chemistry, Southern Methodist University, Dallas, Tx 75275 U.S.A.

Abstract - The first azido-tetrazolo valence tautomerism of a π-deficient N-oxide, 3-azidopyrazine-1-oxide, is reported. It exists in its azido form in $CDCl_3$ and in the tetrazolo form in the solid state or in DMSO-d_6. Both valence tautomers are present in acetone-d_6.

The azido-tetrazolo equilibrium (1 ⇌ 2) in a considerable number of heterocyclic compounds has been scrutinized.[1] The techniques used to study this process involve ultraviolet, infrared, and proton and carbon NMR spectroscopy, among others.[2]

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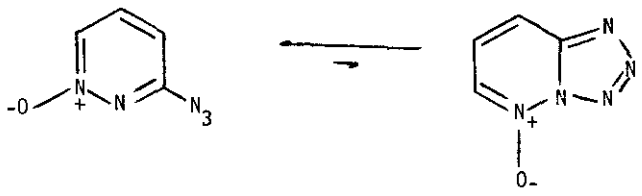
In polar or non-polar solvents, as well as in the solid state, 2-azidopyridine,[3,4] 2-azidopyrazine,[5] 3-azidopyridazine,[6] and 3-azido-1,2,4-triazine[8] exist almost exclusively as their tetrazolo isomers. However, 2-azido-1,3,5-triazine[9] in either dimethyl sulfoxide or chloroform solution exists exclusively in the azido form, while 2-azidopyrimidine[10] in DMSO is present to the extent of only 10% in this form. It is, however, totally in the azido form in chloroform.

In contrast to the tendency of many "azido" compounds to exist as tetrazolo isomers, the N-oxides behave differently. The 3-azidopyridazine-1-oxide (3)[7] and the 3-azido-1,2,4-triazine-1- and 2-oxides[8] exist, both in polar as well as non-polar solvents and in the solid state, in the azido form.



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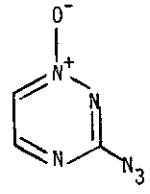
Since 3-azido-1,2,4-triazine-1-oxide (5) exists as such rather than in the tetrazolo form and because it was observed that N-2 rather than N-4 in the nonoxygenated *1,2,4-triazines is the* preferred site for cyclization,[8] we decided to prepare



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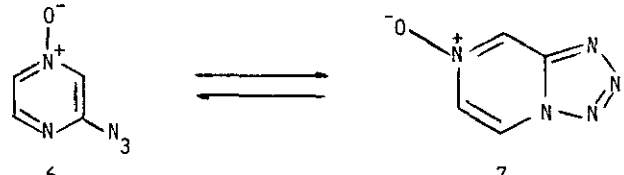
and study 3-azidopyrazine-1-oxide (6). In this instance, the possibility of cyclization proceeding to one of two possible sites does not exist.

The 3-azidopyrazine-1-oxide (6) was prepared from 3-hydrazinopyrazine-1-oxide by treatment with nitrous acid (see Experimental). The infrared spectrum of this compound in $CDCl_3$ has a strong azido absorption band at 2155 cm^{-1}. Its proton NMR spectrum in $CDCl_3$ shows only one set of peaks: a doublet at δ 7.77, a doublet at δ8.19 and a quartet at δ7.88 ($J_{5,6}$ = 3.5 Hz, $J_{2,6}$ = 2.0 Hz coupling across the N-oxide) typical of 3-substituted pyrazine-1-oxides (see Table I). Therefore, in $CDCl_3$ solution, 3-azidopyrazine-1-oxide exists exclusively in the azido form. However, in Nujol or potassium bromide, the infrared spectrum shows no azido absorption, and the compound thus exists in its tetrazolo form (7) in the solid state.



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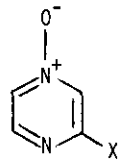
(a) in $CDCl_3$
(b) 15 % in acetone-d_6

(a) in DMSO-d_6
(b) 85 % in acetone-d_6
(c) in the solid state

TABLE I. Some Representative PMR Data of 3-Substituted Pyrazine-1-oxides*



Substituent (X)	H-2	H-5	H-6	Solvent	$J_{5,6}$**	$J_{2,6}$**	$J_{2,5}$**
$-OCH_3$	7.77	7.99	7.75	$CDCl_3$	4.0	1.5	-
$-OCH_3$	8.06	8.16	7.97	DMSO[14]			
$-OCH_3$	8.35	8.57	8.24	TFAA	4.0	1.5	-
-Cl	8.12	7.96	8.22	$CDCl_3$[15,16]	-	-	-
-Cl	8.70	8.44	8.30	DMSO[14]	-	-	-
-Cl	8.69	8.77	8.60	TFAA	4.0	2.0	-
$-N_3$	7.77	8.19	7.88	$CDCl_3$	3.5	2.0	-
$-N_3$(tetrazolo)	9.57	9.55	9.28	DMSO	6.0***	2.0	-
$-N_3$	7.90	8.33	8.05	d_6-acetone	3.5	2.0	-
tetrazolo	9.17	9.27	8.10		6.0	2.0	0.5
$-N_3$	8.19	8.66	8.32	TFAA	3.5	2.0	-

* Chemical shifts are in δ (ppm)

** In Hz.

*** The larger o-coupling constant (6 Hz) in the tetrazolo compounds in comparison to the azido structures (3.5-4.0 Hz) is noteworthy and offers confirmatory structural evidence.

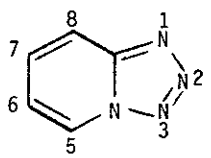
The proton NMR spectrum of the compound in perdeuteriodimethyl sulfoxide (DMSO-d_6) is considerably different from that in deuteriochloroform. That this difference is not a solvent effect is easily demonstrated by comparing the proton NMR spectra of some 3-substituted pyrazine-1-oxides in $CDCl_3$ with those in DMSO-d_6 (see Table I). Clearly, the DMSO-d_6 solvent effect is much less in the 3-chloro- as well as 3-methoxypyrazine-1-oxides than in the 3-azido instance. Thus, we suggest that in DMSO-d_6 the 3-azido compound exists in the tetrazolo form 7. This conclusion is confirmed by the fact that in acetone-d_6 the proton NMR spectrum shows two ABX systems (see Table I). One of these has similar chemical shifts to those of the $CDCl_3$ spectrum while the other has chemical shifts closely akin to those observed for the compound in DMSO-d_6. Integration of the two ABX patterns establishes that in acetone-d_6 a mixture of 15% 3-azido- and 85% tetrazolo isomer is present.

DISCUSSION

Earlier studies of azido-substituted π-deficient nitrogen heterocyclic systems have established that the azido-tetrazolo equilibrium is strongly affected by: (a) the π-deficiency of the azine nitrogen heterocycle, (b) the stability of the tetrazolo compound, (c) the polarity of the solvents, and (d) to some extent, the temperature. The following statements have been made:[11,12]

1. In tetrazolo-azines the azine part of the molecule is responsible for the magnitude of the charge on the nitrogen atom common to both rings.
2. If the electrons from the azido group can be localized on more than one nitrogen atom, in the meta position with respect to the azine nitrogen atom, the azido form is stabilized.
3. In those instances where the additional nitrogen atom(s) is present at a site other than meta with respect to the nitrogen atom common to both rings, the stability of the tetrazole must be considered.[8]

Since 2-azidopyridine exists in the tetrazole form exclusively and because nitrogen substitution of the carbon either α and/or γ to the bridgehead nitrogen (N-4), C-5 and/or C-7 in structure 10, does not cause azido formation, the inductive effect of the additional nitrogen atom does not significantly destabilize the tetrazolo structure. If any of these ring nitrogens are N-oxidized, the azido form is sufficiently stabilized to become a major, if not the exclusive, contributor to the azido-



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tetrazolo equilibrium. The substitution of C-5 (α to N-4) by an N-oxide leads to the predominance of the azido form. Thus, while 3-azidopyridazine exists as a tetrazole in the solid state, in polar and in nonpolar solvents, as well as in trifluoroacetic acid (TFAA), the 3-azidopyridazine-1-oxide exists in the azido form in all of these media. Replacement of C-7 (γ to N-4) by a nitrogen atom, to form 2-azidopyrazine, generates the tetrazole both in the solid state and in DMSO. In $CDCl_3$, 10% of the compound exists in the azido form while in trifluoroacetic acid an approximately equal mixture of azido and tetrazolo form is present. When N-4 is oxidized (3-azidopyrazine-

1-oxide), the compound behaves like its non-oxide in the solid state as well as in polar solvents. But, in a non-polar solvent or in trifluoroacetic acid, it exists exclusively in the azido form. Thus, N-oxidation, in this case, stabilizes the azido form only in non-polar solvents and in trifluoroacetic acid solution. 3-Azido-1,2,4-triazine-1-oxide exists exclusively in the azido form in all media studies.[8,13]

In summary, in those cases where the N-oxide function is α to the bridgehead nitrogen atom (N-4), the azido form is the dominant structure. Since, when the N-oxide is in the position γ to the bridgehead nitrogen atom (N-4), (3-azido-pyrazine-1-oxide), both forms are present, it appears that the controlling factor for these cyclizations is the inductive effect of the N-oxide function, an effect that is greater than that of the sp^2 nitrogen itself. Thus, we would predict that an N-oxide in a position β to the bridgehead nitrogen atom (N-4), such as would be found in 4-azidopyrimidine-1-oxide, would cause azido-stabilization by the resonance effect of the azido function.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded with a Varian HA-100 spectrometer. IR spectra were recorded with a Beckman ACCuLab 1 instrument.

3-Azidopyrazine-1-oxide (6). 3-Hydrazinopyradine-1-oxide[13] (200 mg, 1.46 mmole) was dissolved in 3 ml of conc. HCl. To this solution was added, with cooling in an ice-bath, 2 ml of water containing 120 mg of sodium nitrite. The resulting reaction mixture was allowed to stand at ice-bath temperature for 20 min. After this time, it was slowly (20 min.) allowed to warm up to 15 °C (during this process a reddish-orange precipitate formed). The mixture was then made basic with solid sodium bicarbonate and extracted with methylene chloride (3 x 20 ml). The extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The remaining light-sensitive solid (117 mg, 54%) was recrystallized from acetone to afford transparent crystals (mp 139-140 °C). Anal. Calcd. for $C_4H_3N_5O$: C, 35.04; H, 2.21; N, 51.09. Found: C, 34.88; H, 2.05; N, 51.72.

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