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Structural Studies by Nuclear Magnetic Resonance. IX. Configurations and Conformations of N-Nitrosamines

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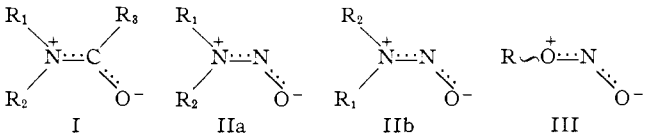
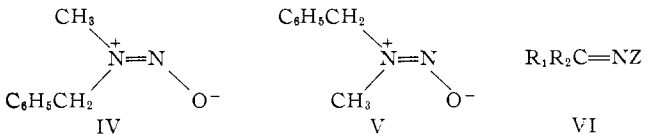
Configurations, and in some cases conformations, were assigned to thirteen nitrosamines from analysis of their 60-Mc. n.m.r. spectra. In contrast to α-methyl, α-methylene, and β-methyl protons, which resonate at higher magnetic fields by about 0.3–0.8 p.p.m. when *cis* than when *trans* to the nitroso oxygen, α-methine protons resonate at lower fields by about 0.2–0.6 p.p.m. As a result of stereospecific association between nitrosamine and benzene, whereby the ring is closer to the *trans* than to the *cis* protons, *trans* protons experience a greater upfield shift than *cis* protons when the solvent is changed from aliphatic to aromatic. This shift inequality can be used as a reliable criterion of assigning configurations. For the *trans* isomers the data are in accord with conformations in which the nitrogen–nitrogen bond is eclipsed with a substituent on the tetrahedral carbon. The detection of only one set of resonances for methyl phenyl nitrosamine is due to the presence of only the *cis*-methyl isomer, not to rapid isomer interconversion. Both isomers of ethyl phenyl nitrosamine and isopropyl phenyl nitrosamine were detected.

Nuclear magnetic resonance has been used extensively and successfully in the study of problems arising from restricted rotation about single bonds, double bonds, and partial double bonds. Amides (I), nitrosamines (II), and nitrites (III) fall in the category of compounds involving restricted rotation about partial



I IIa IIb III

double bonds. In contrast to amides which have been studied extensively,[2] nitrites[3] and nitrosamines[4] have attracted little attention. Configurations[5] IIa and IIb were determined[4] for several nitrosamines by assuming that protons will resonate at lower magnetic fields when *cis* than when *trans* to the nitroso oxygen. This assumption led to the conclusion that the ratio [IV]/[V] is about three.



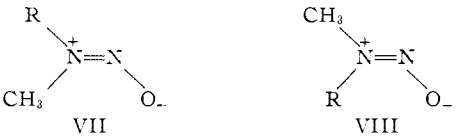
IV V VI

The n.m.r. spectra of nitrosamines should show similarities to those of amides and to those of VI. From our experience[6] with the n.m.r. of VI, we doubted the correctness of configurational assignments to nitrosamines; *e.g.*, protons usually resonate at higher fields when *cis* than when *trans* to Z. Furthermore, when R_1 is methyl and R_2 is benzyl, the thermodynamically more stable isomer has Z *cis* to the methyl rather than to the benzyl group.

This paper summarizes our studies on nitrosamines.

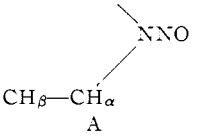
Results

Figure 1 shows the 60-Mc. n.m.r. spectra of dimethyl, methyl ethyl, methyl isopropyl, and methyl *t*-butyl nitrosamines. The configurational assignments are made on the reasonable assumption that the ratio VII/VIII increases as R changes from ethyl to isopropyl to *t*-butyl. The assignments therefore by previous investigators[4] should be reversed.



VII VIII

Table I summarizes the chemical shifts and *syn/anti* ratios of thirteen nitrosamines. The chemical shifts are accurate to ± 0.03 p.p.m. with relative values between *cis* and *trans* protons being accurate to ± 0.01 p.p.m. The notation used to distinguish the various protons on the R groups is shown in A, each proton being referred to as *cis* or *trans* with respect to the



A

nitroso oxygen. The *syn/anti* ratios were determined by integration of peak areas and are accurate to $\pm 5\%$.

Two observations are pertinent to subsequent discussion of conformations: (a) In $R(CH_3)NNO$ the resonance of the *trans*-β-methyl of the R group shifts to lower fields as R changes from ethyl (τ = 8.62) to isopropyl (τ = 8.58) to *t*-butyl (τ = 8.46). (b) In $R[CH(CH_3)_2]NNO$ the resonance of the *trans*-α-methine shifts to higher fields by 0.3–0.4 p.p.m. as R changes from methyl (τ = 5.15) to benzyl (τ = 5.43) to isopropyl (τ = 5.74).

Table II summarizes the differences in the chemical shifts of *cis* and *trans* protons. A positive $\Delta\delta$ means that *cis* protons resonate at higher fields than *trans*, a negative reverse. The pertinent points are: (a) While

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(2) (a) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955); (b) H. S. Gutowsky, *Discussions Faraday Soc.*, **19**, 247 (1955); (c) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); (d) R. A. Ogg, Jr., J. D. Ray and L. Piette, *J. Mol. Spectry.*, **2**, 66 (1958); (e) C. Franconi, *Z. Elektrochem.*, **65**, 645 (1961); *Scienza e Technica, n.s.*, **4**, 183 (1960); (f) D. G. de Kowalewski, *Arkiv Kemi*, **16**, 373 (1960); (g) V. J. Kowalewski and D. G. de Kowalewski, *J. Chem. Phys.*, **32**, 1272 (1960); (h) E. W. Randall and J. D. Baldeschwieler, *J. Mol. Spectry.*, **8**, 365 (1962); (i) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960); **5**, 139 (1962); (j) M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962); (k) L. A. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.*, **85**, 3728 (1963); **86**, 337 (1964); (l) R. M. Moriarty, *J. Org. Chem.*, **28**, 1296 (1963).

(3) (a) L. H. Piette, J. D. Ray, and R. A. Ogg, Jr., *J. Chem. Phys.*, **26**, 1341 (1957); (b) W. D. Phillips, C. E. Looney, and C. P. Spaeth, *J. Mol. Spectry.*, **1**, 35 (1957); (c) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

(4) C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Am. Chem. Soc.*, **79**, 6136 (1957).

(5) We shall use the term configuration for structures IIa and IIb in order to avoid confusion with subsequent discussion of the conformations of R_1 and R_2.

(6) Previous paper in the series: G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Am. Chem. Soc.*, **86**, 3351 (1964).

TABLE I

CHEMICAL SHIFTS (τ-VALUES) OF NITROSAMINES

R_1R_2NNO			$H\alpha(CH)$		$H\alpha(CH_2)$		$H\alpha(CH_3)$		$H\beta(CH_3)$		%
R_1	R_2	Solvent	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*syn/anti*[a]
CH_3	CH_3	Neat					6.98	6.23			
CH_3	CH_3	CCl_4					7.04	6.24			
CH_3	CH_3	C_6H_6					7.60	7.04			
CH_3	CH_2CH_3	Neat			6.41	5.83	7.00	6.28	8.98	8.67	78/22
CH_3	CH_2CH_3	CCl_4			6.48	5.85	7.07	6.29	8.95	8.62	73/27
CH_3	CH_2CH_3	C_6H_6			6.91	6.49	7.54	7.01	9.42	9.26	79/21
CH_3	$CH(CH_3)_2$	Neat	4.97	5.17			7.05	6.34	8.88	8.59	89/11
CH_3	$CH(CH_3)_2$	CCl_4	4.97	5.15			7.13	6.38	8.91	8.58	89/11
CH_3	$CH(CH_3)_2$	C_6H_6	5.12	5.60			7.52	6.99	9.41	9.15	90/10
CH_3	$C(CH_3)_3$	Neat					7.03			8.46	100/0
CH_3	$C(CH_3)_3$	CCl_4					7.11			8.46	100/0
CH_3	$C(CH_3)_3$	C_6H_6					7.44			8.91	100/0
CH_3	$(CH_2)_3CH_3$	Neat			6.44	5.87	7.02	6.28			79/21
CH_3	$(CH_2)_3CH_3$	CCl_4			6.53	5.91	7.08	6.30			78/22
CH_3	$(CH_2)_3CH_3$	C_6H_6			6.86	6.45	7.51	6.96			77/23
CH_3	$CH_2C_6H_5$	Neat			5.21	4.72	7.15	6.41			74/26
CH_3	$CH_2C_6H_5$	CCl_4			5.28	4.70	7.14	6.33			79/21
CH_3	$CH_2C_6H_5$	C_6H_6			5.64	5.26	7.56	6.99			78/22
CH_3	C_6H_5	Neat					6.68				100/0
CH_3	C_6H_5	CCl_4					6.62				100/0
CH_3	C_6H_5	C_6H_6					7.19				100/0
CH_2CH_3	$CH_2C_6H_5$	Neat			5.22 (6.58)[b]	4.77 (5.98)[b]			9.18	8.81	50/50
CH_2CH_3	$CH_2C_6H_5$	CCl_4			5.28 (6.58)[b]	4.76 (5.93)[b]			9.08	8.67	53/47
CH_2CH_3	$CH_2C_6H_5$	C_6H_6			5.57 (6.85)[b]	5.22 (6.42)[b]			9.50	9.20	55–45
$CH_2C_6H_5$	$CH(CH_3)_2$	Neat	5.10	5.45	5.22	4.78			9.10	8.70	84/16
$CH_2C_6H_5$	$CH(CH_3)_2$	CCl_4	5.13	5.43	5.30	4.75			9.02	8.58	82/18
$CH_2C_6H_5$	$CH(CH_3)_2$	C_6H_6	5.23	5.82	5.54	5.16			9.36	9.01	88/12
CH_2CH_3	C_6H_5	Neat			5.99	5.54			8.97	8.78	~96/4
CH_2CH_3	C_6H_5	CCl_4			5.99	5.47			8.85		~97/3
CH_2CH_3	C_6H_5	C_6H_6			6.39				9.26		
$CH_2C_6H_5$	C_6H_5	CCl_4			4.84						~100/0
$CH_2C_6H_5$	C_6H_5	C_6H_6			5.15						~100/0
$CH(CH_3)_2$	C_6H_5	Neat	4.87	5.06					8.94	8.68	57/43
$CH(CH_3)_2$	C_6H_5	CCl_4	4.88	4.97					8.82	8.55	64/36
$CH(CH_3)_2$	C_6H_5	C_6H_6	4.92	5.28					9.17	8.95	58/42
$CH(CH_3)_2$	$CH(CH_3)_2$	CCl_4	5.11	5.74					8.85	8.48	
$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_6	5.19	6.25					9.20	8.82	

[a] *Syn* is the isomer having R_1 *cis* to the oxygen. [b] Methylene of the ethyl group.

TABLE II

$\Delta\delta$ ($\delta_{cis} - \delta_{trans}$) VALUES, IN P.P.M., OF NITROSAMINES

R_1R_2NNO		$\Delta\delta(\alpha\text{-}CH_3)$			$\Delta\delta(\alpha\text{-}CH_2)$			$\Delta\delta(\alpha\text{-}CH)$			$\Delta\delta(\beta\text{-}CH_3)$		
R_1	R_2	Neat	CCl_4	C_6H_6	Neat	CCl_4	C_6H_6	Neat	CCl_4	C_6H_6	Neat	CCl_4	C_6H_6
CH_3	CH_3	+0.75	+0.80	+0.56									
CH_3	CH_2CH_3	+ .72	+ .78	+ .53	+0.58	+0.63	+0.42				+0.31	+0.33	+0.16
CH_3	$(CH_2)_3CH_3$	+ .74	+ .78	+ .55	+0.57	+0.62	+0.41						
CH_3	$CH(CH_3)_2$	+ .71	+ .75	+ .53				−0.20	−0.18	−0.48	+0.29	+0.33	+0.26
CH_3	$CH_2C_6H_5$	+ .74	+ .81	+ .57	+0.50	+0.58	+0.38						
CH_2CH_3	C_6H_5				+0.45	+0.52					+0.19		
CH_2CH_3	$CH_2C_6H_5$				+0.60	+0.65	+0.43				+0.37	+0.41	+0.30
					(+0.45)[a]	(+0.52)[a]	(+0.35)[a]						
$CH(CH_3)_2$	$CH(CH_3)_2$							[b]	−0.63	−1.06	[b]	+ .37	+ .38
$CH(CH_3)_2$	$CH_2C_6H_5$				+0.44	+0.55	+0.38	−0.35	− .30	−0.59	+0.40	+ .44	+ .35
$CH(CH_3)_2$	C_6H_5							−0.21	− .09	−0.36	+0.26	+ .27	+ .22

[a] Methylene of benzyl group. [b] Compound is a solid.

α-methyl and α-methylene protons resonate at higher fields when *cis* than when *trans* to the nitroso oxygen, α-methine protons resonate at lower fields (negative $\Delta\delta$). (b) While positive $\Delta\delta$ values are smaller in benzene than in carbon tetrachloride—with diisopropyl nitrosamine the notable exception—negative $\Delta\delta$ values are larger in benzene. (c) While $\Delta\delta$ values for α-methyl, α-methylene, and β-methyl vary over small ranges, those for the α-methine vary over large ranges.

Table III summarizes $\Delta\nu$ ($\nu_{\text{in benzene}} - \nu_{\text{in carbon tetrachloride}}$) values compiled from the data of Table I. The pertinent points are: (a) $\Delta\nu$ values are higher for the *trans* than for the corresponding *cis*-protons, with the β-methyls of diisopropyl nitrosamine again the notable exception. In this respect nitrosamines behave similarly to amides and in direct opposition to compounds having the structure $R_1R_2C{=}NNHX$. (b) As the sizes of R_1 and R_2 of dialkyl nitrosamines increase $\Delta\nu$ values for *cis*-α-methine protons are very small and decrease as the R of $R[CH(CH_3)_2]$-NNO increases in size.

Table IV summarizes the effect of several solvents on the chemical shifts of methyl ethyl nitrosamine.

Figure 2 shows the effect of dilution (benzene solvent) on the chemical shifts of methyl ethyl nitrosamine. Figure 3 compares the effect of dilution on the chemical

TABLE III

COMPARISON OF CHEMICAL SHIFTS OF NITROSAMINES IN BENZENE AND CARBON TETRACHLORIDE

R_1R_2NNO		$\Delta\nu^a(\alpha\text{-}CH_3)$		$\Delta\nu^a(\alpha\text{-}CH_2)$		$\Delta\nu^a(\alpha\text{-}CH)$		$\Delta\nu^a(\beta\text{-}CH_3)$	
R_1	R_2	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
CH_3	CH_3	32.4	48.0						
CH_3	CH_2CH_3	28.2	43.2	25.8	38.4			28.2	38.4
CH_3	$(CH_2)_3CH_3$	25.8	39.6	19.8	32.4				
CH_3	$CH(CH_3)_2$	23.4	36.6			9.0	27.0	30.0	34.2
CH_3	$C(CH_3)_3$	19.8							33.0
CH_3	$CH_2C_6H_5$	25.2	39.6	21.6	33.6				
CH_3	C_6H_5	34.2							
CH_2CH_3	$CH_2C_6H_5$			17.4 (16.2)[b]	27.6 (29.4)[b]			25.2	31.8
CH_2CH_3	C_6H_5			24.0				24.6	
$CH_2C_6H_5$	$CH(CH_3)_2$			14.4	24.6	6.0	23.4	20.4	25.8
$CH_2C_6H_5$	C_6H_5			18.6					
$CH(CH_3)_2$	$CH(CH_3)_2$					2.4	30.6	21.0	20.4
$CH(CH_3)_2$	C_6H_5					2.4	18.6	21.0	24.0

[a] $\Delta\nu = \nu_{\text{in benzene}} - \nu_{\text{in carbon tetrachloride}}$; for convenience the differences are expressed in c.p.s. [b] Methylene of the ethyl group.

shifts of methyl ethyl nitrosamine and methyl *t*-butyl nitrosamine. When dimethyl sulfoxide or carbon tetrachloride are used as solvents dilution has practically no effect on the chemical shifts.

TABLE IV

SOLVENT EFFECTS ON THE CHEMICAL SHIFTS OF METHYL ETHYL NITROSAMINE

Solvent	$\tau(\alpha\text{-}CH_2)$ *cis*	$\tau(\alpha\text{-}CH_2)$ *trans*	$\tau(\alpha\text{-}CH_3)$ *cis*	$\tau(\alpha\text{-}CH_3)$ *trans*	$\tau(\beta\text{-}CH_3)$ *cis*	$\tau(\beta\text{-}CH_3)$ *trans*
Carbon tetrachloride	6.48	5.85	7.07	6.29	8.95	8.62
Cyclohexane	6.53	5.92	7.14	6.39		
Acetone	6.42	5.82	7.01	6.28	8.97	8.67
Dimethyl sulfoxide	6.44	5.86	7.02	6.31	9.01	8.71
Methanol		5.82	6.94		8.92	8.63
Benzene	6.91	6.48	7.54	7.01	9.42	9.26
Toluene	6.90	6.43	7.53	6.95	9.37	9.19
o-Xylene	6.92	6.44	7.54	6.94	9.37	9.16
m-Xylene	6.88	6.41	7.51	6.92	9.35	9.15
p-Xylene	6.88	6.41	7.51	6.90	9.34	9.14
Isodurene	6.91	6.42	7.51	6.91	9.34	9.12
Chlorobenzene	6.67	6.18	7.28	6.67	9.20	8.97
Bromobenzene	6.72	6.22	7.32	6.71	9.24	9.02
Iodobenzene	6.73	6.21	7.32	6.69	9.24	9.01
m-Dichlorobenzene	6.60	6.06	7.19	6.53	9.13	8.86
Anisole		6.32	7.40	6.82	9.29	9.09
N,N-Dimethylaniline		6.44		6.94	9.37	9.17
Nitrobenzene	6.36	5.81	6.93	6.27	8.94	8.66
Pyridine	6.50	5.99	7.07	6.46	9.12	8.88
Phenol	6.85	6.55	7.43	7.01	9.36	9.21

Table V summarizes some pertinent ultraviolet spectral values of nitrosamines in cyclohexane.

TABLE V

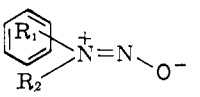
PARTIAL ULTRAVIOLET SPECTRA OF NITROSAMINES IN CYCLOHEXANE[a]

R_1R_2NNO		λ_{max}, mμ	$\epsilon \times 10^3$
R_1	R_2		
CH_3	CH_3	232	5.87
CH_3	CH_2CH_3	233	5.79
$(CH_3)_2CH$	$(CH_3)_2CH$	235	6.23
CH_3	C_6H_5	274	7.02
CH_3CH_2	C_6H_5	275	6.77
$(CH_3)_2CH$	C_6H_5	250	5.53
		224	7.69

[a] In 95% ethanol a hypsochromic shift occurs of about 3–5 mμ.

Discussion

Solvent Effects.—The larger upfield shift of the resonances of the *trans* protons over those of the *cis* protons when the solvent is changed from carbon tetrachloride to benzene suggests stereospecific association between the benzene ring and nitrosamine, whereby the ring is attracted by the positive charge on the nitrogen and repelled by the negative charge on the oxygen (IX).[7] The data amply justify such an association.



IX

For example: (a) Figure 2 shows that on dilution with benzene the resonances of the *trans* protons shift to higher fields more rapidly than those of the corresponding *cis*. (b) $\Delta\nu$-values (Table III) of alkyl methyl nitrosamines decrease as the alkyl group is changed from methyl to *t*-butyl. Such a change is consistent with IX, since increase in the size of R_1 and/or R_2 should decrease the equilibrium constant for (1) by destabilizing IX. The more rapid upfield shift of the

$$R_1R_2NNO + C_6H_6 \rightleftharpoons R_1R_2NNO \cdot C_6H_6 \qquad (1)$$

resonances of methyl ethyl nitrosamine over those of methyl *t*-butyl nitrosamine (Fig. 3) illustrates the same point.

The behavior of the chemical shifts of methyl ethyl nitrosamine as a function of solvent (Table IV) is also consistent with IX. Alkyl substitution on the benzene ring shifts the resonances—with respect to those in benzene—of the *trans* protons to slightly lower fields, probably as a consequence of destabilization of IX by increased nonbonded interactions.[8]

Conformations.—In the absence of coupling between protons of R_1 and those of R_2 (II), elucidation of the conformations of R_1 and R_2 must rely solely on chemical shifts. Accurate knowledge of the anisotropy of the NNO group would simplify the problem and permit the assignment of reliable conformations. In the absence of such information, however, the simplest avenue open is intelligent guessing of the anisotropic effects of NNO by comparing it with other groups. From the practically identical behavior of the chemical shifts of nitrosamines and $R_1R_2C{=}NZ$ compounds it is reasonable to assume that the anisotropic effects of NNO and C=NZ are qualitatively similar. From

(7) Similar interactions have been suggested for amides: ref. 2i,k,l.

(8) Similar effects were observed with phenylhydrazones: G. J. Karabatsos and R. A. Taller, *J. Am. Chem. Soc.*, **85**, 3624 (1963).

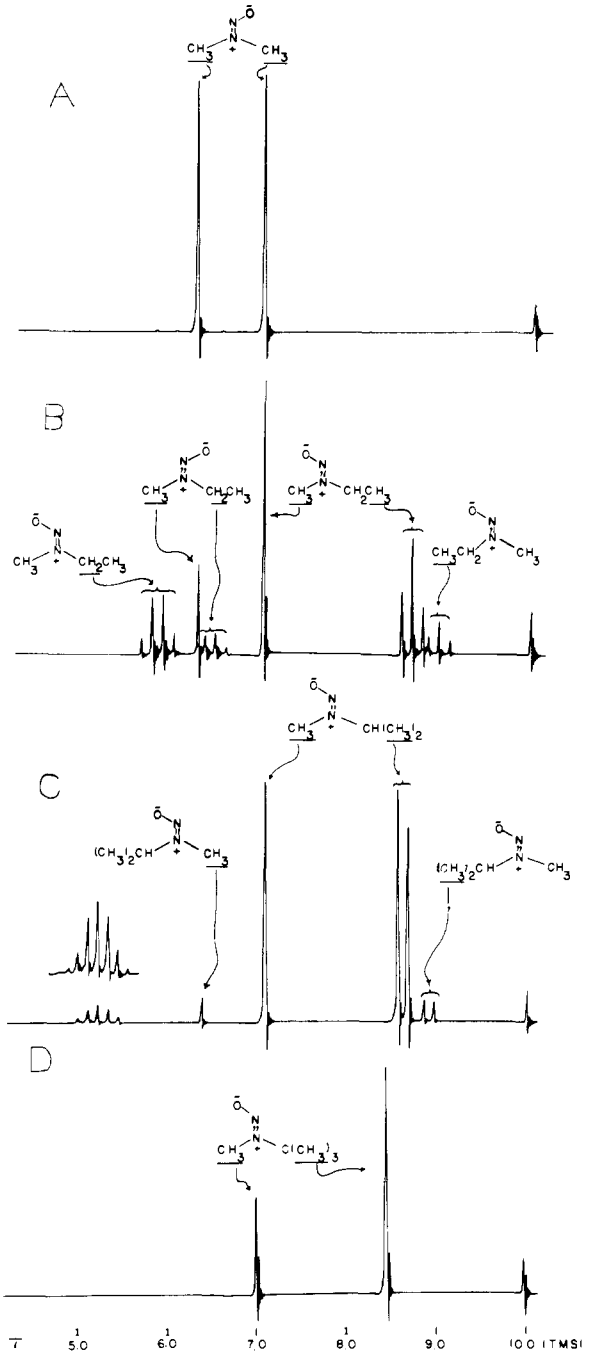


Fig. 1.—60-Mc. n.m.r. spectra of dimethyl nitrosamine (A), methyl ethyl nitrosamine (B), methyl isopropyl nitrosamine (C), and methyl *t*-butyl nitrosamine (D) in 4% (w./w.) carbon tetrachloride.

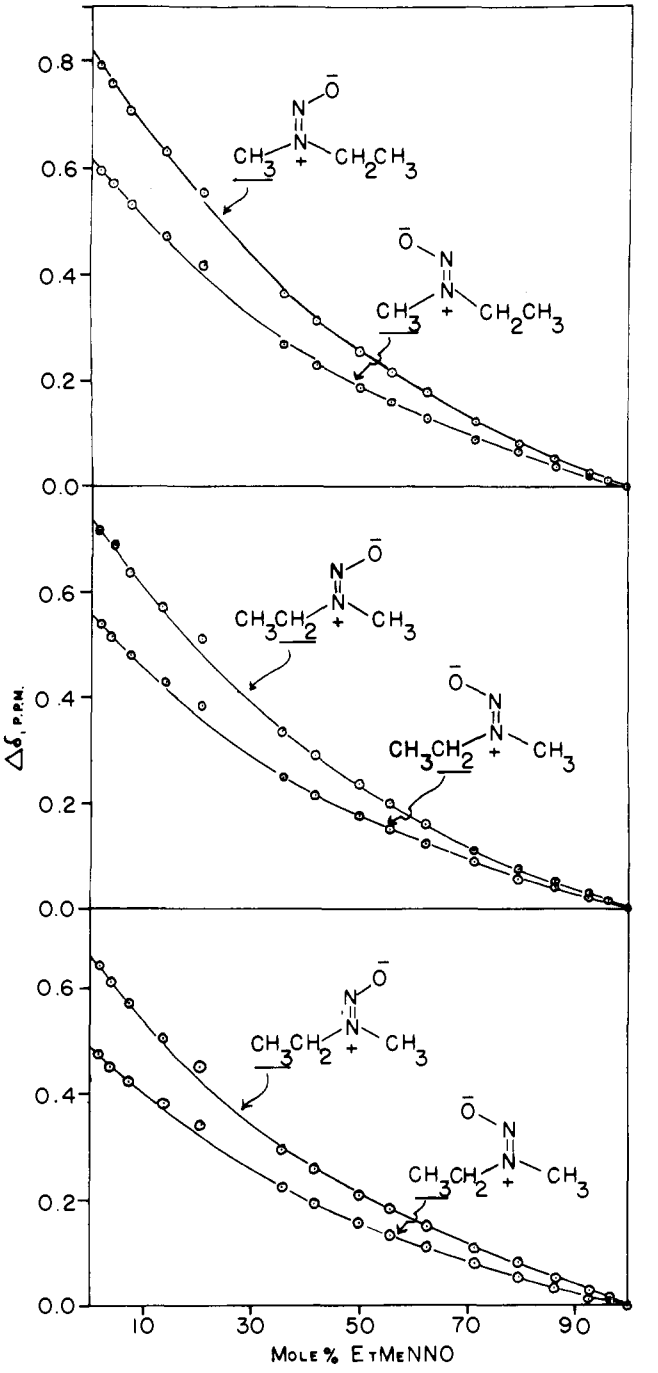
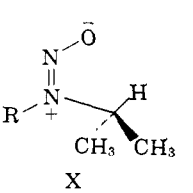


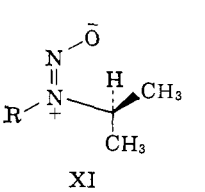
Fig. 2.—Upfield shift of the proton resonances of methyl ethyl nitrosamine on dilution with benzene.

spin–spin coupling and chemical shifts it was concluded[6,9] that the region in the C=NZ plane is deshielded with respect to the region above and below the plane. We will base our discussion therefore on the assumption that this is also true with the NNO group.

Conformations of *cis* Groups.—Of the *cis* groups the data afford reasonably accurate conformational assignments only for the isopropyl group. Of the two conformations, X and XI, only X is consistent with the results; *e.g.*, it explains the fact that α-methine protons, in contrast to α-methyl and α-methylene, resonate at lower fields when *cis* than when *trans* to the oxygen; it also explains the fact that Δν-values for *cis*-α-methine are very small, since in X the methine is farthest away from the associated benzene ring and



X

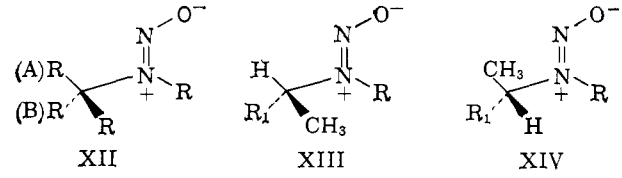


XI

should experience a smaller anisotropic effect.

Conformations of *trans* Groups.—We will discuss our results in terms of conformation XII (eclipsing between R and N=N) by assuming again that site A, which is in the plane of NNO, is deshielded with respect to site

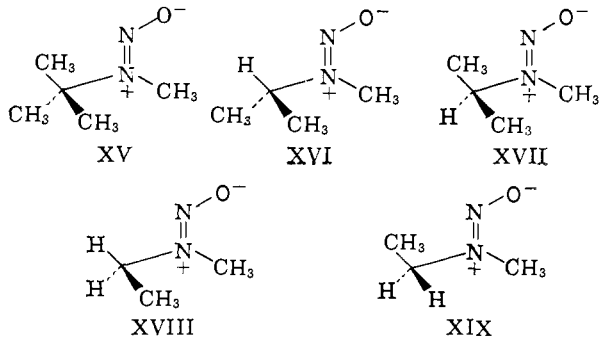
(9) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 2327 (1963).



XII XIII XIV

B.[10] Based on these assumptions we will show that when R is methyl XIII is favored over XIV, and that the ratio [XIII]/[XIV] decreases when R is changed from methyl to isopropyl.

Consider the conformations of methyl *t*-butyl nitrosamine, (XV), of methyl isopropyl nitrosamine XVI and XVII (with XVII statistically twice as probable as XVI), and of methyl ethyl nitrosamine XVIII and XIX, (with XVIII statistically twice as probable as XIX). If XVI is energetically equivalent to XVII,

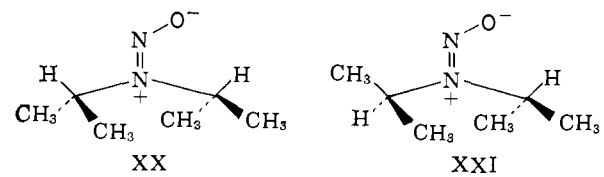


XV XVI XVII

XVIII XIX

and XVIII to XIX, then in all three compounds the methyl group should spend one-third time at site A and two-thirds time at site B. Consequently the *trans*-β-methyls of all three compounds should resonate at about the same field, with the *t*-butyl resonating at slightly higher fields than the isopropyl and the isopropyl at higher fields than the ethyl (inductive effect). If XVI is favored over XVII, and XVIII over XIX, then the methyl group should spend one-third time at site A in the *t*-butyl compound and progressively less than one-third in the isopropyl and ethyl compounds. Consequently the *t*-butyl should resonate at lower fields than the isopropyl and the isopropyl at lower than the ethyl. The data support the last assumption.

The pertinent conformations of diisopropyl nitrosamine are XX and XXI. Because of more severe interactions (methyl groups) in XX than in XXI it is reasonable to expect the ratio [XXI]/[XX] to be



XX XXI

larger than the ratio [XVII]/[XVI]. By comparing the chemical shifts of diisopropyl nitrosamine with those of methyl isopropyl nitrosamine it can be shown that such is the case. (a) The *trans*-α-methine of diisopropyl nitrosamine should be shifted upfield with respect to that of methyl isopropyl nitrosamine. The shift in carbon tetrachloride is 0.59 p.p.m. (b) The *trans*-β-methyl should be shifted downfield. The shift in carbon tetrachloride is −0.10 p.p.m. (c) The $\Delta\nu$-value for the *trans*-α-methine should be larger for diisopropyl than for methyl isopropyl nitrosamine. Table III shows that while the $\Delta\nu$-value for the *cis*-α-methine decreased from 9.0 to 2.4 c.p.s., as a consequence of decrease in complex stability, that of the *trans* increased from 27.0 to 30.6 c.p.s. (d) The $\Delta\nu$-value of the *trans*-β-methyl should decrease more sharply than that of the *cis*-β-methyl in going from methyl isopropyl to diisopropyl nitrosamine. Table III shows that the corresponding decreases are 18 and 7.2 c.p.s. The change of the *trans*-β-methyl is large enough to result in $\Delta\nu_{cis}$ (21.0 c.p.s.) > $\Delta\nu_{trans}$ (20.4 c.p.s.) for diisopropyl nitrosamine.

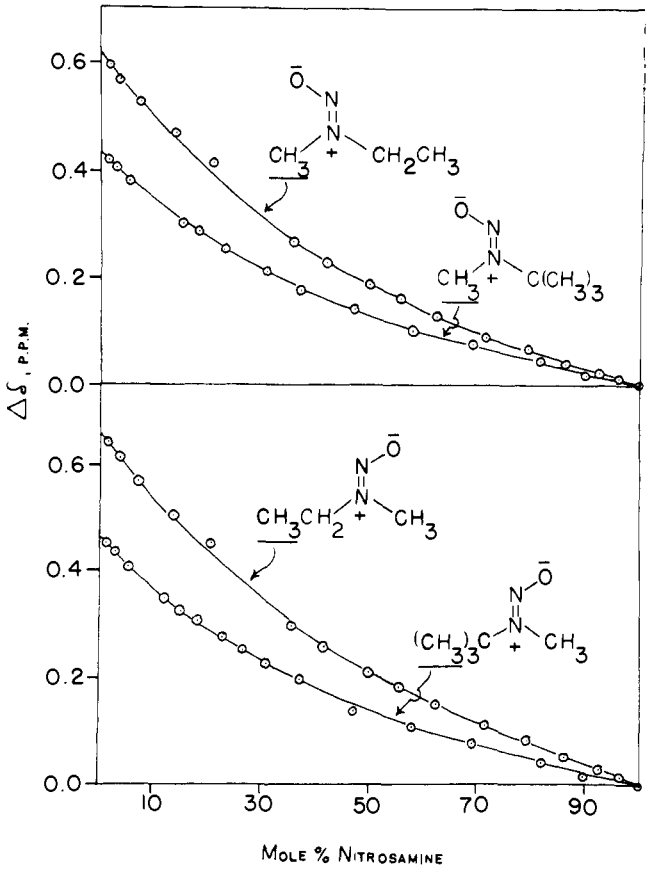
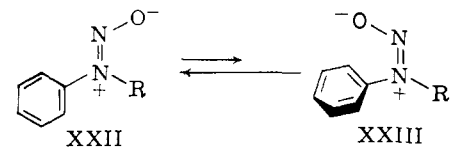


Fig. 3.—Relative upfield shifts of the proton resonances of methyl ethyl nitrosamine and methyl *t*-butyl nitrosamine on dilution with benzene.

syn-anti **Isomers.**—The *syn/anti* ratios of nitrosamines are identical with those of $R_1R_2C{=}NZ$ compounds. In effective size, the ethyl, benzyl, and *n*-butyl groups are identical. The phenyl group, as found in the $R_1R_2C{=}NZ$ compounds, has a large effective size. Apparently in isomer XXIII the loss of overlap energy is sufficient to shift the equilibrium in favor of XXII.



XXII XXIII

When R is methyl only one set of resonances, attributed to the presence of only the *cis*-methyl isomer, is observed. The possibility that this may arise from rapid isomer interconversion[4] is excluded by the fact that

(10) We have chosen conformation XII mainly on evidence obtained from carbonyl and olefinic compounds. For a summary of several references see A. A. Bothner-By, C. Naar-Colin, and H. Gunther, *J. Am. Chem. Soc.*, **84**, 2748 (1962).

both isomers are detected when R is ethyl or isopropyl. From the ultraviolet spectra, *e.g.*, decrease of λ_{max} from 275 (R = CH_3, CH_2CH_3) to 250 mμ (R = isopropyl), it is deduced that when R is isopropyl the interactions between phenyl and isopropyl in isomer XXII are sufficiently large to cause loss of overlap between the phenyl and the NNO groups. The 224 mμ band, when R is isopropyl, could conceivably be the absorption of isomer XXIII.

Experimental

Amines used in the preparation of nitrosamines were commercially available compounds. Methyl-*t*-butylamine and ethylbenzylamine were prepared by lithium aluminum hydride reduction[11] of *t*-butylformamide and N-benzylacetamide.

Nitrosamines were prepared from the reaction of the corresponding amines with nitrous acid.[11]

N.m.r. spectra were determined at 60 Mc. on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.), at a temperature of about 36°. Undegassed solutions were used with tetramethylsilane as internal reference.

Ultraviolet spectra were taken with a Cary 14 recording spectrophotometer.

Acknowledgment.—We thank the United States Atomic Energy Commission for financial support, Grant COO-1189-12.

(11) D. F. Heath and A. J. Mattocks, *J. Chem. Soc.*, 4226 (1961).

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Conformational Analysis. II. Use of the Chemical Shift of the Hydroxyl Proton in Conformational Analysis

BY ROBERT J. OUELLETTE

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Dilution studies have been carried out to determine the chemical shift of the monomeric hydroxyl proton in *cis*-4-*t*-butylcyclohexanol and *trans*-4-*t*-butylcyclohexanol in carbon tetrachloride. The hydroxyl proton in the axial position occurs at higher field than the hydroxyl proton in the equatorial position. The conformational preference of the monomeric hydroxyl group in cyclohexanol is 0.75 kcal./mole. The chemical shifts of the hydroxyl proton in pyridine and dimethyl sulfoxide are examined. These solvents do not significantly affect the conformational preference of the hydroxyl group.

Introduction

The conformational preference of the hydroxyl group in cyclohexanol has been determined by kinetic,[1,2] equilibrium,[3,4] infrared,[5,6] and n.m.r.[7-9] methods. The n.m.r. methods are the most direct and powerful available at this time. Eliel[7] utilized the chemical shift of the α-hydrogen in cyclohexanol and established an approximate value of 0.6 kcal./mole for the conformational preference of the hydroxyl group. However, the signal of the α-hydrogen is broad and unresolved and, in order to improve the accuracy of the method, selective deuteration has been employed.[8,9]

Recently the conformational preference of the ethynyl group was determined indirectly from the conformation of 1-ethylcyclohexanol.[10] It was shown that the chemical shift of the hydroxyl proton is linearly related to concentration in the range of 0.002 to 0.02 mole fraction of alcohol in carbon tetrachloride. The conformational preference of the ethynyl group was found to be 0.60 kcal./mole smaller than that of the hydroxyl group. Winstein's[8] value of 0.78 kcal./mole for the conformational preference of hydroxyl group was used in evaluating the conformational preference of the ethynyl group. Winstein's value was determined in a 20% solution in carbon tetrachloride. The hydroxyl group is strongly associated under these conditions and it is conceivable that the steric size of the hydroxyl group is a function of the degree of association. Therefore it was decided to investigate the hydroxyl group under conditions where hydrogen bonding is minimal. As a result of this investigation, the effect of intermolecular hydrogen bonding and association with solvent should be directly available.

(1) S. Winstein and J. N. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
(2) E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957).
(3) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5992 (1957).
(4) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).
(5) R. A. Dickering and C. C. Price, *J. Am. Chem. Soc.*, **80**, 4931 (1958).
(6) G. Chiurdoglu and W. Masschelein, *Bull. soc. chim. Belges*, **69**, 154 (1960).
(7) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, **3**, 97 (1962).
(8) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).
(9) F. A. L. Anet, *ibid.*, **80**, 4931 (1958).
(10) R. J. Ouellette, *ibid.*, **86**, 3089 (1964).

Results

In the previous paper of this series,[10] it was shown that the chemical shift of the hydroxyl proton is linearly related to concentration at low mole fractions. The chemical shift of the monomeric hydroxyl proton can be obtained by extrapolation to infinite dilution.

The chemical shifts of the hydroxyl protons of *cis*-4-*t*-butylcyclohexanol and *trans*-4-*t*-butylcyclohexanol are derivable from the data given in Table I. Figure 1 shows the dependence of the chemical shift as a function of the mole fraction of compound in carbon tetrachloride containing 0.001 mole fraction of tetramethylsilane as the internal standard. The extrapolated chemical shifts of the axial and equatorial hydroxyl protons expressed in c.p.s. downfield from tetramethylsilane are 25.7 and 46.4, respectively. By comparison with previous work,[10] the ethynyl group deshields the hydroxyl proton by approximately 46 c.p.s.

The data for the chemical shifts of the hydroxyl group in cyclohexanol are given in Table I and are illustrated in Fig. 1. The chemical shift at infinite dilution is 41.6 c.p.s. The equilibrium constant for the axial equatorial conversion is 3.3 ± 0.2 at 40°. This equilibrium constant corresponds to a free-energy change of 0.75 kcal./mole at 40°.

The chemical shift of the hydroxyl proton is independent of concentration in either pyridine or dimethyl sulfoxide in the concentration range used for the studies in carbon tetrachloride. Both pyridine and dimethyl sulfoxide shift the hydroxyl proton resonance signal to low field owing to hydrogen bonding. The chemical