Electronic Effects in the *N*-Nitrosation of *N*-Benzylpivalamides

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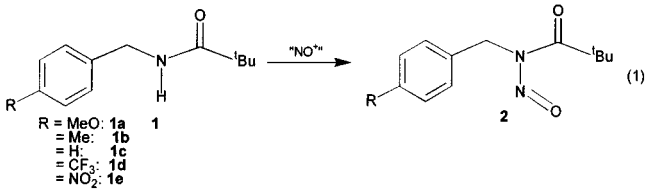
A series of *N*-4-R-benzylpivalamides (R = MeO, Me, H, CF_3, and NO_2) was nitrosated using a standardized solution of N_2O_4 in $CDCl_3$ at −40 °C. The reactions, which produced the corresponding *N*-4-R-benzyl-*N*-nitrosopivalamides, were followed by ^{1}H NMR spectroscopy. The rate of nitrosation was found to vary in a systematic way with the nature of the 4-R-group on the aromatic ring. Thus, electron-releasing groups increased the rate of the reaction, whereas electron-withdrawing ones decelerated *N*-nitrosation. In a similar fashion, the nitrosations were accelerated in polar solvents but were slower in solvents of low polarity. The sensitivities of *N*-nitrosation to these intra- and intermolecular electronic effects are compared to those from a previous study examining the dependence of the kinetics of nitrosoamide thermolyses on the same factors.

Introduction

N-Alkylamides (e.g., *N*-benzylpivalamides, **1**; eq 1) undergo a rich and varied chemistry that has been well-studied and documented.[1] Despite their sluggishness toward reactions at the amidic N, as compared to their more nucleophilic amine counterparts, amides do undergo a number of interesting substitutions at nitrogen.[1] Nitrosating agents such as alkyl nitrites, nitrous acid, nitrosonium salts, nitrosyl halides (NOX), and dinitrogen tetroxide (N_2O_4), for example, successfully convert primary and secondary amides into their corresponding *N*-nitrosoamides (**2**; eq 1).



The *N*-nitrosoamides themselves are labile compounds of significant interest in physical organic chemistry as probes for the elucidation of reaction mechanisms, especially those believed to involve carbocations as intermediates.[2a−c] They have also been employed as novel initiators of addition polymerization[2d] and in unique synthetic methods.[2e−g] *N*-Nitroso compounds, in general, possess intriguing properties with impact in medicine[2h,i] and biochemistry;[2j] for example, they have been implicated in mutagenesis[2h] and carcinogenesis[2i] but have also been successfully employed in enzyme inhibition and active site mapping.[2j]

In vivo nitrosation/denitrosation phenomena are fairly recently discovered,[3] but wide ranging reactions that occur via the intermediacy of nitric oxide (NO),[3a] *Science*'s 1992 "molecule of the year".[3b] These reactions proceed using nitric oxide synthases (NOS)[3a,c] and are believed to mediate effects including generation of NO in the brain,[3d] neurotransmission,[3e] and long-term potentiation,[3e] as well as the regulation of smooth muscle and vascular tone[3f] and immunological responses to microorganisms and tumors.[3g]

N-Nitrosations are very useful reactions in vitro, allowing access to a variety of *N*-nitroso compounds of synthetic[2e−g] and mechanistic value.[2h−j,4] Among these compounds are the *N*-nitrosoamides. Many details concerning *N*-nitrosation of amides have been elucidated.[1] For example, the amide → *N*-nitrosoamide conversion is known to be generally most efficient when NOX or N_2O_4 is used in nonaqueous media.[1] Additionally, steric crowding at either the *N*-alkyl or acyl groups evidently decrease the efficiency of the reaction to the extent, for example, that *N*-nitrosation of *N*-*tert*-butylpivalamide does not occur.[5a] There is a surprising dearth of information available, however, concerning the effects of intra- and

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(1) Smith, P. A. S. In *Open-chain nitrogen compounds. 2*, 1st ed.; W. W. Benjamin, Inc.: New York. 1965; pp 137−202.

(2) (a) Lee, K.; Gold, B.; Mirvish, S. *Mutat. Res.* **1977**, *48*, 131. (b) Preussman, R.; Stewart, B. W. *Chemical Carcinogenesis*; Searle, C., Ed.; ACS Monograph No. 182; American Chemical Society: Washington, DC, 1984; p 643. (c) White, E. H.; Jelinski, L. W.; Politzer, I. R.; Branchini, B. R.; Roswell, D. R. *J. Am. Chem. Soc.* **1981**, *103*, 4231. (d) Darbeau, R. W.; Delaney, M. S.; Ramelow, U.; James, K. R. *Org. Lett.* **1999**, *1* (5), 796. (e) White, E. H.; De Pinto, J. T.; Polito, A. J.; Bauer, I.; Roswell, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 3708. (f) Darbeau, R. W.; White, E. H. *J. Org. Chem.* **1997**, *62*, 8091. (g) Darbeau, R. W.; White, E. H.; Nunez, N.; Coit, B.; Daigle, M. *J. Org. Chem.* **2000**, *65*, 1115. (h) White, E. H.; Darbeau, R. W.; Chen, Y.; Chen, D.; Chen, S. *J. Org. Chem.* **1996**, *61*, 7986. (i) Darbeau, R. W.; Gibble, R. E.; Pease, R. S. Siso, L. M.; Heurtin, D. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1084. (j) Darbeau, R. W.; Gibble, R. E.; Pease, R. S. *submitted to J. Chem. Soc., Perkin Trans. 2.* (k) Gibble, R. E. *M.S. Thesis*, McNeese State University, Lake Charles, LA, 2001.

(3) (a) Huang, H.; Hah, J. M.; Silverman, R. B. *J. Am. Chem. Soc.* **2001**, *123*, 2674. (b) Koshland, D. E., Jr. *Science* **1992**, *258*, 186. (c) Steuhr, D. J. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *22*, 477. (d) Schmidt, H. H. H. W.; Murad. F. *Biochem. Biophys. Res. Commun.* **1991**, *181*, 1372. (e) Schmidt, H. H. H. W.; Walter, U. *Cell* **1994**, *78*, 919. (f) Förstermann, U.; Pollock, J. S.; Schmidt, H. H. H. W.; heller, M.; Murad. F. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1788. (g) MacMicking, J.; Xie, Q. W.; Nathan, C. *Annu. Rev. Immunol.* **1997**, *15*, 323.

(4) Darbeau, R. W.; Perez, E. V. Sobieski, J. I.; Rose, W. A.; Yates, M. C.; Boese, B. J.; Darbeau, N. R. *J. Org. Chem.* **2001**, *66*, 5679.

(5) (a) Darbeau, R. W.; Pease, R. S.; Guillory, M.; Perez, E. V.; Delaney, M. S. In preparation. (b) Pease, R. S.; Guillory, M.; Davis, G.; Perez, E. V.; Darbeau, R. W. In preparation.

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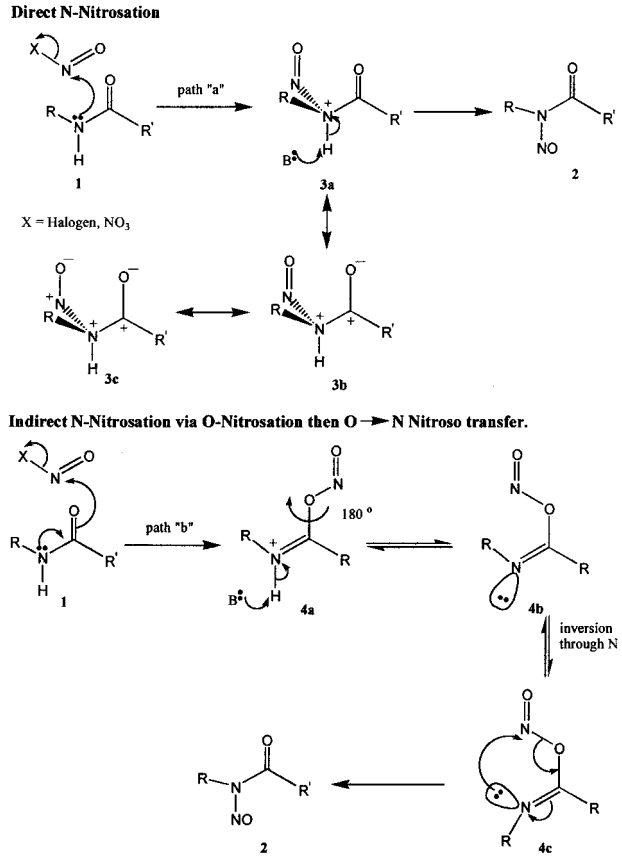
Scheme 1. Potential Pathways for *N*-Nitrosation of *N*-Alkylamides



intermolecular electronic factors on the kinetics of *N*-nitrosation.

Darbeau et al recently presented evidence for the existence of an electronic modulation of the thermal stability of *N*-alkyl-*N*-nitrosoamides.[6a] Electron-releasing groups (ERGs) and polar solvents were found to accelerate *N*-nitrosoamide thermolysis, whereas electron-withdrawing groups (EWGs) and nonpolar media enhance the thermal stability of the nitrosoamides.[6a] The identification of this electronic effect in *N*-nitrosoamide thermolysis complements the steric effects observed almost a half century ago.[6b,c] Further, it allows workers in deamination chemistry to rationally and more efficiently exploit the decomposition of nitrosoamides as a route to carbocations.

We decided to launch a companion investigation of the role (if any) of electronic effects on the rate of *N*-nitrosation of amides. This study would complement the related one on *N*-nitrosoamide thermolysis (vide supra)[6a] and would also be of practical use to chemists interested in amide/nitrosoamide chemistry, especially with regard to efficient nitrosoamide preparation and storage.

The *N*-nitrosation of amides may arguably occur via two pathways (Scheme 1). In pathway "a", there is a direct attack by the lone pair of electrons of the amidic N on the nitrosating agent. Rapid deprotonation of the resultant ammonium ion (**3**) then derives the *N*-nitrosoamide. This mechanism is somewhat suspect, because the nonbonded pair of electrons on the amidic N is strongly

(6) (a) Darbeau, R. W.; Pease, R. S.; Gibble, R. E. *J. Org. Chem.* **2001**, *66*, 5027. (b) Huisgen, R.; Ruchardt, C. *Justus Liebigs Ann. Chem.* **1956**, *601*, 1. (c) White, E. H.; Dolak, L. A. *J. Am. Chem. Soc.* **1966**, *88*, 3790.

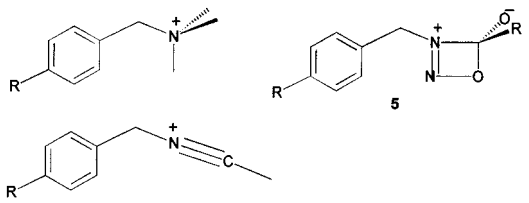


Figure 1. Examples of ammonium ions containing N^+ β to the 4-R-benzyl system.

delocalized over the N−C−O system and is therefore of limited availability to an electrophile. Additionally, the *N*-protonated nitrosoamide (**3**) is a high-energy species because the positive charge on the N is adjacent to both a carbonyl C and a nitrosyl N with significant positive dipoles (**3a** ↔ **3b** ↔ **3c**; Scheme 1).

The more likely scenario for *N*-nitrosation is shown in Scheme 1, path b and involves attack by the carbonyl O on the nitrosating agent to generate the *O*-nitroso species (**4a**). Rapid deprotonation and rotation about the C−O bond derives the conformer **4b** in which the nitroso group but not the lone pair of electrons on the amidic N meets the stereoelectronic requirement for intramolecular O → N nitroso transfer. Inversion through N derives **4c**, in which both the n-pair and the N═O group are properly oriented for the isomerization to the *N*-nitrosoamide (**2**) (Scheme 1, path b). Presumably, on the basis of the relative steric bulk of the acyl and alkyl groups flanking the amide unit, *O*-nitrosation may conceivably yield **4b** directly.[5a]

It has been recently demonstrated[1i−k,6a] that 4-R substituents on aromatic rings can modulate the chemistry of hypervalent positively charged nitrogen atoms separated from the aromatic ring by the sp^3-hybridized benzylic methylene group (Figure 1).[1i−k,6a] These observations are interesting in the context that para-substituents are able to modulate the chemistry at a site seven positions away in such a fashion that simple conjugation is not possible. It may be argued though that the polarizability of the aromatic nucleus and the paucity of electron density at the benzylic carbon due to its attachments to the aromatic ring and to a positively charged, sp-hybridized nitrilium N may facilitate transmission of the electronic "information" between the para-substituent and the nitrilium C.[1i−k,6a]

To the extent that an entity like **4a** (which also possesses the generic structure in Figure 1) is present along the reaction pathway, then the variation in the 4-R substituent on the starting amide should result in systematic modulation of the rates of *N*-nitrosation. Similarly, the reaction would also be expected to be susceptible to solvent effects, since the entity **4a** is charged whereas the starting amide is neutral. An interesting question also arises as to whether the *N*-nitrosation is more or less sensitive to substituent/solvent effects than the corresponding deamination reaction, which progresses via a charge-separated entity **5** akin to **4a** (Figure 1). This information would be useful in the preparation, storage, and use of *N*-nitrosoamides, since workers would be able to determine the ideal conditions under which to effect nitrosoamide formation based upon the structure of the amide.

The present study was aimed at investigating the effects of substituents and solvent polarity upon *N*-nitrosation of amides. It involved ^{1}H NMR spectroscopic

Table 1. Kinetic Data from the *N*-Nitrosation of *N*-4-R-Benzylpivalamides in Chloroform-*d*[a] at −40 °C

R	rate constant ($\times 10^{-2}$ s^{-1})	half-life (min)	σ_p
MeO	3.33	21	−0.27
Me	2.04	34	−0.14
H	1.23	57	0.00
CF_3	0.344	202	0.53
NO_2	0.179	388	0.78

[a] [Nitrosoamide] ~ 0.045 M.

Table 2. Kinetic Data from the *N*-Nitrosation of *N*-Benzylpivalamide in Various Solvents[a] at −40 °C

solvent[b]	ϵ[c]	π^* [d]	rate constant ($\times 10^{-2}$ s^{-1})	half-life (min)
CD_3CN	35.9	0.75	0.03	1684
CD_2Cl_2	8.93	0.82	1.61	43
$CDCl_3$	4.80	0.58	1.23	57
toluene-d_8	2.38	0.54	0.815	85

[a] [Benzylpivalamide] ~ 0.045 M. [b] Deuterated solvents used. [c] Values from ref 7c. [d] Values from refs 7b,c.

determinations of the rates of nitrosations of a series of *N*-4-R-benzylpivalamides in various solvents at constant temperature. *N*-4-R-Benzylpivalamides (**1a**−**e**; R = MeO, Me, H, CF_3, NO_2) were used because variation of the R-group allowed systematic examination of any operating intramolecular electronic effects. Dinitrogen tetroxide was used as the nitrosating agent.

Results and Discussion

***N*-Nitrosation of *N*-4-R-Benzylpivalamides (1a−e) in $CDCl_3$.** Standard solutions of *N*-4-R-benzylpivalamides (**1a**−**e**) in chloroform-*d* (ϵ = 4.80, π^* = 0.58)[7] at −40 °C in NMR tubes were treated with freshly prepared standard solutions of N_2O_4 in $CDCl_3$ also at −40 °C. The reactions were followed by ^{1}H NMR spectroscopy examining the product distribution as a function of time by looking specifically at the ^{1}H NMR signals of the benzylic methylene protons of the product nitrosoamides (singlets, ~δ 4.9) and the starting amide (doublets, ~δ 4.4) (Table 1). Nitrosations of *N*-benzylpivalamide (**1c**) were also performed in toluene (ϵ = 2.38, π^* = 0.54),[7] methylene chloride (ϵ = 8.93, π^* = 0.82),[7] and acetonitrile (ϵ = 35.9, π^* = 0.75),[7] to probe the effects, if any, of external electronic (substrate-solvent) interactions (Table 2).

For the nitrosations in $CDCl_3$, plots (e.g. Figure 2)[8] of the data (Table 1)[8] using ln(% amide) vs time (min) yielded straight lines (R^2 values 0.998−1.000), confirming that the nitrosations are first-order in the amide. From the rate constants for each decomposition, the half-lives were calculated and were found to vary systematically from 21 min for R = MeO to 34 min for R = Me, to 57 min for R = H, to 202 min for R = CF_3, and to 388 min for R = NO_2 (Table 1). These data suggest that an intramolecular electronic component is present in the *N*-nitrosation of amides to the extent that ERGs accelerate nitrosoamide formation, whereas EWGs stabilize the amides to nitrosation.

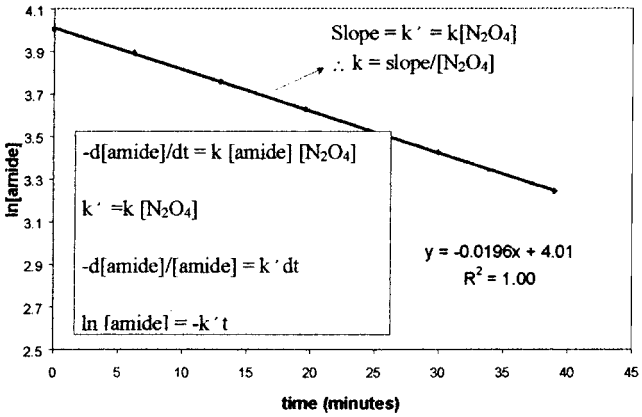


Figure 2. Plot of ln(% *N*-benzylpivalamide) vs time for the *N*-nitrosation reaction in $CDCl_3$ at −40 °C.

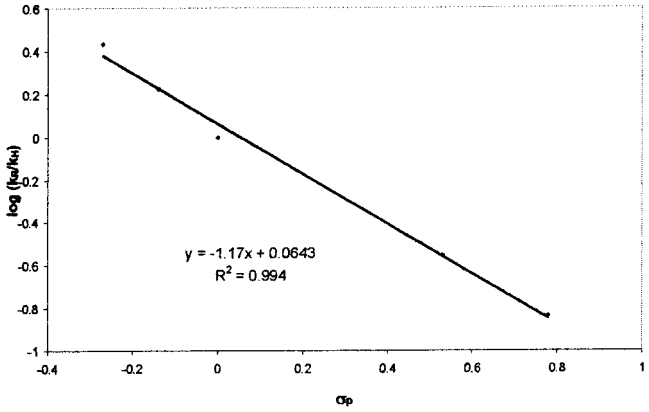


Figure 3. Hammett-type plot of log k_R/k_H vs the appropriate σ_p for the *N*-nitrosations of *N*-4-R-benzylpivalamides in $CDCl_3$ at −40 °C.

A Hammett-type plot (Figure 3) of the log(k_R/k_H) (k = rate constants) for the thermolyses vs the appropriate σ_p values yields a straight line (R^2 = 0.994) with a "ρ" value of −1.17. The linearity of the plot confirms the existence of a correlation between electronic effects in the alkyl portion of the nitrosoamide and the rate of *N*-nitrosation. Further, the negative sign of "ρ" supports the notion of developing positive charge at the benzyl carbon in the transition state (TS), which would be the case during formation of species **4a**. Evidently then, ERGs stabilize the developing positive charge at the benzyl carbon in the TS, thus facilitating the nitrosation; the converse is true of EWGs.

Nitrosation of *N*-Benzyl-*N*-Nitrosopivalamide (1c) in Solvents of Varying Polarity. The existence of the internal electronic perturbation of the rate of nitrosation would suggest that similar modulation by external factors might occur. Since there is development of positive charge involved in going from **1** to **4a**, then increasing the polarity of the medium would be expected to preferentially stabilize **4a** (vs **1**), leading to an enhancement in the rate of *N*-nitrosation.

To investigate this effect, the pivalamide that undergoes nitrosation at the most convenient rate (**1c**) was treated with a 5-fold excess of N_2O_4 at −40 °C in solvents of varying polarity (toluene, chloroform, methylene chloride, and acetonitrile; Table 2; e.g., Figure 4).[8] The data (Table 2) show that as the solvent polarity rises, the rate of nitrosation also rises. Indeed, a plot (Figure 4) of log

(7) (a) The π^*_{azo} value is a general dipolarity/polarizability index that gauges the ability of a solvent to stabilize an ionic or polar species by means of its dielectric effect. Values of π^* are based upon the solvochromatic parameters of azomerocyanine dyes.[5b,c] (b) Kamlet, M. J.; Aboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877. (c) Buncel, E.; Rajagopal, S. *Acc. Chem. Res.* **1990**, *23*, 226 and references therein.

(8) Only representative data and plots are given.

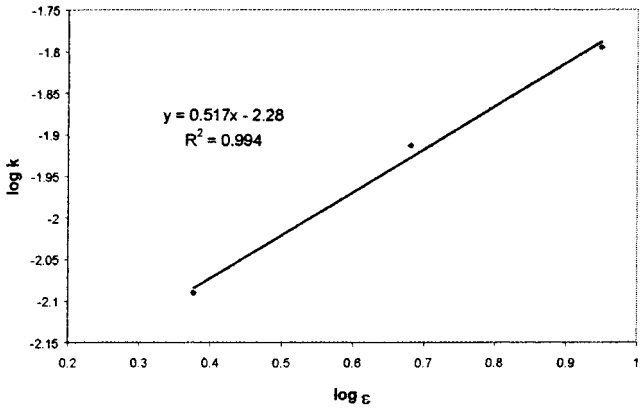


Figure 4. Plot of log k vs log ϵ for the *N*-nitrosations of *N*-benzylpivalamide in various solvents at − 40 °C.

k vs log ϵ for nitrosations of **1c** is linear (R^2 = 0.994), confirming the correlation between solvent polarity and the rate of nitrosoamide decomposition.

The observation of inter- and intramolecular electronic modulation of the kinetics of N-nitrosation of amides appears to be novel.

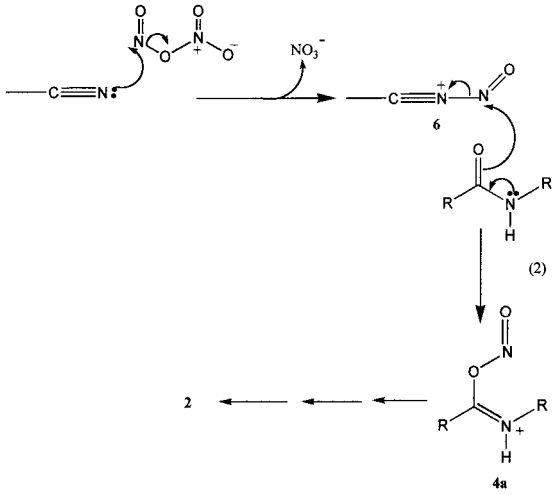
Rate Constants from *N*-Nitrosation of *N*-Alkyl Amides. The rate constant (k) for the first-order thermolysis of nitrosoamides, for example, can be readily determined from plots of ln[nitrosoamide] vs time.[6a] In such cases, the slope of the line = k.[6a] On the other hand, the rate of the *N*-nitrosation reaction, a second-order reaction, depends on the concentrations of both the amide and dinitrogen tetroxide in the solution. Consequently, the slope of a ln[amide] vs time plot (Figure 2) does not represent the true k value but instead gives k' (=k_{true}-[N_2O_4]). The value of k_{true} can then be calculated if the [amide] and [N_2O_4] are known. In this case, the concentration of amide is followed by ^{1}H NMR, and the initial concentration of N_2O_4 is known. Since the N_2O_4 is in significant excess, it can be reasonably assumed that its concentration is constant and that the reaction follows pseudo-first-order kinetics (e.g., Figure 2). This assumption of essential constancy of [N_2O_4] appears to be valid in practice, since plots of ln[amide] vs time yield straight lines (e.g., Figure 2).

A Note on the Choice of Solvents for Low-Temperature *N*-Nitrosation of Amides. In the previous study examining the roles of electronic effects on the thermolyses of *N*-nitrosoamides,[6a] the choice of solvents was limited to those that would be nonnucleophilic to the nitrosoamide. This condition would be necessary because any process (apart from unimolecular thermolysis) that scavenges the nitrosoamide would accelerate its rate of disappearance and skew the kinetics. Additionally, it was preferable for the solvent to undergo little or no reaction with the deaminatively generated benzyl cation, since the ^{1}H NMR signals of the benzylic methylene groups may appear in the region δ 4.9−5.2, where the nitrosoamide and ester respectively appear. The use of a solvent that is nonnucleophilic or poorly nucleophilic to the cation therefore provides a spectrum clear of unwanted signals in the diagnostic region. The solvents used (DMSO, acetonitrile, chloroform, and cyclohexane)[6a] provided a wide range of polarities while conforming to these previously mentioned constraints.

The present investigation of the *N*-nitrosation reaction presented more limitations, however. In addition to being nonnucleophilic to the nitrosoamide, as in the thermolysis reaction, the solvent must be nonnucleophilic to both the amide and N_2O_4. Also, the reaction temperature limited the solvent choice to those with melting points below −40 °C, which eliminated DMSO and cyclohexane, as well as a number of other potential media.

Initially, acetonitrile, methylene chloride, chloroform, and toluene were chosen, since they appeared to conform to all the solvent requirements and provided a reasonably wide range of polarities (ϵ_{tol} = 2.38, ϵ_{CD_3CN} = 35.9). However, amide nitrosation in acetonitrile proceeded at an exceedingly low rate (even lower than in toluene), which is inconsistent with the rest of the data (Table 2).

One possible explanation for this observation could be interaction between the lone pair of electrons on acetonitrile and N_2O_4 (eq 2). Since the nucleophilicity of the



amide is low as a result of delocalization of the lone pair of electrons on the nitrogen (eq 2) and the acetonitrile (=solvent) is abundant, the latter is apparently able to successfully compete with the amide for reaction with N_2O_4 at low temperatures (eq 2). Nitrosation appeared to occur as the solution quickly changed from blue (due to the presence of N_2O_4 at low temperature) to yellow (due to formation of the yellow *N*-nitrosoamide) as it warmed to room temperature. The implication, therefore, is that the acetonitrile generates an intermediate (e.g., **6**; eq 2) on reaction with N_2O_4. This species then transfers NO^+ to the amide at elevated temperature. A reasonable structure of the intermediate and a mechanism for its formation and decay are shown in eq 2.

A study is currently underway to investigate the details of this proposed intermolecular N → O nitroso transfer reaction, including the activation energy and threshold temperature for trans-nitrosation and other potential reaction pathways of the hypothesized *N*-nitrosonitrilium ion **6**.[5b]

Comments on the Use of N_2O_4 as the Nitrosating Agent. The analyses presented thus far have centered on the properties of the substrate and the solvent. However, interesting effects could potentially arise due to the use of N_2O_4 as the nitrosating agent. For example, some authors believe that the active concentration of the NO-carrier forms of N_2O_4 is influenced by the solvent polarity.[9a] Thus, the predominant $N_2O_4 \rightleftharpoons 2NO_2$ equilibrium converts one species with formal charges on two atoms into two equivalent molecules each with formal charges on two atoms. The reaction as written then would

be encouraged in polar solvents that could better stabilize NO_2 over N_2O_4. Consequently, as the solvent's polarity changes, $[N_2O_4]$ also changes and the rate of nitrosation would vary as well. However, this factor is believed to be very minor, if at all active, in the present study for the following reasons:

(1) As solvent polarity rises, the concentration of the principal NO-carrier form falls and a rate deceleration should be observed. This is not the case. Indeed, the reaction rate rises as the polarity of the inert solvent rises.

(2) A plot of log k vs log ϵ is linear ($R^2 = 0.994$; Figure 4). If the $[N_2O_4]$-decreasing effect of rising solvent polarity was significant, then because it is diametrically opposed to the polar solvent's role in preferentially stabilizing the transition state for nitrosation (vide supra), nonlinearity would have been expected in Figure 4.

(3) The $[N_2O_4]$ was kept deliberately high, thus even with equilibria decreasing the $[N_2O_4]$, because of the large initial $[N_2O_4]$, there would be a permanent kinetic excess of nitrosating agent. This is particularly so because no nitrations are effected under these conditions by the NO_2-carrier forms present in the system (vide infra).

(4) Finally, since the NO_2 is not consumed in this reaction (no nitrosations occur; vide infra), any N_2O_4 that reacts should be rapidly replaced by the reversion of the inactive NO_2 in equilibrium with it. Hence the actual amount of N_2O_4 should be essentially in constant excess.

A second phenomenon important to this discussion is the $ONONO_2 \leftrightharpoons NO^+ + NO_3^-$ equilibrium that would increase the nitrosating activity of the system in polar solvents. However, $ONONO_2$, from which the nitrosonium ion is generated, is likely to be less abundant in polar solvents than is N_2O_4, since the latter possesses a larger degree of charge separation. In any event, the linearity of the log k vs log ϵ plot (Figure 4) in the face of the plethora of counterpoised equilibria suggests that these equilibria probably do not affect the concentration of active nitrosating agents to a significant degree. Alternatively, the *N*-nitrosation of amides may be so facile as to be insensitive to the slight (or modest) changes in the concentrations and activities of the various nitrosating agents encountered in the present system. In all likelihood, the correct answer may derive contributions from both postulates.

From a more practical standpoint, we did not purify the N_2O_4 used for these experiments, despite the fact that commercial N_2O_4 contains some NO and N_2O_3, which are nitrosating agents.[9b] However, even if some fraction of the nitrosations were effected by agents other than the prevalent N_2O_4, it should be true universally in all the systems examined and evidently leads to a constant effect, since all of our plots involving log k are linear. In any event, this study focused on the roles of electronic factors (intramolecular and substrate-solvent) on the rates of amide nitrosation; hence, identification of all potential nitrosating agents is not crucial to the study.

A Comparison of the Electronic Sensitivities of *N*-Nitrosoamide Formation and Decay. No attempts to compare the rate constants for nitrosation and deamination for a given R group have been made, because the former reaction was performed at −40 °C and the latter at room temperature. The *N*-nitrosations would be far too rapid to be monitored by ^{1}H NMR at room temperature, even in nonpolar solvents. Conversely, the deaminations would be prohibitively slow at −40 °C. Consequently, since the values of k are temperature-dependent and a common reaction temperature is somewhat elusive, determinations of $k_{R(nitrosation)}/k_{R(deamination)}$ are impractical.

Comparisons of series rate constants between both reactions, however, are feasible and interesting. Thus the ratio of k_{MeO}/k_{NO_2} for *N*-nitrosation of amides is 18.6 (Table 1), whereas that for thermal deamination of the corresponding *N*-nitrosoamides is 8.2.[6a] The implication then is that the formation of nitrosoamides (via *N*-nitrosation of amides) is somewhat more sensitive to electron effects than is their thermolytic deamination. This result presumably arises because the characters of the transition states of both reactions are similar in terms of the presence of the hypervalent positive *N*-atom β to the aromatic nucleus (Figure 1), resulting in somewhat similar electronic perturbations from the various 4-R groups. However, since the entity **4a** is actually charged, whereas **5** is zwitterionic (vide supra), a greater field effect may be operational in the nitrosation reaction than in deamination, resulting in a slightly greater sensitivity, as observed. The origin of the somewhat greater value of ρ for nitrosation (−1.17) than that for deamination (−0.88)[6a] presumably also lies in the field effect argument.

Summary

Novel evidence for the existence of an electronic modulation of the kinetics of *N*-nitrosation of *N*-alkylamides has been presented. Electron-releasing groups and polar solvents accelerate *N*-nitrosoamide formation, whereas electron-withdrawing groups and nonpolar media enhance the resistance of the amide to nitrososation. The identification of this electronic effect in *N*-alkylamide nitrosation allows workers in deamination chemistry to rationally and more efficiently exploit the preparation and decomposition of nitrosoamides as a route to carbocations. It would also appear that the factor determining the relative rates of nitrosoamide formation and decay is the reaction temperature. Thus, in the present case −40 °C allows successful and rapid nitrosation without appreciable nitrosoamide deamination. The rapid rate of *N*-nitrosation apparently exerts a kind of nitrosative leveling effect and renders the reaction insensitive to subtle changes in the concentrations and activities of the various nitrosating agents in dissolved N_2O_4.

Experimental Section

Materials and Methods. All commercial reagents were reagent grade and were used without further purification. Spectra were recorded on 300 MHz FT-NMR, FT-IR, and UV−vis spectrometers.

Stability of *N*-4-R-Benzyl-N-nitrosopivalamides; Handling and Storage. The *N*-4-R-benzyl-*N*-nitrosopivalamides are thermolabile and unstable in the presence of acids, bases, and moisture; being photolabile, they were handled in the dark. The dry, neutral oils were stored in desiccators under N_2 in capped tubes immersed in liquid nitrogen. **Caution!** Nitrosoamides should be handled with extreme care because of their possible mutagenicity[2a] and carcinogenicity (local and systemic).[2b] Efficient fume hoods and appropriate personal

(9) (a) Churney, K. L. *Dissertation Abstr. Int.* **1962**, 46. (b) Cotton, F. A.; Wilkinson, G. In *Advanced Inorganic Chemistry: A Comprehensive Text*, 6th ed.; John Wiley and Sons: New York, 1999; pp 328−330.

protection (chemical-resistant gloves, safety glasses, lab coat, etc.) are recommended when handling these compounds.

***N*-4-R-Benzylpivalamides** were prepared by the method of Heyns and von Bebenburg.[10a]

***N*-4-Methoxybenzylpivalamide:** mp 88−90 °C;[10b] IR (Nujol) 3331, 1636, 1538, 1518, 1461 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 3.78 (s, 3H), 4.35 (d, 2H, $J = 7$ Hz), 5.84 (bs, 1H), 6.82−7.20 (dd, 4H).

***N*-4-Methylbenzylpivalamide:** mp 94−96 °C;[10b] IR (Nujol) 3334, 1636, 1536, 1518, 1461 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 2.38 (s, 3H), 4.44 (d, 2H, $J = 7$ Hz), 5.87 (bs, 1H), 7.20 (s, 4H).

***N*-Benzylpivalamide:** mp 81−82 °C (lit.[10a] mp 81−82 °C); IR (KBr) 3309, 1689, 1510, 1390, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 4.44 (d, 2H, $J = 7$ Hz), 5.90 (bs, 1H), 7.26−7.32 (m, 5H).

***N*-4-Trifluoromethylbenzylpivalamide:** mp 111−113 °C;[10b] IR (Nujol) 3359, 1641, 1518, 1458, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 4.54 (d, 2H, $J = 7$ Hz), 6.08 (bs, 1H), 6.39−8.22 (dd, 4H).

***N*-4-Nitrobenzylpivalamide:** mp 119−121 °C;[10b] IR (Nujol) 3359, 1641, 1518, 1462, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 4.54 (d, 2H, $J = 7$ Hz), 6.08 (bs, 1H), 6.39−8.22 (dd, 4H).

Nitrosation of *N*-4-R-Benzylpivalamides. A stock solution of ~1.6 M N_2O_4 solution was prepared by bubbling N_2O_4-(g) by syringe through a Teflon cap (vented with a needle and blanketed with nitrogen gas) into 4.5 mL of $CDCl_3$ at −20 °C until the volume increased to 5.0 mL. The resulting solution was kept at −20 °C using a dry ice−acetone bath. Individual samples were prepared by adding 4.52×10^{-5} mol of each *N*-4-R-benzylpivalamide (R = MeO, Me, H, CF_3, and NO_2) and 800 μL of 0.2825 M 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) solution into separate NMR tubes and capping with Teflon tape and a serum stopper. For each run, the *N*-4-R-benzylpivalamide sample was loaded into the NMR probe and cooled to −40 °C and a prenitrosation ^1H NMR spectrum was taken. The sample was ejected and 140 μL of the cold N_2O_4 solution was injected by syringe into the NMR tube; the mixture was then rapidly shaken and quickly loaded back into the probe. A time = 0 ^1H NMR spectrum was taken immediately, followed by a minimum of four additional spectra at appropriate time intervals, while a temperature of −40 °C was maintained. Integrals of the *N*-4-R-benzyl-*N*-nitrosopivalamides and the unreacted *N*-4-R-benzylpivalamides were measured.

Proof of the Presence of *N*-Nitrosoamide and the Absence of *N*-Nitroamides. FT-IR, ^1H NMR, and UV−vis spectra were recorded on samples obtained from nitrosations. From the nitrosation of *N*-benzylpivalamide, for example, the data are as follows: IR (neat) 1720, 1605, 1502, 1390, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 4.97 (s, 2H), 7.05−7.40 (m, 5H); UV (CH_2Cl_2) λ_{max} 275 nm ($\epsilon = 500$), 400 nm ($\epsilon = 63$), 394 (sh), 432 nm ($\epsilon = 66$). No signals indicative of other species, e.g. of *N*-nitroamides [e.g., *N*-benzyl-*N*-nitroacetamide: IR (neat) 1580, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.27][11] were observed.

Nitrosation of *N*-Benzylpivalamide in Solvents of Varying Polarity. Individual samples were prepared by adding 8.6 mg of *N*-benzylpivalamide and 46.3 mg of DBMP into each of three NMR tubes. For each run, 800 μL of solvent (toluene-d_8, acetonitrile-d_3, or methylene chloride-d_2) was added to a sample that was loaded into the NMR probe and cooled to −40 °C, and a pre-nitrosation spectrum was taken. The sample was ejected and 140 μL of the cold N_2O_4 solution (prepared in $CDCl_3$ as described above) was injected by syringe into the NMR tube, and the tube was shaken and quickly loaded into the probe. A time = 0 ^1H NMR spectrum was taken immediately, followed by a minimum of four additional spectra at appropriate time intervals, while a temperature of −40 °C was maintained. Integrals of the *N*-4-R-benzyl-*N*-nitrosopivalamides and the unreacted *N*-4-R-Benzylpivalamides were measured.

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(10) (a) Heyns, K.; v. Bebenburg, W. *Chem. Ber.* **1953**, *86*, 278. (b) *Beilstein*, 3rd; Vol. 12, Suppl. p 2346.

(11) (a) Darbeau, R. W. *Ph.D. Thesis*, the Johns Hopkins University, Baltimore, MD, 1996. (b) Darbeau, R. W.; White, E. H.; Song, F.; Darbeau, N. R.; Chou, J. C. *J. Org. Chem.* **1999**, *64* (16), 5966.