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# EFFECTS OF STEREOCHEMISTRY ON THE STABILITY OF ALPHA-NITROSAMINO CARBANIONS

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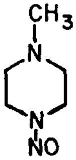
Evidence for the formation of alpha-nitrosamino carbanions was recently provided by Keefer and Fodor[1] who observed the base-catalysed H-D exchange of the protons alpha to the nitrosamino group in 1. The explanation suggested by the authors for the lability of these protons (in the presence of 1.3 M NaOD in $D_2O$ at 100°) was that the carbanion was stabilized by the positive charge on the nitrogen as a result of resonance involving 2a since "canonical structures involving resonance delocalization cannot be formulated".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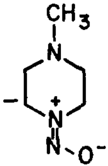
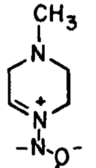
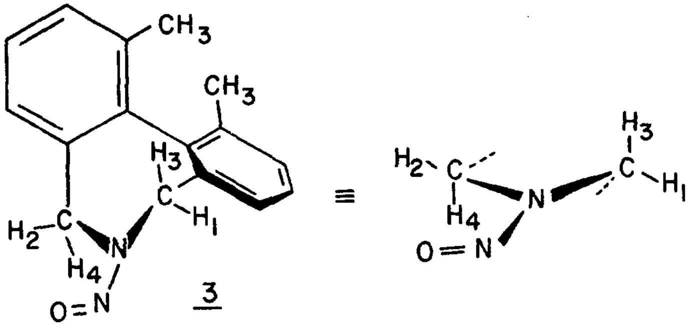

2a


2b

In view of the much more rapid exchange observed for 1 than for quaternary ammonium salts investigated by other workers[2], and the possibility that resonance stabilization might indeed occur via contribution 2b, we have investigated the influence of structure and stereochemistry on this interesting exchange reaction.

The conformationally rigid nitrosamine, N-nitroso-6, 7-dihydro-1, 11-dimethyl-5H-dibenz[c, e]azepine, 3[3], was chosen for this study. Because rotation about the central biaryl bond is prevented by the methyl groups in positions 1 and 11[4], and rotation about the N-N bond is slow, the four protons alpha to the nitrosamino function are magnetically nonequivalent. In the 100 MHz NMR spectrum of 3 in $CDCl_3$ four doublets appear for the four alpha protons at $\tau$ 4.546 ($H_1$), 4.588 ($H_2$), 5.250 ($H_3$) and 6.591 ($H_4$). The geminal coupling constants between the diastereotopic pairs were $J_{1,3}$ = 13.5 Hz and $J_{2,4}$ = 14.9Hz. These assignments were made in analogy with those of Chow and Colon[5] for the alpha protons of N-nitroso-4-benzylpiperidine, 4. It can be seen as depicted in the 3-dimensional formulae for 3 and 4, that the alpha protons in 3 and 4 have almost identical dispositions with respect to the nitrosamino group. This presumably causes the similarity in shifts for $H_2$, $H_3$ and $H_4$ relative to $H_1$ in both compounds.



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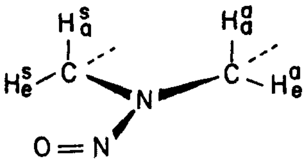

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Because of this similarity in geometry, we will refer to $H_3$ and $H_4$ as quasi-axial, $H_1$ and $H_2$ as quasi-equatorial. In order to confirm these assignments, the effect of added $Eu(DPM)_3$ on the chemical shifts of 3 was determined. The downfield shifts induced by the addition of 0.14 equivalents of $Eu(DPM)_3$ to 3 in $CCl_4$ were 0.56, 1.34, 0.53 and 0.93 ppm for $H_1$-$H_4$ respectively. The observed order of magnitudes $H_2 > H_4 > H_1 > H_3$ is the same as the order of the distances between these protons and the oxygen atom as measured from Dreiding models. In view of the established distance dependence of these shifts[6], the assignments are confirmed.

Exchange of the alpha protons of 3 in t-butanol-O-d was followed by NMR integration measurements over a time interval sufficiently short to ensure that rotation about the N-N bond is negligible. For 3 in t-butanol-O-d, this rate of rotation was determined by measuring the redistribution of a deuterium atom stereoselectively substituted in place of $H_4$. The measured half-life for randomization of deuterium between the two quasi-axial positions was 10 hr. at 33°. The sample used for this purpose had been prepared by treating 3 in THF at -70° with one equivalent of methyl lithium, then quenching by rapid addition of $D_2O$. The resultant 3-$d_1$ contained only 10% of residual $H_4$ and 91% of residual $H_3$ (deuteration at this position probably results from rotation about the N-N bond during work-up).*

In view of this 10 hr. half-life for the process which interconverts syn and anti protons, rotation will be negligble ($<$ 3%) during a kinetic run of thirty min.or less. This time limitation required the use of three different concentrations of potassium-t-butoxide for the exchange experiments, the results of which appear in the table.

| Conc. of KO-t-bu | $H_1$ | $H_2$ | $H_3$ | $H_4$ |
|---|---|---|---|---|
| 0.006 M | | 1 | | $>30$ |
| 0.10 | | 2.7 | 1 | |
| 0.20 | 1 | | 3.5 | |
| Relative rates | 1 | 10 | 3.5 | $>300$ |

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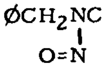
* There is a large solvent effect on the rate of rotation of the nitroso group in 3, the half-life in $CDCl_3$ being only 80 minutes.

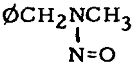
When a 0.006 M concentration of base was used, a 70% diminution in the $H_4$ signal was the only observable exchange after 27 min. If exchange of up to 5% of $H_2$ went undetected during this time then a lower limit of 30:1 can be calculated for the relative rate $H_4/H_2$. Rate constants for the exchanges in 0.1 and in 0.2 M solutions of base were obtained by monitoring the exchange at five intervals covering more than 50% exchange of the more labile proton. From these data the overall relative rates were derived.

The large preference for exchange of $H_4$ over $H_2$ and the lesser preference for $H_3$ over $H_1$ are believed to reflect the stereochemical requirement for carbanion stabilization via the resonance interaction depicted in 2b, i.e. overlap is greater for the carbanions derived from abstraction of the quasi-axial protons. The difference in these two relative rates is likely caused by unequal steric effects in the syn and anti positions. A steric influence of the biaryl system cannot be responsible for the above rates as it has been shown that, in the closely related thiepin dioxide system[7], the quasi-axial protons are more hindered. One other factor, preferred stabilization of the carbanions derived from $H_4$ and $H_3$ via overlap with the benzene rings also appears negligible. This preference is small and should amount to only 30% of the total accelerating influence of the benzene rings[7]. Acceleration of a benzene ring relative to hydrogen was found to be 2.3 by measurement of the rates of exchange of the benzyl protons in the anti nitrosamine 5a[8] relative to the methyl protons in the syn isomer, 5s[8]. Thus the preference for



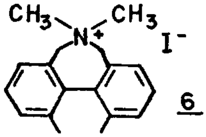
$\phi CH_2\underset{O=N}{\underset{|}{N}}CH_3$

5a



$\phi CH_2\underset{N=O}{\underset{|}{N}}CH_3$

5s



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exchange of $H_4$ over $H_2$ and $H_3$ over $H_1$ can reasonably be attributed to the geometric preference for resonance stabilization of the resultant carbanions*.

Evidence against the importance of an ylide type of stabilization is perhaps more conclusive. In another set of exchange experiments the quaternary iodide, 6[4], when heated at 80° for 45 hours then at 100° for 24 hours in t-butanol-O-d:$CD_3OD$(1:4.1) containing 0.3 M $CD_3ONa$, failed to undergo exchange. In contrast, at 35° in the same medium (0.22 M in $CD_3ONa$), the half-life for $H_4$ in 3 was 20 min. These results clearly

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* A referee has proposed that the preference for abstraction of $H_4$ over $H_2$ may be due to steric retardation of attack by base at $H_2$ in view of the established instability of alpha equatorial methyl groups in nitrosopiperidines[9]. Such a steric effect would be markedly less in the transition state for exchange of $H_2$ but it could nevertheless have an influence on the relative rate $H_4/H_2$.

eliminate ylide type stabilization as being important for the nitrosamino carbanions derived from 3.

The observation of the faster exchange of syn than anti protons in 3 is perhaps not ununusual. A similar stereochemical course has been observed in the base-catalysed isomerization of allyl to propenyl ethers[10]. For example t-butoxide-catalysed isomerization of allyl phenyl ether gave 97% cis phenyl propenyl ether in glyme and 99% cis ether in dimethylsulfoxide. Coordination of the cation with the terminal carbon and ether oxygen of the cis carbanion was proposed to explain the preferential formation of cis product. A similar coordination of potassium with the carbon and oxygen atoms in the syn anion may account for the greater exchange rate of the syn protons.

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## References

1. L.K.Keefer and C.H.Fodor, J.Amer.Chem.Soc., 92, 5747 (1970).
2. W.v.E.Doering and A.K.Hoffmann, ibid., 77, 521 (1955); M.Saunders and E.H.Gold, ibid., 88, 3376 (1966).
3. Treatment of the parent azepine with nitrous acid gave 3, m.p. 123-123.5°. Satisfactory C, H and N analyses were obtained for both the azepine and the nitrosamine.
4. K.Mislow, M.A.W.Glass, H.B.Hopps, E.Simon and G.H.Wahl, Jr., J.Amer.Chem.Soc., 86, 1710 (1964).
5. Y.L.Chow and C.J.Colon, Can.J.Chem., 46, 2827 (1968).
6. C.C.Hinckley, J.Amer.Chem.Soc., 91, 5160 (1969); C.C.Hinckley, J.Org.Chem., 35, 2834 (1970); J.K.M.Sanders and D.H.Williams, Chem.Comm., 422 (1970); P.V.Demarco, T.K.Elzey, R.B.Lewis and E.Wenkert, J.Amer.Chem.Soc., 92, 5734 (1970); G.H.Wahl, Jr., and M.R.Peterson, Jr., Chem.Comm., 1167 (1970); R.R. Fraser and Y.Y.Wigfield, ibid., 1471 (1970).
7. R.R.Fraser and F.J.Schuber, Chem.Comm., 1474 (1969).
8. G.J.Karabatsos and R.A. Taller, J.Amer.Chem.Soc., 86, 4373 (1964).
9. Y.L.Chow, C.J.Colon and J.S.Tam, Can.J.Chem., 46, 2821 (1968).
10. P.Caubere and M.Hochu, Bull.Soc.Chim.Fr., 459 (1968); T.J.Prosser, J. Amer.Chem.Soc., 83, 1701 (1961); C.C.Price and W.H.Snyder, ibid., 83, 1773 (1961).