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Stability and nitrosation efficiency of substituted *N*-methyl-*N*-nitrosobenzenesulfonamides

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ABSTRACT: A series of substituted *N*-methyl-*N*-nitrosobenzenesulfonamides [2,4,6-$(CH_3)_3$, 4-CH_3O, 4-CH_3, 4-Cl and 4-NO_2] were synthesized. All of them transfer their nitroso group to *N*-methylaniline in a quantitative manner, the more reactive being those substituted with electron-withdrawing groups, thus resembling some of the known alkyl nitrites. Studies of their acid denitrosation and base-catalysed hydrolysis demonstrated that the nitrosobenzenesulfonamides are fairly stable in aqueous media between pH 2 and 11. Their relative stability in aqueous media together with their ability to transfer the nitroso group to nucleophiles suggest their use as excellent alternatives to alkyl nitrites in both neutral and basic media. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: *N*-methyl-*N*-nitrosobenzenesulfonamides; stability; nitrosation efficiency

INTRODUCTION

The chemistry of nitroso compounds has attracted considerable research effort owing to the proven toxic, carcinogenic, mutagenic and teratogenic effects of these substances[1,2] on many animal species.[3] Particularly since the discovery that nitrosamines are powerful carcinogens in all animal species which have been tested, the nitrosation of secondary (and tertiary) amines has been thoroughly studied, mainly from the viewpoint of the possible *in vivo* formation of nitrosamines from naturally occurring secondary amines and sources of nitrous acid in foods and in water supplies. In this sense, nitrosation from nitrosamines to amines has important repercussions, since non-carcinogenic nitrosamines or those with only a weak activity have the potential to generate more powerfully carcinogenic nitrosamines by nitrosation *in vivo*, particularly in the acidic environment in the stomach, where additional catalysis from naturally occurring nucleophiles might also arise.

Nitroso compound formation is basically controlled by the ability of nitrosating agents to donate the nitroso group under various conditions. In acidic medium ($pH < 4$), the main nitrosating species for nucleophiles such as amines, thiols and ketones are nitrosonium ion, dinitrogen trioxide (N_2O_3) and nitrosyl halides.[4,5] Exhaustive studies of the reactivities of these reagents with a variety of nucleophiles (especially amines) have shown that NO^+, NOCl, NOBr and N_2O_3[5] are extremely efficient in the nitrosation of moderately strong nucleophiles, the overall reaction rate often being totally or partially diffusion controlled.

In basic or neutral medium, nitroprussiate and alkyl nitrites are effective nitrosating agents, their sole limitation being their relative instability. We have recently demonstrated that *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) is an effective nitrosating agent for strong nucleophiles such as amines,[6] carbanions[7] and other sulfur and oxygen nucleophiles.[8] In this paper, we report a reactivity study on other substituted *N*-nitrosobenzenesulfonamides, with a nitrosating behaviour very similar to that of MNTS. Their power as nitrosating agents is basically modulated by the substituent effect.

EXPERIMENTAL

Sulfonamides substituted with electron-withdrawing groups were prepared as exemplified for *N*-methyl-4-nitrobenzenesulfonamide as follows. Methylamine solution in THF (Aldrich) (0.02 mol) was added to 4-nitrobenzenesulfonylchloride (2.2 g, 0.01 mol) in THF (5 ml). The crude product was purified by thin-layer chromatography using silica gel as adsorbent and

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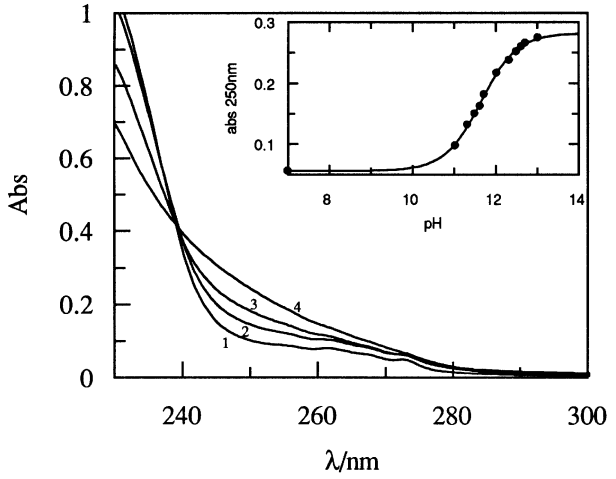


Figure 1. Absorbance spectra of *N*-methyl-*p*-toluenesulfonamide at different pH values: (1) 7.00; (2) 11.02; (3) 11.62; (4) 12.02. Inset: absorbance–pH dependence at 250 nm

dichloromethane as eluent (yield *ca* 30%). Sulfonamides substituted with electron-donating groups were prepared as exemplified for *N*-methyl 4-methoxybenzenesulfonamide as follows. Methylamine in aqueous solution (Aldrich) was added to 4-methoxybenzenesulfonyl chloride (2.1 g, 0.01 mol), and the precipitate was recrystallized from light petroleum (yield *ca* 40%). *N*-Methyl-*N*-nitrosobenzenesulfonamides were obtained by nitrosation of the corresponding *N*-methylbenzenesulfonamide with N_2O_4 in organic media according the method developed by White.[9]

All kinetic experiments were carried out at 25 °C under pseudo-first-order conditions, with the *N*-methyl-*N*-nitrosobenzenesulfonamide always in deficiency. Because of the poor solubility in water of *N*-methyl-*N*-nitrosobenzenesulfonamides, they were dissolved in a small quantity of organic solvent (usually dioxane) prior to preparation of aqueous solutions. The final concentration of organic solvent in the medium was usually 3.3% (v/v), except for nitrosation to *N*-methylaniline (see below). Reaction kinetics were studied by following the change in absorbance (generally in the range 280–300 nm for acid denitrosation and basic hydrolysis and 340 nm for nitrosation to *N*-methylaniline) using a Uvikon 930 or Milton Roy Spectronic 3000 array spectrophotometer. Absorbance–time data always fitted the first-order integrated equation, and k_0, the corresponding first-order pseudo-constant, was reproducible to within 3%.

RESULTS AND DISCUSSION

pK_a of *N*-methylbenzenesulfonamides

The pK_a values of substituted *N*-methylbenzenesulfonamides were measured spectrophotometrically. Figure 1 shows the dependence of the absorbance spectra of *N*-methyl-*p*-toluenesulfonamide on the acidity of the medium between pH 7 and 12.02. The pK_a values for *N*-methylbenzenesulfonamides were obtained at wavelengths of 250, 245, 250, 250 and 300 nm for the 2,4,6-$(CH_3)_3$, 4-CH_3O, 4-CH_3, 4-Cl and 4-NO_2 derivatives, respectively, and the equation

$$A = \frac{A_a + A_b 10^{(pH - pK_a)}}{1 + 10^{(pH - pK_a)}} \quad (1)$$

where A_a and A_b are the absorbance of the acidic and basic species of *N*-methyl benzenesulfonamides, respectively.

Table 1 shows the pK_a obtained values, which are compatible with results reported in the literature.[10] A value of $\rho(K_a) = 1.0 \pm 0.1$ was obtained from the Hammett correlation, showing the effect of electron-withdrawing groups on the stabilization of the negative charge. The pK_a of 2,4,6-trimethyl-*N*-methylbenzenesulfonamide deviates from this correlation, probably owing to a steric effect.[11]

Nitrosation to *N*-methylaniline

N-Methyl-*N*-nitrosobenzenesulfonamides (X-MNBS) can easily transfer their nitroso group to moderate nucleophiles. Quantitative nitrosation (yield of *N*-nitrosamine > 90%) of X-MNBS to *N*-methylaniline was studied under pseudo-first-order conditions, with deficiency of the nitrosating agent. The reaction medium was chosen to be water–dioxane (1:1, v/v) because of the low solubility of *N*-methylaniline in an aqueous medium. Plotting k_0 against total amine concentration yielded good straight lines (Fig. 2), showing that the reaction was of first order with respect to the amine and occurs by nucleophilic attack of neutral amine at the nitroso group of X-MNBS. Second-order rate constants for this reaction are given in Table 2 together with the corresponding constants for alkyl nitrites of similar reactivity.

Rate constants for nitrosation of *N*-methylaniline by alkyl nitrites were estimated considering that MNTS reacts similarly to 2-ethoxyethyl nitrite.[6] Substituent effects on alkyl nitrites were based on values previously

Table 1. pK_a values of substituted *N*-methylbenzenesulfonamides

X	2,4,6-$(CH_3)_3$	4-CH_3O	4-CH_3	4-Cl	4-NO_2
pK_a	12.66	11.73	11.64	11.10	10.71

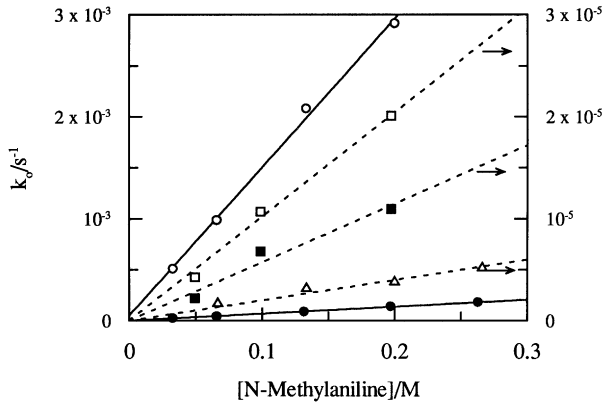


Figure 2. Influence of amine concentration on k_0 for nitrosation to *N*-methylaniline from substituted *N*-methyl-*N*-nitrosobenzenesulfonamides. Substituent: (○) 4-NO_2; (●) 4-Cl; (□) 4-CH_3; (■) 4-CH_3O; (△) 2,4,6-$(CH_3)_3$ at 25 °C

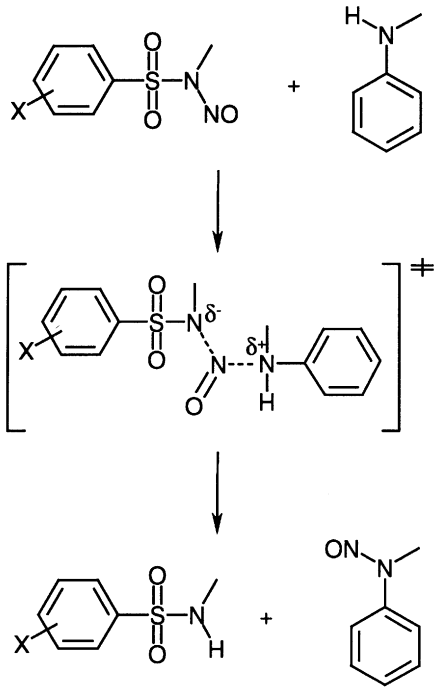
obtained from their reactivity with other amines[12] and were extrapolated for *N*-methylaniline. X-MNBS are thus found to behave very similarly to the more activated alkyl nitrites.

Reaction rates are sensitive to aromatic substituents [the 4-NO_2 derivative is 1000 times more reactive than the 2,4,6-$(CH_3)_3$ derivative]. The rate increase observed with electron-withdrawing substituents must be related to the electrophilic character of the nitroso group and stabilization of the partial negative charge generated in the transition state of the reaction (Scheme 1).

For the deprotonation equilibrium of substituted *N*-methylbenzenesulfonamides, the Hammett ρ value is $(K_a) = 1.0 \pm 0.1$. A value of $\rho(K_1) = 1.47$ for the equilibrium (1) can be estimated using the values of the equilibrium constants K_2 and K_3 (Scheme 2). The equilibrium constant K_2 was calculated using $k_2 = 7.78 \times 10^{10}$ (Ref. 13) and $k_{-2} = 0.188$ was calculated in turn using literature data for acidic denitrosation of the *N*-methyl-*N*-nitrosoaniline[14] and considering a pK_a of -5.85 for the former compound. The values of K_3 for the different sulfonamides were obtained in our laboratory.[15] For the nitrosation reaction, $\rho(K_a) = 2.21 \pm 0.04$, i.e. the rate of nitrosation is more sensitive to substituent effects

Table 2. Second-order rate constants for nitrosation of *N*-methylaniline by *N*-methyl-*N*-nitrosobenzenesulfonamides in dioxane–water (1:1, v/v) compared with the extrapolated values of the corresponding nitrosation by activated alkyl nitrites

X in X-MNBS	k ($M^{-1}s^{-1}$)	R in RONO	k (M^{-1}/s^{-1})
2,4,6-$(Me)_3$	1.67×10^{-5}	CH_3CH_2	1×10^{-5}
4-MeO	5.68×10^{-5}	$EtOCH_2CH_2$	1×10^{-4}
4-Me	1.05×10^{-4}	$BrCH_2CH_2$	6.5×10^{-4}
4-Cl	6.97×10^{-4}	Cl_2CHCH_2	6.5×10^{-3}
4-NO_2	1.27×10^{-2}	Cl_3CCH_2	7×10^{-2}



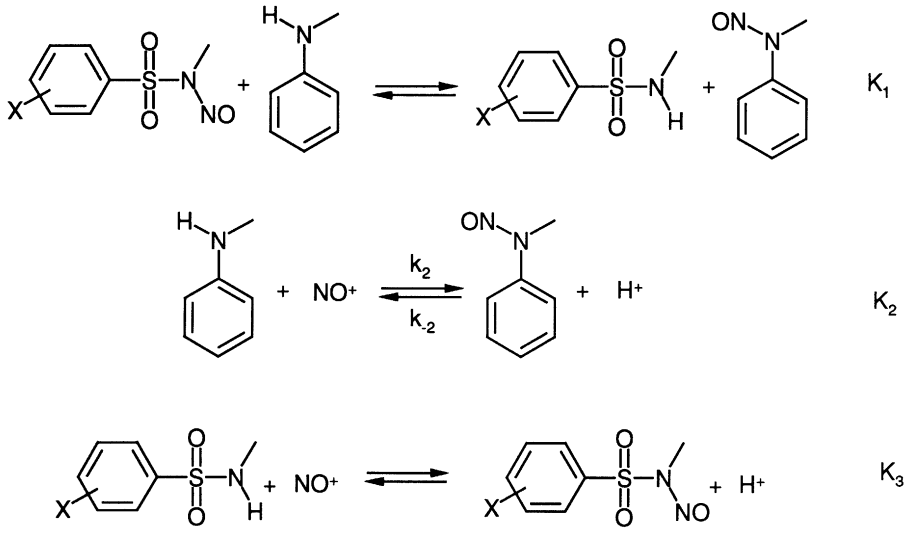
Scheme 1

than the equilibrium, implying that the transition state is subject to greater stabilization by electron-withdrawing substituents than the product ion.

These anomalous values have been observed in the deprotonation of nitroalkanes.[16] The 'anomalies' arise because the substituent 'sees' more than one bond change. In example given by Bordwell *et al.*,[17] for deprotonation of nitroalkanes, the carbon is more negative in the transition state than in the product state because the charge is not delocalized on the oxygen of the nitro group at that stage. Anomalous effects should also arise even if one of the major electronic changes were not a bonding change but a solvation or hybridization change.[18] A condition could hold where solvation of an atom does not keep in step with the bonding change. A β_{lg} more negative than β_{eq} might occur owing to the weaker solvation in the transition state than in the product state. There is some evidence than this phenomenon occurs in the alkaline hydrolysis of aryl esters of phenylmethanesulfonic acid.[19] The oxygen is considered to be less solvated in the transition state than in the product, thus leading to a less dispersed charge, which will be more susceptible to substituents than is the more solvated ion.[20]

Stability of substituted *N*-methyl-*N*-nitrosobenzenesulfonamides

The stability in aqueous media is determined by their acid hydrolysis (denitrosation) and also their basic hydrolysis



Scheme 2

by the direct attack of HO^- on the sulfonyl group of X-MNBS. Kinetic studies were carried out under pseudo-first-order conditions with [X-MNBS] much lower than $[H^+]$ or $[OH^-]$, keeping the ionic strength ($NaClO_4$) constant. Denitrosation and basic hydrolysis show a linear dependence of the first-order pseudo-constant, k_0, with H^+ or HO^- concentration, so that both processes are first order in both X-MNBS and catalyst (H^+ or HO^-). Second-order rate constants for denitrosation are not sensitive to the presence of substituents in the aromatic ring of X-MNBS. This is consistent with a concerted mechanism previously proposed for acid denitrosation of MNTS.[21] In the transition state, both the breaking of the bond [N···N=O] and protonation of sulfonamide nitrogen [(O=N)—N···H^+] occur concurrently via a slightly imbalanced transition state. The first step is facilitated by the presence of electron-withdrawing substituents whereas, in contrast, the second is facilitated by electron-donating groups. The final result is therefore a balance between these two effects, yielding the observed insensitivity of X-MNBS to acid denitrosation.

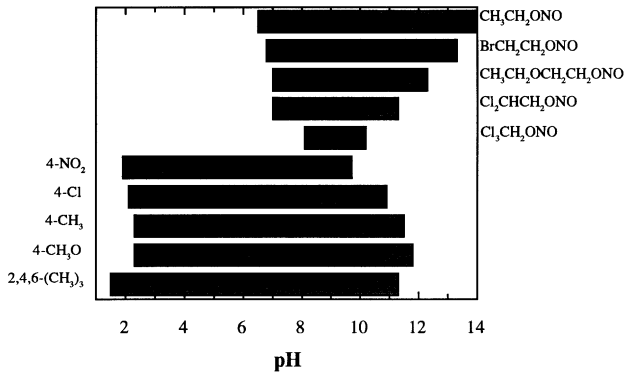


Figure 3. pH stability range of alkyl nitrites and substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (defined by half-lives > 60 min)

Basic hydrolysis of MNTS is often used to produce diazomethane and this is the main reason why it has been so much studied.[22,23] This reaction occurs by direct attack of HO^- on the sulfonyl group of X-MNBS and is greatly accelerated by electron-withdrawing groups. These groups increase the electrophilic character of SO_2 and thus facilitate the cleavage of the S—N bond.

CONCLUSIONS

The main inconvenience for the use of alkyl nitrites (RONO) as nitrosating agents arises from their instability in aqueous medium due to their acidic[24] and basic hydrolysis.[25] This is the reason why they are only used between pH 8 and 11 and only with strong nucleophiles. The stabilities of highly reactive alkyl nitrites (those with electron-withdrawing substituents in the alkyl group) and X-MNBS are compared in Fig. 3. The criterion used for stability was a half-life of the nitrosating agent of >60 min. As can be seen, X-MNBS are stable over a much larger pH range than alkyl nitrites. In fact, they are efficient even in the pH range 3–8 where no other nitrosating species is reactive.

X-MNBS are less stable than alkyl nitrites in basic medium, but as the nucleophilic character increases with increasing pK_a of nucleophiles, it is expected that competition between the reaction of X-MNBS with OH^- or with any other nucleophile would favour the nucleophiles susceptible to nitrosation, especially those with high pK_a.

The great advantage of using X-MNBS instead of alkyl nitrites as nitrosating agents comes from their great stability in acidic media, making possible efficient nitrosation of moderate nucleophiles in the pH range 3–8.

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REFERENCES

1. R. Montesano and H. Bartsch. *Mutat. Res.* **32,** 179 (1976); A. E. Pegg. *Adv. Cancer Res.* **25,** 195 (1977).
2. L. Tomatis and U. Mohr (Eds). *Transplacental Carcinogenesis*, IARC Scientific Publications No. 4. IARC, Lyon (1973); D. Yarosh. *Mutat. Res.* **145,** 1 (1985).
3. P. N. Magee, R. Montesano and R. Preussmann. in *Chemical Carcinogenesis*, edited by C. E. Searle, p. 141. American Chemical Society, Washington, DC (1976).
4. D. L. H. Williams. *Nitrosation*. Cambridge University Press, Cambridge (1988).
5. J. H. Ridd. *Adv. Phys. Org. Chem.* 1978, **16,** 1; A. Castro, J. R. Leis and M. E. Peña. *J. Chem. Res. (S)* 216 (1986); J. Casado, A. Castro, J. R. Leis, M. A. López-Quintela and M. Mosquera. *Monatsh. Chem.* **114,** 639 (1983).
6. A. Castro, J. R. Leis and M. E. Peña. *J. Chem. Soc., Perkin Trans. 2* 1861 (1989).
7. J. R. Leis, M. E. Peña and A. Rios. *J. Chem. Soc., Perkin Trans. 2* 1233 (1993).
8. J. R. Leis, M. E. Peña and A. Rios. *J. Chem. Soc., Perkin Trans. 2* 587 (1995).
9. E. H. White. *J. Am. Chem. Soc.* **77,** 6008 (1955).
10. G. Dauphin and A. Kergomard. *Bull. Soc. Chim. Fr.* **5,** 486 (1961).
11. J. E. Leffler and E. Grunwald. *Rates and Equilibria of Organic Reactions*. Wiley, New York (1963).
12. L. García-Río, E. Iglesias, J. R. Leis, M. E. Peña and A. Rios. *J. Chem. Soc., Perkin Trans. 2* 29 (1993).
13. E. Fabricio, E. Kalatzis and J. H. Ridd. *J. Chem. Soc.* 533 (1966).
14. I. D. Biggs and D. L. H. Williams. *J. Chem. Soc., Perkin Trans. 2* 107 (1975).
15. L. Garcia Rio, J. R. Leis, J. A. Moreira and F. Norberto. *J. Chem. Soc., Perkin Trans. 2*. 1613 (1998).
16. C. F. Bernasconi. *Adv. Phys. Org. Chem.* **27,** 119 (1992).
17. F. G. Bordwell, W. J. Boyle, J. A. Hautala and Y. C. Yee. *J. Am. Chem. Soc.* **91,** 4002 (1969).
18. A. Williams. *Adv. Phys. Org. Chem.* **27,** 1 (1992).
19. S. Thea, M. G. Harun and A. Williams. *J. Chem. Soc., Chem. Commun.* 717 (1979).
20. W. P. Jencks, S. R. Brant, J. R. Gandler, G. Fendrick and C. Nakamura. *J. Am. Chem. Soc.* **104,** 7045 (1982).
21. D. L. H. Williams. *J. Chem. Soc., Perkin Trans. 2* 691 (1976).
22. Th. J. de Boer and H. J. Backer. *Recl. Trav. Chim. Pays-Bas* **73,** 229 (1954); M. Pearce. *Helv. Chim. Acta* **63,** 887 (1980).
23. T. H. Black. *Aldrichim. Acta* **16,** 3 (1983).
24. L. García-Río, E. Iglesias, J. R. Leis, M. E. Peña and D. L. H. Williams. *J. Chem. Soc., Perkin Trans. 2* 1673 (1992).
25. S. Oae, N. Asai and K. Fujimori. *J. Chem. Soc., Perkin Trans 2* 571 (1977).

