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Decoding Nitric Oxide Release Rates of Amine-Based Diazeniumdiolates

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Abstract

Amine-based diazeniumdiolates (NONOates) have garnered widespread use as nitric oxide (NO) donors and their potential for nitroxyl (HNO) release has more recently been realized. While NO release rates can vary significantly with the type of amine, half-lives of seconds to days under physiological conditions, there is as yet no way to determine *a priori* the NO or HNO production rates of a given species and no discernible trends have manifested other than that secondary amines produce only NO (i.e., no HNO). As a step to understanding these complex systems, here we describe a procedure for modeling amine-based NONOates in water solvent that provides an excellent correlation ($R^2 = 0.94$) between experimentally measured dissociation rates of seven secondary amine species and their computed NO release activation energies. The significant difference in behavior of NONOates in the gas and solvent phases is also rigorously demonstrated via explicit additions of quantum mechanical water molecules. The presented results suggest that the as-yet unsynthesized simplest amine-based NONOate, the diazeniumdiolated ammonia anion [$\text{H}_2\text{N}-\text{N}(\text{O})=\text{NO}^-$], could serve as an unperturbed HNO donor. These results provide a step forward toward the accurate modeling of general NO and/or HNO donors as well as for the identification of tailored prodrug candidates.

INTRODUCTION

The established role of nitric oxide (NO) in a diverse array of biological processes such as immune response, cell signaling, and blood pressure regulation^{1,2} has led to the demand and design of bioactive NO delivery systems.³ To this end, secondary amine diazeniumdiolates (NONOates) have proven to be effectual NO donors,⁴ particularly under physiological conditions (Scheme 1) whereby hydrolysis rates of **1** can vary from seconds to days depending on the amine.^{5,6} As such, they have shown remarkable potential as antibacterial and anti-cancer pharmacological agents.^{4,7,8} More recently, in addition to releasing NO, primary amine analogues ($\text{R}^1 = \text{H}$ in Scheme 1) have been shown to also produce nitroxyl (HNO),^{9,10} thus enhancing their prospective pharmacological applications to include treatments for alcoholism¹¹ and heart disease.¹²

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Supporting Information Available

Full details regarding the reference active spaces used in the MRMP2 and MR-CISD+Q computations, IRC generations, and all geometries and energies. This information is available free of charge via the Internet at <http://pubs.acs.org>.

While NO release rates of secondary amine NONOate anions can vary widely, no discernible trends that relate the natures of R^1 and R^2 (Scheme 1) with decomposition speed have manifested. Furthermore, precise NO vs. HNO release profiles are difficult to ascertain experimentally, particularly under physiological conditions. The ability to determine *a priori* accurate NO and/or HNO release half-lives would allow for the efficient identification of ‘tailored’ prodrugs having desired properties. As a first step towards this capability we developed a procedure to compute accurate activation energies for NO dissociation of anions of type **1**.

Previous computational studies have found that amine-based NONOates should be able to exist in both *Z* and *E* forms;^{13–16} however, for unclear reasons, only the *Z* form has been directly synthesized. While primary amine NONOates were theoretically predicted,¹⁵ and later experimentally confirmed,^{15,17} to have possible $Z \rightleftharpoons E$ interconversion routes via amine deprotonation, no such low energy pathway is possible for secondary amine analogues; therefore, only *Z* isomers are considered here. Houk and coworkers have shown through computational studies^{14,16} and Davies et al. have confirmed experimentally¹⁸ that NO release is initiated via amine protonation. Accordingly, we have used a similar mechanism in our computations of activation barriers.

Here, we first demonstrate the disparate behaviors of amine-based NONOate anions in the gas and solvent phases whereby in the former amine protonation leads to spontaneous decomposition – a finding that holds for three levels of theory including two that are benchmark. In contrast, however, as explicit water molecules are added (up to seven) a barrier to NO release is noticeably enhanced, i.e., a corresponding transition state becomes apparent. Second, we show that treating solvent effects with a polarized continuum model (PCM) provides commensurate results to those obtained using explicit water molecules. Last, we compute activation barriers for a test bed of seven secondary amine NONOates and find that our predictions correlate very well ($R^2 = 0.94$) against experimentally measured decomposition rates. Secondary amine NONOates were selected for the reason that they only release NO and do not have competing HNO release pathways; therefore, their experimentally determined NO release rates are expected to be unambiguous. Nonetheless, we expect that NO release rates of primary amine NONOates can be modeled similarly and future work will describe modeling of HNO release rates together with elucidations of NO vs. HNO decomposition profiles.

METHODS

Computations used the correlation-consistent cc-pV n Z ($n = D, T, Q$),¹⁹ denoted here as n Z, and aug-cc-pVDZ,²⁰ denoted here as ADZ, basis sets. Gas phase studies of the diazeniumdiolated ammonia anion (DD-AA: $H_2N-N(O)=N-O^-$), its unstable amine-protonated counterpart (N^3p -DD-AA: $H_3N^+-N(O)=N-O^-$), and the weakly-bound dissociated products complex ($NH_3---(NO)_2$) utilized three diverse levels of theory: i) second-order Møller-Plesset perturbation theory (MP2),^{21–23} ii) multireference MP2 (MRMP2),^{24,25} and iii) multireference singles and doubles configuration interaction²⁶ including quadratic correction²⁷ (MR-CISD+Q).²⁸ MRMP2 computations used 20 electron, 15 orbital (20,15) and (14,12) complete-active-space self-consistent-field (CASSCF)^{29–32} references. MR-CISD+Q calculations used CASSCF(2,2) references. Geometries of DD-AA and the dissociated products complex were optimized at the MP2/ n Z ($n = D, T, Q, AD$), MRMP2(20,15)/DZ, MRMP2(14,12)/TZ, and MR-CISD+Q/DZ levels of theory. MRMP2(20,15) energies computed with the TZ and QZ basis sets used MRMP2(14,12)/TZ-optimized geometries while MRMP2(20,15)/ADZ energies used MRMP2(20,15)/DZ-optimized geometries. MR-CISD+Q energies were computed using geometries optimized with the DZ basis.

Gas phase dissociation properties of dimethylamine diazeniumdiolate anion (DMA/NO, structure $\text{Me}_2\text{N}-\text{N}(\text{O})=\text{NO}^-$) were computed at the MP2/ADZ level of theory. Properties of the NO radical were determined using the second-order Z-averaged perturbation theory (ZAPT) method.^{33,34}

Geometries were optimized using analytic gradients for the MP2 and ZAPT levels of theory^{23,34} and numerical gradients³⁵ for the MRMP2 and MR-CISD+Q methods. Hessians at the MP2 level were computed semi-numerically with analytic gradients. Minimum energy paths were determined using the second-order intrinsic reaction coordinate (IRC) method of Gonzalez and Schlegel.³⁶

Water solvent effects at the MP2/ADZ level of theory were modeled by: i) inclusions of explicit water molecules in the quantum calculations, ii) use of the polarized continuum model (PCM),³⁷⁻⁴¹ and iii) inclusion of an explicit quantum mechanical water molecule within the PCM model (PCM + H_2O).

See Supporting Information for full details regarding the reference active spaces, IRC computations, and all geometries and energies. Molecular structures and orbitals were illustrated using MacMolPlt.⁴² All computations were performed using a local version of the GAMESS package⁴³ whereby default parameters were used throughout except where explicitly stated.

RESULTS AND DISCUSSION

Gas phase behavior of amine-based NONOate anions

We first studied the simplest species of type **1** in which $\text{R}^1 = \text{R}^2 = \text{H}$, diazeniumdiolated ammonia anion (DD-AA), since we could use the very-high-level theories MR-CISD(2,2)+Q and MRMP2(20,15) with a range of basis sets to probe its properties. Such high-level computations are not feasible for the much larger systems so we also used the medium-level MP2 method to gauge its accuracy.

At all three levels of theory DD-AA is predicted to exist in two very similar forms differing only in the hydrogen orientations (Supplementary Figure S1) and having an electronic energy separation of within 1.6 kcal/mol (Supplementary Table S1). However, upon protonation of the amine nitrogen (denoted by N^3p), the species N^3p -DD-AA spontaneously decomposed, i.e., without barrier, to the dissociated products $\text{NH}_3\text{---}(\text{NO})_2$ where the $(\text{NO})_2$ group is representative of the weakly-bound NO dimer (Figure 1a). This spontaneous dissociation was observed at the MP2/ $n\text{Z}$ ($n = \text{D}, \text{T}, \text{Q}, \text{AD}$), MR-CISD(2,2)+Q/DZ, and MRMP2(20,15)/DZ levels of theory suggesting that this phenomenon is not an artifact of an incomplete level of theory but rather a real property. Furthermore, dimethylamine diazeniumdiolate anion (DMA/NO), a well-studied experimentally isolable system, also underwent spontaneous decomposition upon amine protonation at the MP2/ADZ level of theory indicating that this gas phase volatility is general to amine-based NONOate anions (see Supporting Information). It is clear that the electronic rearrangements that transpire during decomposition are complex (two bonds are dissolved including a nitrogen-nitrogen double bond!) but inspection of the MRMP2(20,15) natural orbitals (that describe *all* bonding and anti-bonding orbitals) during dissociation shows that the process is essentially closed-shell, i.e., all electrons are paired for the most part. Post dissociation the exception is the weakly-bound NO dimer, $(\text{NO})_2$, product component which is known to be a notoriously difficult case for quantum chemistry. However, we have previously shown that a similarly constructed MRMP2 computation provides extremely accurate results for this system and that the medium level MP2 theory also performs (perhaps somewhat fortuitously) very well.⁴⁴

Figure 1a illustrates the MP2/QZ minimum energy IRC path describing the exothermic dissociation reaction and it is evident that the initial zwitterion is meta-stable; however, decomposition ultimately occurs. Although the overall energy release is unsurprisingly large (~350 kcal/mol) the energy drop from the meta-stable zwitterion is only some 40 kcal/mol (see Supporting Information for full details regarding generations of initial amine-protonated structures and dissociation reaction profiles). Figure 1b shows that the computed electronic dissociation energies steadily decrease for all methods as the basis is improved from DZ to TZ to QZ and that the high level MR-CISD(2,2)+Q and MRMP2(20,15) results are concordant suggesting good reliability of these results. Our best prediction for the electronic energy release of $\Delta E_e = -359$ kcal/mol is obtained at the MRMP2(20,15)/QZ level; however, use of the ADZ basis gives results comparable to those of the much larger QZ set. This is likely due to the additional diffuse functions (that augment the DZ set) adequately spanning the medium-range NO---NO and NH₃---(NO)₂ interactions. We also find that the significantly cheaper MP2 theory performs well with computed release energies within 4.1 kcal/mol (~1 % of total) of the MRMP2(20,15) predictions when using the QZ and ADZ basis sets. The only experimentally measured gas phase decomposition energy that we know of is $\Delta H_{298} = -335.7 \pm 4.4$ kcal/mol for the *N*-methylaniline derivative dissociating two NO radicals (this study also included density functional theory computations)⁴⁵ and at the MP2/ADZ level we obtain a very similar result of $\Delta H_{298} = -330.8$ kcal/mol for the decomposition of DMA/NO into the separated products NHMe₂ + 2NO.

The results described here indicate that, with regard to protonation energetics of DD-AA, the results of MP2/ADZ computations are comparable to those using higher level theories and larger basis sets. As such, we are confident that the MP2/ADZ level of theory is suitable for the modeling of solvent effects upon the dissociation reaction as well as for the subsequent study of larger amine-based NONOates.

Water solvent effect upon dissociation kinetics

We first modeled the influence of water solvent upon NO dissociation by adding explicit water molecules that were treated quantum mechanically, i.e., the total systems including waters were incorporated in the MP2/ADZ computations. The first three waters were placed successively at the H-N-N-N and two H-N-N-O bridging sites of the zwitterion amine-protonated N³p-DD-AA species (Figure 2a). Addition of a single water molecule was enough to stabilize the zwitterion in that a minimum could be optimized together with a corresponding transition state (TS) that has exactly one imaginary frequency. As the three waters were added to form the first-level solvation cage (Figure 2a and Supplementary Figures S5–S7) the height of the N³p-TS barrier steadily increased from 0.3 to 1.3 to 2.9 kcal/mol (Figure 2c) and in each case the TS and zwitterion minimum were shown to be connected by minimum energy IRC paths.

Subsequent water molecules, up to a total of seven, were added individually by sampling reasonable starting structures and optimizing corresponding zwitterion and TS stationary points. In each of these cases (Figure 2b and Supplementary Figures S8–S11), the lowest-energy minima and TSs that were located (and confirmed by computations of vibrational frequencies) were shown to be connected by optimizing on TS-like structures having slightly shortened N—N bond lengths. We found that the energy barrier to dissociation continues to increase steadily from 5.5 to 9.5 kcal/mol as four to seven water molecules are added. It is not clear how much further, if at all, the barrier would increase with additional explicit water molecules. We feel that with seven waters we have almost reached a second-level solvation cage; however, this is difficult to substantiate without actually performing the larger computations. In any case, it is clear that solvent water molecules serve to stabilize the amine-protonated zwitterion minimum, thus enhancing a barrier to decomposition that leads to dissociation kinetics that are contrary to those in the gas phase.

Although the solvent-induced barrier to decomposition is our primary interest, we modeled dissociation energies by minimizing products ($\text{NH}_3\text{---}(\text{NO})_2$) with sequentially added water molecules up to a total of seven (Figure 2 and Supplementary Figures S5–S11). For two or more waters we tested several initial placements and observed that the water molecules preferred to form cage-type clusters (incorporating the amine at a vertex) that only weakly interacted with the NO species, in accord with the latter's hydrophobicity. It is seen that the dissociation energy (relative to the amine-protonated zwitterion minimum) steadily decreases as water molecules are added (Figure 2c), in a style converse to that of the TS barrier, so that in saturated water solvent the exothermicity of the decomposition would appear to substantially reduce to approximately 10 kcal/mol or less. Of course, for these water-inclusive computations we cannot guarantee to have located the absolute lowest-energy stationary points since the sampling space for the water molecules is large; nonetheless, we feel that we have added water molecules in a balanced and consistent manner and that the results provide a good guide as to the solvent effects.

Since it is impractical to add even a few explicit quantum water molecules to the larger and more complex amine-based NONOates we probed the performance of the far cheaper PCM³⁷ solvent method together with the effect of incorporating an explicit quantum water molecule analogous to the one-water system (PCM + H_2O) (Figure 2c and Supplementary Figures S12, S13). At the MP2/ADZ level, both PCM and PCM + H_2O solvent methodologies predict the zwitterion $\text{N}^3\text{p-}(\text{DD-AA})$ to be a stable minimum with computed NO dissociation barriers of 8.2 kcal/mol and 10.6 kcal/mol, respectively. Both barriers, particularly the latter, are very near to the seven-water result of 9.5 kcal/mol showing an overall concordance, and reliance, of the solvent modeling techniques used here. However, the MP2/ADZ [PCM] and MP2/ADZ [PCM + H_2O] dissociation energies are slightly larger (Figure 2c) than the seven-water result. Nonetheless, the rate of dissociation is expected to be guided by the height of the TS barrier rather than the exothermicity of the reaction, particularly since the nature of the separated products means reversibility is unlikely. Therefore, we are confident that at the MP2/ADZ level the PCM and (in particular) the PCM + H_2O methodologies will accurately describe relative rates of decomposition when applied to other, larger, amine-based NONOates.

Protonation sites and dissociation activation energies

As Houk and colleagues have shown, although NO dissociation is initiated by protonation of the amine, other protonation sites are energetically preferred.^{14,16} Figure 3 shows optimized geometries (MP2/ADZ [PCM + H_2O]) and relative electronic energies computed here for the various protonated DD-AA species (MP2/ADZ [PCM] structures and relative energies given in Supplementary Figure S14). While we are confident to have found lowest-energy structures at the MP2/ADZ [PCM] level, for the MP2/ADZ [PCM + H_2O] computations we have located lowest-energy structures whereby the water molecule was uniformly placed as to be simultaneously hydrogen-bonded to the terminal nitrogen atoms or their associated protons. This approach, which is also used for the secondary amine species described later, was chosen after careful analyses of the multiple-water systems.

While the MP2/ADZ [PCM + H_2O] structures (Figure 3) are not global minima, we feel that the explicit water is most uniformly mediating amine protonation and NO dissociation. As expected, protonation of DD-AA is preferred at the O^2 site followed by the O^1 and N^2 locales. Amine protonation is least likely and the corresponding NO dissociation $\text{N}^3\text{p-TS}$ lies some 27 kcal/mol above the lowest-energy O^2p species - the significance of the value of this activation energy in terms of the likelihood, or rate, of decomposition will become apparent later.

In the previous section we have probed the solvent effect upon the NO dissociation barrier height relative to the amine-protonated zwitterion minimum; however, as just indicated, the total activation energy to be overcome should be determined relative to the O²p species. Since the amine-based NONOates have had their NO release rates measured under physiological conditions represented by 0.1 M pH 7.4 phosphate buffer at 37 °C, we expect that amine protonation (leading to NO dissociation) will compete with O² protonation via solvent-mediated proton transfer, i.e., the ratio of the concentrations of the O²p and N³p species is a Boltzmann measure of their energy difference.

Modeling NO release rates of secondary amine NONOates

We have specifically opted to test our approach - computation of O²p → N³p-TS activation energies in the manner described above - using secondary amine NONOates since they only have a NO release dissociation route, i.e., there is no competing HNO release pathway. As such, their experimentally-determined NO release rates are expected to be reliable and unambiguous. Figure 4a shows the seven species studied here (all alkyl derivatives) together with their measured dissociation half-lives ($t_{1/2}$)^{5,46} which range from a few seconds to about an hour under physiological conditions. For each system we have located the lowest energy O²p and N³p-TS structures at the MP2/ADZ [PCM] level of theory whereby all alkyl configurations, rotations about the single N³-N¹ bond, and N³N¹N²-O¹/O² torsional angles were considered (Supplementary Figure S15) with the only proviso that piperidine derivatives had the chair conformation with equatorial methyl and N(O)NO groups (Supplementary Figure S16). With regard to the O²p geometries the NNN plane was perpendicular to the N³ lone pair (direction) for PYRRO/NO, DMA/NO, and PIPERIDI/NO but eclipsed (in line) for the other species. All N³p-TS structures had the H-(NN)-N atoms in almost eclipsed arrangements. When a water molecule was added, i.e., at the MP2/ADZ [PCM + H₂O] level, all O²p and N³p-TS structures had eclipsed H-(NN)-N arrangements and alkyl groups were found to have equivalent conformations to those of the MP2/ADZ [PCM] computations (Figure 4b). Additionally, for the N³p-TS structures we located two essentially degenerate 'left' and 'right' hydrogen-bonded orientations of the water molecule (lowest-energy structures shown in Figure 4b).

For each system we have computed the following O²p → N³p-TS activation energy (E_a) quantities: i) electronic energy difference ($\Delta E_e^\ddagger$), ii) zero-point energy difference ($\Delta E_0^\ddagger$), iii)

change in enthalpy at 310 K ($\Delta H_{310}^\ddagger$), and iv) change in Gibbs free energy at 310 K ($\Delta G_{310}^\ddagger$) (Supplementary Tables S3, S4). Rearranging the Arrhenius equation:

$$k = Ae^{-E_a/RT} \rightarrow E_a = (-\ln k + \ln A) * RT, \quad (1)$$

where $k = (\ln 2/t_{1/2})$ is the dissociation rate constant (s⁻¹), implies that a plot of E_a vs. $-\ln k$ will yield a straight line with slope $RT = 0.62$ kcal/mol if the pre-exponential factor A is equivalent for all secondary amine NONOates studied here.

Figure 5a illustrates the results obtained at the MP2/ADZ [PCM] level. We find that the best correlation is observed using the electronic energy difference $\Delta E_e^\ddagger$ (Pearson $R^2 = 0.57$) while the other three thermochemical quantities, which are all similar and 1–2 kcal/mol lower, have slightly smaller correlations (R^2 values of 0.46 – 0.54). In all cases the DEA/NO and DIPA/NO NONOates appear to be the outliers. Although slopes of best fit lines ($m = 0.23 - 0.29$) are somewhat lower than the value of $RT = 0.62$ they are of a similar magnitude. When an explicit water molecule is added to formulate the MP2/ADZ [PCM + H₂O] level of theory, the results are significantly improved as shown in Figure 4b. Once more, use of $\Delta E_e^\ddagger$ for the activation energy provides the best correlation with a very high R^2 value of 0.94

while the other thermochemical quantities, again very similar and lower by 1–2 kcal/mol, also show very good correlations (R^2 values of 0.78 – 0.91). Furthermore, slopes of best fit lines for the $\Delta E_e^\ddagger$, $\Delta E_{0^\ddagger}$ and $\Delta H_{310}^\ddagger$ quantities ($m = 0.61 - 0.72$) are in excellent agreement with RT . It is unclear why the computed $\Delta G_{310}^\ddagger$ values are the least performing while the corresponding $\Delta H_{310}^\ddagger$ energies fare very well; perhaps the calculation of entropies introduces undesired variability. In fact the most ‘raw’ quantity, the electronic energy difference $\Delta E_e^\ddagger$, provides the best correlation. These values essentially form a straight line, except for the DEA/NO outlier, prompting us to re-determine its dissociation half-life; however, an identical measurement to that previous was obtained. In reality all species have continuous motions about rotatable bonds and, therefore, they do not exist in single lowest-energy configurations. In this regard DEA/NO likely has more conformational flexibility than the other species; however, accounting for this consideration is not straightforward. The lesser reliability of the other thermochemical quantities may arise from their additional reliance upon vibrational frequencies which are expected to be more challenging to compute accurately. It is also very probable that anharmonic effects are non-negligible for these flexible systems, particularly the transition states.

It is of interest to analyze the $O^2p \rightarrow N^3p$ -TS activation energies in terms of their two stepwise components: i) $O^2p \rightarrow N^3p$, and ii) $N^3p \rightarrow N^3p$ -TS. The N^3p minimum-energy structures and energies were computed by optimizing on N^3p -TS structures (MP2/ADZ [PCM + H_2O]) whereby the N^3-N^1 and N^1-N^2 bond lengths were compressed slightly (Supplementary Table S5). Figure 5c shows that the component electronic energy differences correlate less with the rate constants than the total electronic activation energies. While the $N^3p \rightarrow N^3p$ -TS transitions are seen to account for the bulk of the variability in dissociation rates, clearly it is the total $O^2p \rightarrow N^3p$ -TS activation energy that should be considered in order to obtain the most reliable results.

CONCLUSIONS

The simplest amine-based NONOate, DD-AA, is shown to spontaneously dissociate NO in the gas phase upon amine protonation – a result obtained using three levels of theory including two very nearly benchmark. In contrast, as quantum mechanical water molecules are added one-by-one, the amine-protonated zwitterion species is increasingly stabilized whereby a transition state to NO dissociation is enhanced. Use of the PCM model, without and with an explicit water molecule, produced results comparable to that of the seven-water full quantum computation.

Modeling dissociation kinetics of seven secondary amine NONOates at the MP2/ADZ [PCM + H_2O] level provides an excellent correlation ($R^2 = 0.94$) between previous experimentally measured NO release rates (under physiological conditions) and computed electronic activation energies. The results show that, as Houk and coworkers have inferred earlier,^{14,16} the appropriate activation energy to consider is that describing the $O^2p \rightarrow N^3p$ -TS transition, i.e., use of the lowest-energy protonated species as the starting point; however, one should be careful to locate the lowest-energy conformations. In fact, a near-perfect correlation is obtained here, with the DEA/NO species being the only outlier. The results confirm that the current simplistic approach is closely approximating the experimental environment and corresponding energetics, at least in a relative sense, when in reality the solvent and solute molecules exist in a complex ensemble of all possible structures and conformations over Boltzmann averages. It is probable that DEA/NO and other species would be more accurately modeled by kinetically considering other low-lying conformations but this is difficult to accomplish in a consistent way.

Although the MP2 and PCM methodologies have been used in this work, a careful analysis of the performance of other quantum mechanical methods, e.g., density functional theory (DFT), and solvent modeling techniques, e.g., solvation model density (SMD)⁴⁷ and effective fragment potential (EFP),^{48,49} is of interest. In fact, since the solvent clearly affects the kinetics for the systems studied here, perhaps they could serve as a standard test bed for current and future solvent modeling methodologies. However, in the present case appropriate transition state structures do not exist in the gas phase, therefore, direct optimizations of stationary points within the solvent modeling treatment are necessary.

To some extent, the current study was initiated in order to discover the properties of DD-AA which, remarkably, has never been synthesized. The most reliable electronic activation energy computed here of some 27 kcal/mol implies, from Fig. 5b

($\Delta E_c^\ddagger = 0.72 * (-\ln k) + 19.03$), that DD-AA should have a NO release half-life of approximately 10 hours under physiological conditions, i.e., it is expected to be a very poor NO delivery system. We eagerly await the results of future experiments that will reveal the reliability of our prediction. Further work will look at the dissociation kinetics of primary amine NONOates which have competing NO- and HNO-dissociation pathways; the rate of each being very difficult to experimentally measure accurately. By computing NO release rates and HNO release activation energies, total experimental decomposition speeds can be factored into NO vs. HNO production rates. In this way, potential prodrugs having tailored NO and/or HNO release rates can be quickly and efficiently realized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Computational results for gas phase decomposition of DD-AA. (a) Minimum energy path (MP2/QZ) of spontaneous NO dissociation upon amine protonation. (b) Predictions of energy release using medium- (MP2) and very-high-level theories with a range of basis sets.

Figure 2.

Solvent effects upon the kinetics of NO dissociation from N³p-DD-AA. Optimized MP2/ADZ structures of the zwitterion minimum, transition state, and dissociated products (solute atoms highlighted in green) with three (a) and seven (b) solvent water molecules. The order of the successively added three water molecules is indicated in (a). (c) Predictions of electronic barrier heights and dissociation energies when i) incorporating explicit quantum water molecules (one to seven), and ii) using the PCM model (without and with one water molecule).

Figure 3. Structures and relative energies (kcal/mol) of various DD-AA protonated species. MP2/ADZ [PCM + H₂O] optimized geometries and energies relative to the most stable O²p system are shown (PCM (without water) values given in parentheses). The sequence leading to NO dissociation is also indicated.

Figure 4.

The secondary amine NONOates studied here together with their experimentally measured NO dissociation half-lives (a) and corresponding lowest-energy O²p and N³p-TS structures and electronic activation energies computed at the MP2/ADZ [PCM + H₂O] level of theory (b).

Figure 5.

Plots of $-\ln$ (dissociation rate constant: k) vs. $O^2p \rightarrow N^3p\text{-TS}$ activation energy quantities computed at the MP2/ADZ [PCM] (a) and MP2/ADZ [PCM + H_2O] (b) levels of theory; Pearson R^2 correlation coefficients and slopes of best-fit lines (m) also given. Panel (c) shows plots of $-\ln k$ vs. $O^2p \rightarrow N^3p$ and $N^3p \rightarrow N^3p\text{-TS}$ transition electronic energies (MP2/ADZ [PCM + H_2O]) together with correlation coefficients. Lines connecting the points only serve to clarify the data.

Scheme 1.
Nitric oxide release route of amine-based NONOates