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Kinetics and Mechanism of Nucleophilic Addition to Nitric Oxide: Secondary Amine Diazeniumdiolation

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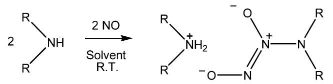
The kinetics of nitric oxide (NO) addition to dipropylamine and pyrrolidine are determined for a range of solvents and NO pressures. A new isobaric technique is utilized to determine the order of NO, and the kinetics are shown to conform to reactions which are either mono- or bimolecular in NO depending upon the conditions. The mechanism is interpreted in terms of competitive addition of amine to either NO or its dimer.

The discovery of nitric oxide's (NO's) pervasive role in biology has led to a renaissance in its chemistry. In spite of the considerable progress in understanding its coordination chemistry[1] as well as its reactions with organic molecules,[2] there remain critical mechanistic issues relating to its reactions. NO has gas-phase reactions with oxygen, chlorine, bromine, and hydrogen that all follow unusual termolecular rate laws that are second-order in NO. These kinetics are most often understood in terms of a rapidly established dimerization equilibrium followed by the rate-determining reaction of the dimer with substrate to give NO_2, NOCl, NOBr, and N_2O, respectively.[3] Subsequent attempts to determine the order and mechanism of the related solution-phase reactions with nucleophiles have been complicated by rapid diffusion-controlled reactions,[4] by NO oxygenation,[5] and by the use of variable nonisobaric NO pressures.[6] Perhaps the most germane recent result is the kinetics of the oxidation of PPh_3 to its oxide by NO, which is second-order in NO.[7] In this case, the solvent dependency was used as evidence for a stepwise mechanism.[7] Herein we report the isobaric kinetics of the reaction of NO with secondary amines to form diazeniumdiolate anions (**I**; eq 1), where the order of the reaction is shown to depend upon the solvent, [NO], and substrate. The kinetics are interpreted in terms of the competitive addition of both NO and its dimer with the amine to give the same product with the same stereochemistry.



(**I**)

(1)

Diazeniumdiolate syntheses generally use diethyl ether or basic methanol as the solvent, with reactions typically giving optimum yields at low temperature.[8] Not only have these important NO donors found widespread biomedical applications, but they also pose fundamental mechanistic questions relating to the origin of the stereospecificity of the pairwise NO addition to give the *Z* isomer (**I**).[9] While nucleophilic addition to the NO dimer might lead to the observed *E*/*Z* stereospecificity, there are no kinetic studies that indicate that the formation of **I** is bimolecular in NO.[10] The enthalpy of NO dimerization is low, and the rates of its formation and dissociation are both rapid.[11] A recent ab initio quantum mechanical prediction proposed that an aromatic host or ring will enhance NO dimerization by forming a face-to-face donor−acceptor complex.[12] For example, in the gas phase, benzene is calculated to increase the K_{eq} for dimerization by more than 150-fold at room temperature.[12]

The kinetics for the reaction of amines with NO were investigated as a function of [NO]. In general, these reactions are slow and not diffusion-controlled and the isobaric kinetics are easily monitored by following the NO consumption across a constant-pressure controller; see the Supporting Information. Pseudo-first-order rate constants for the reaction of NO with dipropylamine (DPA) to form dipropyldiazeniumdiolate (DPA/NO) are presented in Table 1 (entries 1−3). Clearly, under these conditions, there is no enhancement in the rate of NO condensation with aromatic solvents. Because

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Table 1. Initial and Pseudo-First-Order Rate Data for the Reaction of Secondary Amines with NO in Various Solvents at 25 °C[a]

entry	amine	solvent	NO atm ± 0.01	[NO], M	initial rate[b] (atm s^{-1}) ($\times 10^{-5}$)	k_{obs}[c] (s^{-1}) ($\times 10^{-6}$)
1	DPA	diethyl ether	3.4	0.06	_	0.6 (0.1)
2	DPA	benzene	3.4	0.04	_	0.6 (0.2)
3	DPA	anisole	3.4	0.02	_	0.9 (0.1)
4	PYRR	neat	1.7	0.07	2.1 (0.2)	
5			3.4	0.14	9.1 (0.4)	
6			3.9	0.16	10.4 (2.6)	
7	PYRR	pyridine	0.7	0.004	1.2 (0.4)	
8			1.0	0.006	2.3 (0.5)	
9			1.7	0.009	3.0 (1.6)	
10			3.4	0.019	5.9 (1.9)	
11			3.90	0.022	5.4	
12	PYRR	1-methylimidazole	0.7	0.004	1.1 (0.1)	
13			1.0	0.006	1.9 (0.3)	
14			1.7	0.009	1.8 (0.04)	
15			3.4	0.019	5.6 (1.0)	
16			3.90	0.022	7.9	

[a] Concentrations of DPA and PYRR are 3.7 and 4.6 M, respectively. NO solubilities for the various solvents were estimated according to information provided in the Supporting Information. [b] Initial rate. [c] Pseudo-first-order rate constant.

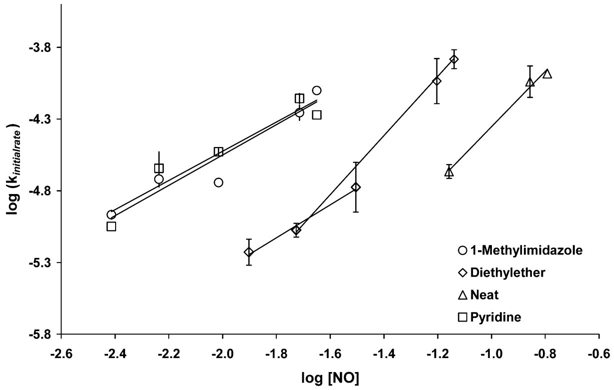


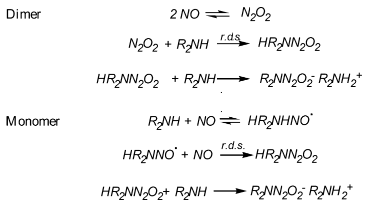
Figure 1. van't Hoff log/log plot of log($k_{\text{initial rates}}$) vs log [NO] for the reaction of PYRR with NO.[14]

the reactions of NO with DPA at 25 °C are uniformly slow, we opted to study the faster reaction of pyrrolidine (PYRR) with NO.[13] The initial rates for this reaction in various solvents are presented in Table 1. Similar initial rates for the formation of the corresponding sodium salt in sodium methoxide are found and presented in the Supporting Information.

The kinetic data allow for the dependence of [NO] on the rate law to be determined. The initial rates over a range of NO concentrations were used to construct a van't Hoff log/log plot (Figure 1). Because of the differences in NO solubility in the various solvents, both high and low NO concentration regimes were probed. Figure 1 clearly illustrates that there is a change in slope from 1 to 2, and thus the reaction order, with an increase in [NO] upon going from 1-methylimidazole and pyridine to neat amine. The reaction is first-order in amine (Supporting Information). The two proposed mechanisms for the formation of these NO adducts with secondary amines involve the addition of the amine to either the dimer or monomer in their rate-determining steps (Scheme 1).[5]

This variation in the order with respect to [NO] reveals that the rate law may not be simple and could involve multiple terms. The proposed two-term rate law under these conditions is therefore the following:

Scheme 1. Proposed Mechanisms for the Formation of Amine-Derived Diazeniumdiolates[5]



$$\frac{d[P]}{dt} = k_1[\text{amine}][NO] + k_2[\text{amine}][NO]^2$$

Integration of this expression leads to an equation of the form (assuming the concentration of amine to be constant)[15]

$$\exp\left(k_1 + \ln\frac{[NO]}{[NO]_0}\right) = \frac{k_1 + k_2[NO]}{k_1 + k_2[NO]_0}$$

In accordance with the integrated rate expression, reactions at low [NO] will be first-order because the second-order kinetic term will not contribute appreciably and k_1 can be ascertained.

Treatment of multiterm rate expressions to explain differences in the reaction order as a function of the reactant concentration is well founded,[15] and by utilization of this approach, it is clear that only at higher [NO] will the second-order kinetic term be significant. This is substantiated by the data in Figure 1, in which at higher NO concentrations there is an increase in the apparent rate constant. The proposed rate law would predict that, under these conditions, k_2 will be significantly larger and the second-order term will predominate. Second-order rate constants (k_2) were calculated following work by Chao and Espenson,[15] in which for the neat reaction k_2 is 5.3×10^{-6} M^{-1} s^{-1}.

While it has been proposed that hydrophobic and aromatic environments allow for the concentration and/or stabilization of the NO dimer,[12,16,17] the acceleration in the rate that would

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be a consequence of dimer enrichment does not appear to be valid in the case of diazeniumdiolate formation under these conditions. If dimer reactivity is attenuated by donor−acceptor adduct formation of the dimer, then anisole should *inhibit* the reaction. Experimentally, the opposite is observed, but the relatively large errors in the rate determinations for these slow reactions limit further interpretation. The rate law for these reactions was determined to involve multiple terms, with a first-order dependence with respect to NO observed at low [NO]. Under these conditions, it is the NO monomer that reacts in a stepwise manner with amine to produce diazeniumdiolate. As the [NO] is increased, the second term in the rate expression becomes significant and the second-order dependency on [NO] becomes much more important. Thus, at elevated [NO], it is the NO dimer that acts as the electrophile in these reactions. Therefore, the formation of these anions proceeds through two parallel pathways, with NO monomer and dimer acting as competitive electrophiles.

Finally, the observed *Z* stereospecificity of NO addition to the amines requires comment. One explanation is that, in analogy to the well-known ability of iodine radicals to equilibrate *cis*/*trans*-olefins,[20] it may be possible that NO catalyzes the *Z*/*E* equilibration of the diazeniumdiolate. In this case, the thermodynamically stable *Z* isomer would predominate.[9] Another explanation is that both amine addition to the dimer and a stepwise addition of two NO molecules to the amine occur with a high degree of stereospecificity. For a stepwise mechanism, this implies that the addition of the two π^* radicals, NO and HR_2NNO in the second step, is stereospecific. If this is the case, then this is the second report of an *E*/*Z* stereospecific reaction of NO with a π^* radical, with the other being the rapid diffusion-controlled reaction of NO and superoxide to give *cis*-peroxynitrite.[18,19] A common thread in both of these reactions is access to cyclic transition states connecting the radicals to their *Z*-condensation products. Experiments to distinguish between these possible explanations are underway.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs./acs.org.

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