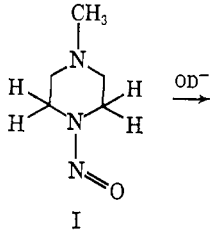
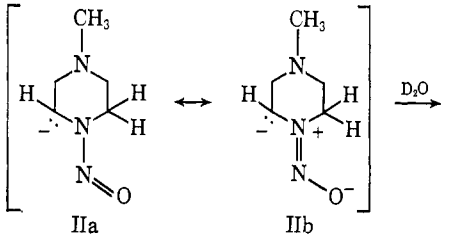
Facile Hydrogen Isotope Exchange as Evidence for an α-Nitrosamino Carbanion

Sir:

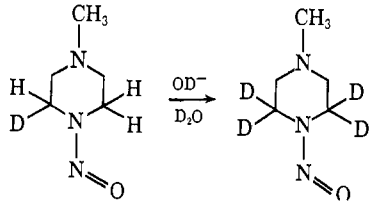
We wish to report that a wide variety of aliphatic nitrosamines readily undergo base-catalyzed exchange with proton sources in the medium. A typical example is that of 1-nitroso-4-methylpiperazine (I), the 2- and 6-methylene protons of which can be seen in Figure 1 to have been virtually completely replaced by deuterium[1] within 150 min when I was exposed to 1.3 *m* sodium deuterioxide in deuterium oxide at 100°.



I



IIa IIb



We have taken this labilizing influence of the nitrosamino group upon the carbon–hydrogen bonds α to it as evidence for the involvement of an α-nitrosamino carbanion (*e.g.*, II) in the exchange.[3] The reaction is definitely base catalyzed, and does not proceed to any measureable extent in either neutral or acidic medium. The variations of exchange rate with structure also support the proposed mechanism. Nitrosomethylcyclohexylamine (III) undergoes detectable incorporation of deuterium only in the methyl group. The relative unreactivity of the methinyl position of III can be attributed to the electron-releasing alkyl substituents at the α position, which should both destabilize the anionic intermediate and sterically interfere with the approach of the attacking hydroxide ion.[5]

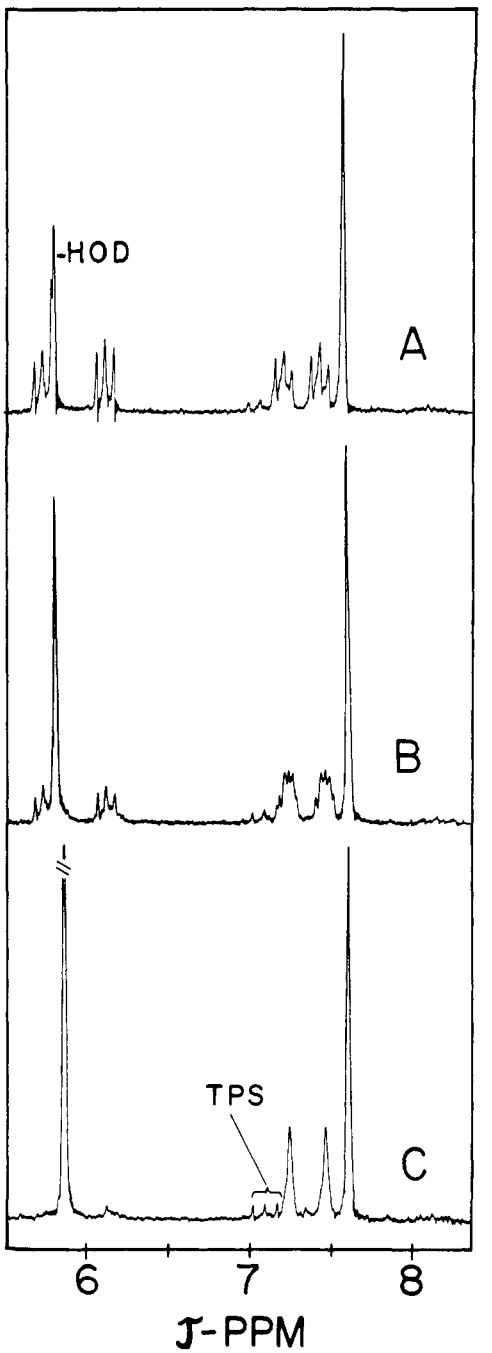


Figure 1. Nmr spectra (100 MHz) of a 1.3 *m* solution of 1-nitroso-4-methylpiperazine (I) in 1.3 *m* sodium deuterioxide in deuterium oxide at 100°: (A) 2 min; (B) 27 min; and (C) 150 min after dissolution; the solution was saturated with sodium trimethylsilylpropanesulfonate (TPS), which served as internal reference.

The existence of such a carbanion suggests that several new series of reactions involving α functionalization of nitrosamines should be possible, and preliminary indications are that this is the case. Alkylation of dimethylnitrosamine (IV) in approximately 15% yield has been effected by refluxing a tetrahydrofuran solution of 77 mg of IV, 2.1 g of methyl iodide, and 240

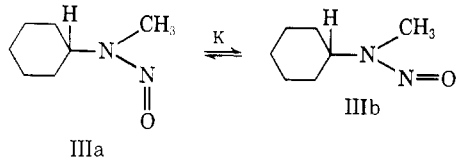
(1) An obvious implication of this finding is that tracer experiments in which deuterium- or tritium-labeled nitrosamines have been subjected at some point to basic conditions should be reviewed in light of the possibility of exchange, particularly where inferences have been derived from quantitative specific activity data. For example, our results offer an explanation for Lijinsky's observation,[2] during the tritiation of a series of secondary amines by the Wilzbach procedure, that the apparent C–T/N–T ratio "varied considerably" from one compound to another. Much of his carbon-bound label must have been lost to the solvent prior to counting, since his work-up involved distillation of the *N*-nitroso derivatives from aqueous alkali.

(2) W. Lijinsky, *J. Label. Compounds*, **2**, 384 (1967).

(3) Daeniker[4] has postulated that carbanionic intermediates are involved in certain rearrangements and elimination reactions of benzyl and cyanomethyl nitrosamines, but such α-nitrosamino carbanions should be regarded as special cases because of the dominant role undoubtedly played by the phenyl and cyano groups in their stabilization.

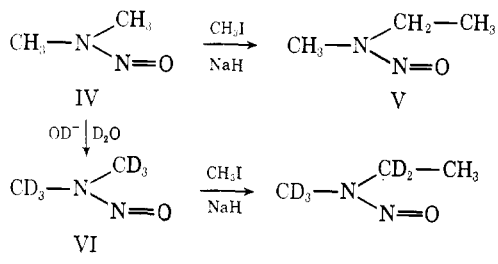
(4) H. U. Daeniker, *Helv. Chim. Acta*, 47, 33 (1964).

(5) It is possible, of course, that the unreactivity of this position might be due in part to a dependence of proton abstraction rate upon the conformation about the nitrogen–nitrogen bond. This factor cannot be of major importance, however, since the equilibrium mixture (IIIa $\rightleftharpoons$ IIIb) in 50:50 (w/w) methanol-d_4–deuterium oxide, the solvent used in the exchange studies, has been shown by nmr to contain substantial amounts of both conformers (K = 14).



IIIa IIIb

mg of sodium hydride for 3 hr. That the methylethylnitrosamine (V) produced in this reaction was the result of direct displacement of iodide, rather than carbene insertion, was demonstrated by subjecting dimethylnitrosamine-d_6 (VI)[6] to these conditions; the isolation of product with a molecular weight of 93 (mass spectrometry) implies that cleavage of the nitrosamine C–D bond preceded the reaction with the alkylating species.



IV V VI

It is noteworthy that canonical structures involving resonance delocalization of the formal negative charge at carbon cannot be formulated, and the facility of the reaction must be attributable entirely to inductive effects. Such a situation was once thought to be impossible,[7] but several groups have amply demonstrated the viability of inductively stabilized carbanions[8] analogous to the one proposed here. It is presumed that polarization of the N–N–O group, as in IIb, is more important in the carbanion than in the nitrosoamine itself, since the formal positive charge at the heterocyclic nitrogen would contribute to the inductive stabilization of the carbanionic center. It is hoped that kinetic studies currently in progress will shed further light on the mechanistic details of this reaction.

Acknowledgment. The authors wish to thank Drs. C. A. Kingsbury and W. Lijinsky for helpful discussions, and Messrs. J. Loo, F. Watson, and D. E. Johnson for able technical assistance. The financial support of the U. S. Public Health Service, Contract No. 43-68-959, is gratefully acknowledged.

(6) Dimethylnitrosamine-d_6 (VI) was prepared by exchange with deuterium oxide in the presence of sodium deuterioxide. The isotopic purity of the redistilled product, bp 149°, was estimated to be 99% using mass spectrometry. No trace of any impurity could be detected by glc or nmr.

(7) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 388.

(8) Several other types of carbanions have been alleged to be purely inductively stabilized, including the α-fluoro- and α-aryloxy carbanions,[9] the quaternary ammonium methylides,[10] and the carbanion derived from 7-ketonorbornane.[11]

(9) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **89**, 5911 (1967).

(10) W. v. E. Doering and A. K. Hoffmann, *ibid.*, 77, 521 (1955).

(11) P. G. Gassman and F. V. Zalar, *ibid.*, **88**, 3070 (1966).

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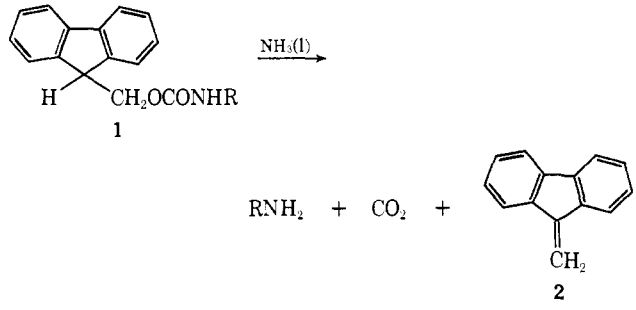
The 9-Fluorenylmethoxycarbonyl Function, a New Base-Sensitive Amino-Protecting Group

Sir:

In contrast to the variety of amino-protecting groups which can be cleaved under nonhydrolytic conditions by acids of varying strengths, there is currently no complementary set of groups cleavable by basic reagents of graded activity. Making use of the process of β elimination,[1-4] we have developed one such hydrocarbon-derived protective function, the 9-fluorenylmethoxycarbonyl group (FMOC), which can be cleaved under extremely mild conditions, most conveniently simply by allowing a solution in liquid ammonia[5] to stand for several hours. Other convenient deblocking conditions involve dissolution in ethanolamine, morpholine, or a similar amine. In addition the group is potentially capable of being modified for greater or lesser sensitivity toward basic reagents.



1 2

The FMOC group may be readily introduced by treatment of the parent amine with 9-fluorenylmethyl chloroformate (**3a**) or the corresponding azidoformate (**3b**) in aqueous dioxane in the presence of sodium carbonate or bicarbonate. The chloroformate (mp 61.5–63°; ir ($CHCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$) δ 4–4.6 (m, 3, $CHCH_2$), 7.1–7.8 (m, 8, aryl)) is obtained (86%) by reaction of 9-fluorenylmethanol[6] with phosgene in methylene dichloride without added base. The azidoformate (mp 83–85°; ir ($CHCl_3$) 2135, 1730 cm^{-1}; nmr ($CDCl_3$) δ 4–4.5 (m, 3, $CHCH_2$), 7.1–7.9 (m, 8, aryl)) is best obtained (82%) by reaction of **3a** with sodium azide in aqueous acetone. Fortunately, for purposes of selectivity in the synthesis of polyfunctional compounds

(1) A. T. Kader and C. J. M. Stirling [*J. Chem. Soc.*, 258 (1964)] have recommended use of the related β-tosylethoxycarbonyl group, although removal conditions involved use of sodium hydroxide or ethoxide and prior acidification to decompose the first-formed carbamate. The β-nitroethoxycarbonyl group has also been examined but found unsuitable for various reasons.[2,3]

(2) P. J. Crowley, M.S. Thesis, University of Massachusetts-Amherst, Amherst, Mass., 1958; L. A. Carpino, unpublished work, 1967–1968.

(3) Th. Wieland, G. J. Schmitt, and P. Pfaender, *Justus Liebigs Ann. Chem.*, **694**, 38 (1966).

(4) The 9-fluorenylmethyl system was first suggested to us in conversations with Professor A. Ceccon regarding the ease of β elimination from 9-fluorenyl thiocyanates and analogous systems relative to the corresponding benzhydryl derivatives [compare A. Ceccon, U. Miotti, U. Tonellato, and M. Padovan, *J. Chem. Soc. B*, 1084 (1969); U. Miotti, A. Sinico and A. Ceccon, *Chem. Commun.*, 724 (1968)]. For recent studies showing that even 9-fluorenylmethanol undergoes ready β elimination (mechanism E1cB), see R. A. More O'Ferrall, and S. Slae, *J. Chem. Soc. B*, 260 (1970); R. A. More O'Ferrall, *ibid.*, *B*, 268, 274 (1970).

(5) One of the classic deblocking systems in peptide chemistry involves reduction of tosyl and other protective groups by means of a solution of sodium in liquid ammonia. Presence of sodium is, however, a distinct disadvantage both in terms of possible competing reactions and isolation difficulties due to the presence of inorganic salts.

(6) W. G. Brown and B. A. Bluestein, *J. Amer. Chem. Soc.*, **65**, 1082 (1943).