N-Nitrosamide-mediated Ritter-type reactions. Part II.† The operation of "persistent steric" and "π*-acceptor agostic-type" effects

Ron W. Darbeau,* Rebecca S. Pease,‡ Edson V. Perez,§ Rebekah E. Gibble,¶ Faith A. Ayo‖ and Aaron W. Sweeney‖

Department of Chemistry, McNeese State University, Lake Charles, LA 70609, USA. E-mail: rdarbeau@mail.mcneese.edu

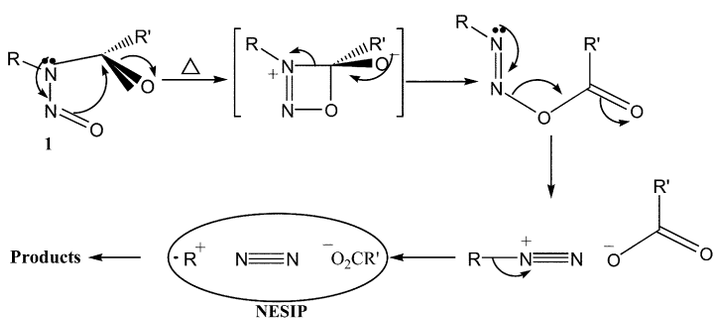
Received (in Cambridge, UK) 2nd May 2002, Accepted 17th September 2002
First published as an Advance Article on the web 24th October 2002

Benzyl cations were generated *via* thermolysis of *N*-benzyl-*N*-nitrosopivalamide in molten 2-R-substituted benzonitriles (R = MeO, Me, H, F, Cl, and Br). The corresponding *N*-2-R-benzonitrilium species, in contrast to their 4-R-benzonitrilium counterparts, underwent limited reaction with pivalate ion to form unsymmetrical diacylamines via rearrangement of their initial imidic anhydrides. The yield of diacylamines, though small, varied systematically with the nature of the R group in a manner suggesting the operation of interesting steric and/or electronic effects on the pivalate ion-nitrilium ion collapse. The ortho-substituent, though present on only one side of the benzonitrilium ion inhibits reaction at both sides via steric hindrance in the near-ground state and steric crowding in the transition state (a "persistent steric" effect). The proposed electronic effect involves a π*-acceptor agostic-type interaction between n or σ electrons (HOMO) and the π* system (LUMO) of the nitrilium ion. Additionally, in many cases, attack by water on the nitrilium ion occurred to a significantly larger extent than attack by the much more nucleophilic and positionally favored pivalate ion on the same species. This observation is interpreted in terms of the differences in the sizes and docking trajectories of both species with the nitrilium ion due to charge and charge distribution on both nucleophiles.

Introduction

The *N*-nitrosoamide-mediated Ritter-type reaction[1a–c] involves thermolyses of *N*-alkyl-*N*-nitrosoamides in molten nitriles. The nitrosoamides' decomposition generates *n*itrogenous-*e*ntity *s*eparated *i*on-*p*airs (NESIPs; eqn. (1)) containing highly reactive carbocations that are competitively scavenged by their nascent counterion and by the solvent.[2,3] The latter reaction reversibly derives nitrilium ions[1a–c] that are themselves attacked by moisture to yield amides, or by the nascent counterion to form imidic anhydrides that isomerize into diacylamines (DAAs) (Scheme 1).[1a–c] The reaction is a variation of the Ritter reaction but differs in the source and reactivity of the carbocation (deamination *vs.* alcohol protolysis), the primary scavenger of the nitrilium ion (carboxylate ion *vs.* water) and the major product (DAA *vs.* amide).[1a–c]

In a previous study,[1a,b] nitrosoamide **1** was allowed to decompose in 4-R-benzonitriles (R = NH_2, Me_2N, MeO, Me, H, F, CF_3) at 60 °C and 90 °C. The yield of DAA rose from 0% (for R = NH_2) to 10.6% (R = H) then fell to 8.1% (R = CF_3) (Table 2, below).[1a,b] These data suggested that in general, electron releasing groups (ERGs) enhance the nucleophilicity of the nitrile N facilitating capture of the benzyl cation; however, they also later exert a yield-decreasing effect with respect to the DAAs by diminishing the electrophilicity of the sp-hybridized C of the nitrilium adduct. Conversely, electron-withdrawing groups (EWGs) diminish the yield of the nitrilium intermediate by reducing the nucleophilicity of the nitrilic N, but subsequently make the nitrilium ion more electrophilic. The %DAA is greatest for R = H since this group does not abate the kinetics of either the nitrile/benzyl cation, or the nitrilium/carboxylate reactions.[1a,b] Although the DAAs



(1)

† For Part I see ref. 1*a*.
‡ Currently a research associate/instructor in the Chemistry Dept, McNeese State University.
§ Currently a graduate student at The University of Texas at Dallas, Richardson, TX, USA.
¶ Currently a graduate student at The Pharmacy School, University of Louisiana at Monroe, LA, USA.
‖ Summer 2001 Louisiana Alliance for Minority Participation (LS-LAMP) Undergraduate Research Students at McNeese State University.

 DOI: 10.1039/b204255j

Table 1 Product distribution[a] from the decomposition of *N*-benzyl-*N*-nitrosopivalamide[b] in 2- and 4-tolunitrile at 60 °C[c]

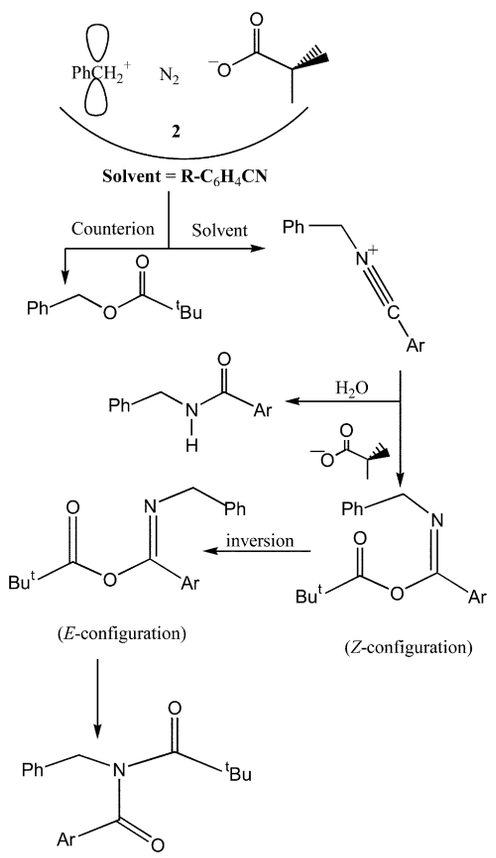
	Relative yield					
		Solvent-derived products				
Position	Ester	DAA	Benzyl benzamides	Benzyl alcohol	%SDP	% Benzamide of SDP
p-Me	86.4	10.7	2.9	0.0	13.6	21.3
o-Me	85.9	0.1	14.0	0.0	14.2	99.3

[a] Average of at least triplicate runs. Max standard deviations: ester ≈ 0.3; DAA ≈ 0.2; Amide ≈ 0.3; alcohol ≈ 0.2. [b] Concentration ≈ 0.045M. [c] Data taken from ref. 1a.

Table 2 Product distribution[a] from the decomposition of *N*-benzyl-*N*-nitrosopivalamide[b] in 2-R-C_6H_4CN at 60 °C

	Relative yield					
		Solvent-derived products				
R	Ester	DAA	Benzyl benzamides	Benzyl alcohol	% SDP	% Benzamide of SDP
Br	90.6	5.3	3.1	1.0	8.4	37.0
MeO	91.5	3.6	3.0	1.0	6.6	45.5
Cl	90.2	0.2	9.1	0.5	9.3	97.8
Me	85.9	0.1	14.0	0.0	14.2	99.3
F	92.8	3.2	3.6	1.0	6.8	52.9
H	84.5	10.6	4.9	0.0	15.1	32.5

[a] Average of at least triplicate runs. Maximum standard deviations: ester ≈ 0.3; DAA ≈ 0.2; Amide ≈ 0.3; alcohol ≈ 0.2. [b] Concentration ≈ 0.045M.



Scheme 1 Reaction pathways for nitrogen-separated ion-pairs in benzonitriles.

are minor products here, they warrant study because they are formed in highly reproducible quantities *via* a novel and mechanistically interesting pathway.

An engaging problem, for example, arose with respect to 2- *vs.* 4-Me-substitution in the benzonitrile. The DAA yields from reaction of the benzyl cation in 4-methylbenzonitrile is ~11%; however, the value falls abruptly by 100-fold to 0.1% when 2-methylbenzonitrile is employed as the solvent (Table 1). Because the polarities and other relevant bulk physical properties of the 2- and 4-methylbenzonitriles are likely to be very similar, the significant diminution in DAA yield is probably derived from interactions on the molecular level. One immediate possibility is the exertion of steric hindrance by the 2-Me group on the approach of the pivalate ion to the nitrilium C.

Our hypothesis in the previous paper[1a,b] was that the nucleophile is obliged to attack in the plane of the aromatic nucleus since the perpendicular p_C-orbital of the C–N π* orbital is unavailable (or less available) because of resonance interaction with the aromatic nucleus (Fig. 1).[1a,c] Consequently, nucleophilic attack on the nitrilium ion is prone to steric hindrance by groups, *e.g.*, methyl, at the *ortho* position. Interestingly, even though only one of the approaches to the nitrilium C is completely impeded, almost no attack from the other side occurs as evidenced by the low yield of DAA. Since only one of two faces is inactive, a ~50% decrease in yield would have been expected based solely upon statistical grounds. The virtual absence of DAA here suggests that the methyl group may be causing more than just steric hindrance of the approach of the nucleophile during its attack on the nitrilium ion. The question arises as to the nature of this additional effect that impedes nucleophilic attack even at the sterically available site.

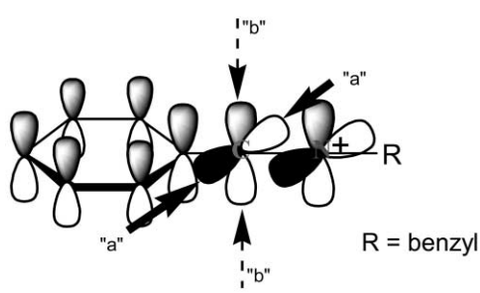


Fig. 1 A simple view of the orientation of the p-orbitals in benzonitrile showing the pathways of approach of pivalate to the nitrilium C. Pathway "a" is favored because the p-orbital on the *ipso* C is orthogonal to the plane of the aromatic sextet.

The present investigation was undertaken to detail the phenomenon and to elucidate the mechanism behind this severe diminution of %DAA in the *o*-substituted benzonitriles. Nitrosoamide **1** was again used as the source of the benzyl cation in this study because of its convenient rate of decomposition [1a,b] arising from steric acceleration of the rearrangement step (eqn. (1)) by the *tert*-butyl group.[4] 2-R-Benzonitriles (R = F, Cl, Br, H, Me, and MeO) were used as solvents; the R-groups were chosen to elucidate any steric and/or electronic effects involved in the reaction.

Possible modes of deactivation of nucleophilic attack on 2-R-benzonitrilium ions by the 2-R-substituent

The diminished yield of DAA is likely due to reduced attack by pivalate on the nitrilium carbon ostensibly arising from some effect [electronic (resonance, inductive, field), steric, and/or orbital interactions]** [5] exerted by the *o*-substituent. It can be reasonably argued that the pure, classical (through-bond) resonance effect for a given substituent in the *para* position would be very similar to that in the *ortho*-position. To the extent that this is true, then the diminution in the yield of the 2-methyl- vs. the 4-methylbenzonitrile case does not arise from differences in classical resonance effects. Similarly, induction is unlikely to be a significant cause of the effect because it should have little impact on the nucleophilicity of the nitrilic N (in the nitrile) four bonds away or on the nitrilium C (in the nitrilium ion) three bonds away. It is likely that the coupled π-system of the aromatic nucleus and the nitrile (nitrilium) facilitates the transmission of field effects. The impact of these effects on the course of these reactions is also likely to be small, however, because (1) the methyl group is very weakly polar and (2) the field effect would enhance the electrophilicity of the nitrilium C, but diminish the reactivity of the nitrilic N. The result, again would be little variation in %DAA.

It would appear then that none of the recognized electronic effects would be largely responsible for the observed diminution of %DAA in the 2-Me case. Indeed, the results would then have to be explained purely on the basis of steric and/or orbital effects; alternatively, the intervention of another type of electronic effect may be at work.

A steric argument: a "persistent steric" ("persisteric" effect)?

One possible explanation for the severe diminution of %DAA in the *o*-tolunitrile case involves the ability of the methyl group to sterically perturb nucleophilic attack in both the near-ground and transition states of the nitrilium ion–pivalate ion reaction. The near-ground state steric effect has already been discussed in terms of hindrance to the approach of the counter-ion on the proximal face of the nitrilium ion (obscured by the methyl group). However, when nucleophilic attack occurs at the face of the nitrilium ion distal to the Me group, a second steric role may be played by the Me substituent. During such attack, the sp-hybridized nitrilium C must become sp^2-hybridized in the formation of the imidic anhydride. This rehybridization requires (1) deposition of an electron pair on the nitrilium N and the concomitant removal of the positive charge on the latter. Additionally, (2) the linear C–N system is required to recoil from the attacking nucleophile and lean toward the *o*-substituent. The latter effect would produce significant steric crowding in the transition state of the reaction. The result then would be diminished nucleophilic attack even at the apparently sterically open distal face.

In this scenario, the same Me group exerts (1) steric hindrance to the approach of the nucleophile during the latter's reaction on the proximal face of the nitrilium ion in the near-ground state. But, it also subsequently generates (2) steric crowding in the transition state from nucleophilic attack on the distal face of the nitrilium ion. We suggest that this ability of a given group to affect a given reaction in both the near-ground and transition states by sterically diminishing reactions at multiple sites of the same reagent in different ways be called a "persistent steric" or "persisteric" effect. We have not been able to identify any other case of such an effect.

An electronic argument: σ ⟶ π* agostic-type interactions?

An intriguing alternative hypothesis regarding diminution in %DAA involves a type of through-space delocalization of an appropriately oriented C–H σ electron pair over the π system of the nitrilium ion. This effect is analogous to agostic interactions [6a,b] between C–H σ electrons and appropriate intramolecular Lewis acid transition metal centers (*vide infra*; Fig. 2a). Whereas Green's phenomenon deals with permanent

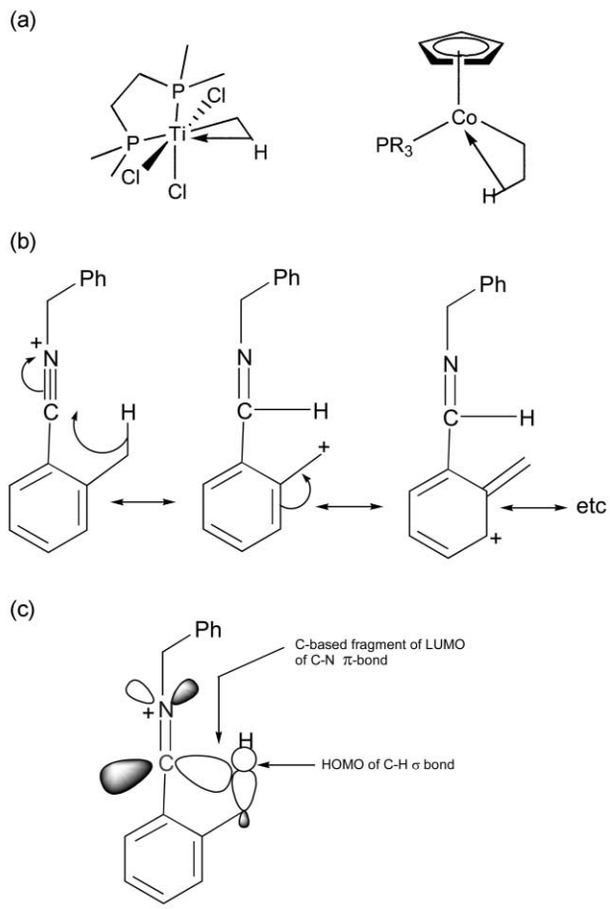


Fig. 2 (a) Examples of organometallic complexes showing agostic interactions. (b) Curved arrow representation of "bridging" hyperconjugation between the methyl and nitrilium carbons in the *o*-methylbenzonitrilium ion. (c) Molecular orbital representation of "bridging" hyperconjugation between the methyl and nitrilium carbons in the *o*-methylbenzonitrilium ion.

σ ⟶ d interaction in stable compounds,[6a,b] we postulate transitory σ ⟶ π* interactions in metastable species in the present case. The fact that the recipient orbital is π-type could also classify the proposed electronic effect as "through-space hyperconjugation" in the sense that σ electrons would be delocalized over a π framework (Figs 2b,c). In this model, which can be illustrated using a curved arrow perspective (Fig. 2b) or an orbital one (Fig. 2c), electron density from the HOMO (σ) of a suitably oriented C–H bond is donated to the LUMO

** The inherent difficulties of identifying, isolating, and quantifying the complex roles that *o*-substituents play in dictating the course of reactions at sites α to the aromatic nucleus, but attached to the *ipso*-carbon are well known.[5a–e] This work does not attempt to comprehensively rationalize this issue; indeed it is doubtful that a simple unified approach to this problem can be found.

(π*) of the C–N bond coplanar with the aromatic skeleton (Fig. 1).

This ordinarily forbidden σ ⟶ π* interaction would appear to be encouraged by the following factors: (1) the transition state for such an interaction is an inherently stable, planar 5-membered ring, (2) the canonical form with the electron-deficient benzylic entity is stabilized by resonance involving the aromatic nucleus (Fig. 2b), (3) the low electron density and hence high electron demand of the nitrilium carbon which makes it an appropriate "sink", and (4) the carbon-based portion of the LUMO of the appropriate C–N π-bond has a relatively swollen lobe leaning toward the *o*-substituent making it capable of extending into interacting distance with the homophasic σ orbital of the C–H bond (Fig. 2c).

To the extent that such sharing of electron density is occurring, then the nitrilium C in the *o*-methylbenzonitrilium ion is already involved in significant intramolecular bonding and is essentially unavailable (at either lobe) for bimolecular interaction with pivalate to form DAA. In this scenario, the *ortho*- methyl group's ability to minimize the yield of DAA results from its exertion of (1) steric hindrance to the approach of the nucleophile, (2) electronic compromising of the sterically available lobe of the p-orbital (i.e. the one distal from the *o*-Me), and (3) orbital effects to deactivate the nitrilium C to nucleophilic attack [although this is related to point (2)].

If this interpretation is true, it is noteworthy that the behavior and effect of an *o*/*p*-methyl substituent relative to the *ipso* nitrilium moiety depends upon its specific position on the aromatic nucleus. Thus, in the *para*-position it behaves as an ERG presumably involving isovalent hyperconjugation where the methyl H's are *protonic*.[7b,d] In the *ortho*-position, it apparently exerts both a steric effect and an electronic one. In the electronic one, however, there would be a type of *umpolung* since in this position, the methyl Hs would be *hydrido-type*. Additionally, the H is not shown "dislodged" from the molecule's framework but "bonded" to another site in the molecule. In all likelihood the H would probably be involved in some degree of bridging between the methyl and nitrilium carbon atoms. Consequently, we suggest the term "*hy*drido-*brid*ging hyperconjugation" or "*hybrid* hyperconjugation" to describe the phenomenon. This "through-space hyperconjugation" is distinct from the usual "through bond" phenomenon.[7] Evidently and quite reasonably, regardless of the type of hyperconjugation and the dipole on the H, the result is always the shunting of electron density to the electron-poor site in the ion.

Sigma ⟶ pi* agostic interactions

Agostic effects are through-space interactions of a C–H bond on a ligand with low-lying d-orbitals on the metal center in a complex.[6a,b] The bonding is often described as a sigma complex of an alkane with a metal.[6c–e] Examples of molecules showing agostic interactions are shown in Fig. 2a. These interactions are easily detected by ^{1}H NMR via (1) significant shielding of the methyl Hs (typically at δ −5 to −15 ppm)[6d,e] and (2) $J_{C/H}$ coupling values of ~70–100 Hz vs. the ~125 Hz typical of sp^3 hybridized carbons.[6d,e] Reduced C–H stretching frequencies are also often observed in the IR.[6d,e]

Unfortunately although organometallic complexes with agostic interactions are stable, isolable entities for which spectroscopic evidence of the σ ⟶ d interactions can be obtained,[6] the proposed interactions in the present case are transient. Nonetheless, to the extent that through-space σ_{C-H} ⟶ d interactions are known, the postulation of σ_{C-H} ⟶ π* interactions have the benefit of precedence. Whether these interactions are labeled "σ_{C-H} ⟶ π* agostic-type", "through-space hybrid hyperconjugation" or some other appropriate name would, in this author's opinion, be subsidiary to the larger matter of an interesting and novel electronic effect that may have significant impact on our understanding and interpretation of physical organic phenomena.

Results

Decomposition of *N*-benzyl-*N*-nitrosopivalamide (1) in *o*-substituted benzonitriles

To test the veracities of the steric and electronic arguments, nitrosoamide **1** was allowed to decompose in a variety of other 2-R-substituted benzonitriles (R = F, Cl, Br, MeO) at 60 °C. The series of substituents was chosen (in lieu of say R = Me, Et, ^{n}Pr, ^{i}Pr, ^{t}Bu, etc.) because (1) both the electronic and steric properties of the groups vary allowing the opportunity to elucidate the potential presence of and interplay between both candidate effects. Additionally, (2) there is a paucity of available 2-R-substituted benzonitriles with melting points around 60 °C.

The yields of DAA were determined by ^{1}H NMR spectroscopy by looking specifically at the benzylic methylene protons of the mixed diacylamines at δ 4.77 to 4.83. The data in Table 2 show that the yield of DAA[1a,b] rises in the order (R =) Me < Cl < F < MeO < Br < H.

Discussion

In the Taft relationship, $\log(k_R/k_H) = \delta E_s$,[8] k_R and k_H are rate constants, and E_s is a steric term derived from the Van der Waals radius of the substituent.[8,9] One immediately striking feature of this result is that the DAA yields fall as the size of the *ortho* substituent (as measured by E_s) increases (Table 3). Since the yields of DAA are related to their rates of formation then a given "*k*" term may be replaced by the corresponding "%DAA".[1a,b,2b] Hence we may employ a modified Taft-type equation as $\log[\%DAA_{(R)}/\%DAA_{(H)}] = \delta E_s$. A plot (Fig. 3) of $\log[\%DAA_{(R)}/\%DAA_{(H)}]$ *vs.* E_s of our data (Table 3) yields a straight line with good correlation ($R^2 = 0.940$) suggesting that the relative yields of DAA and their relative rates of formation depend directly upon the sizes of the groups in 2-R position. The implication therefore is that a steric effect (ostensibly the persisteric one) is operational and dominant in these Ritter-type reactions of 2-R-benzonitriles.

Interestingly, however, plots of the data using the modified Taft equation (*vide supra*) are better fit ($R^2 = 0.965$) to a binomial curve. Indeed, when other steric parameters including Meyer's V[a,9b] and Charton's ν[9c] are employed in lieu of E_s, the double log plots are also best described by smooth curves (Figs. 4 and 5; $R^2 = 0.982$ and 1.000, respectively). One interpretation of the nonlinearity of these plots is that there exists another factor superimposed upon the persisteric one that influences the course of the reaction. Additionally, from the linearity in Fig. 3 but its absence in Figs 4 and 5, the E_s

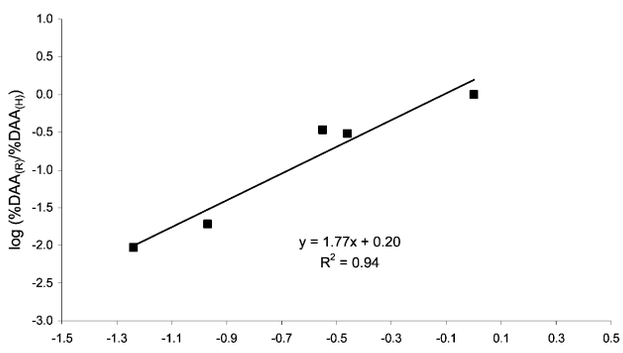


Fig. 3 Plot of $\log[\%DAA_{(R)}/\%DAA_{(H)}]$ *vs.* E_s for the decomposition of *N*-benzyl-*N*-nitrosopivalamide in 2-R-benzonitriles.

Table 3 Steric effects of 2-R-substitution on the product distribution[a] from decomposition of *N*-benzyl-*N*-nitrosopivalamide[b] in 2-R-C_6H_4CN at 60 °C.

	Steric parameter[c]				
R	E_s	10^2V^a	v	%DAA[b]	log[%$DAA_{(R)}$/%$DAA_{(H)}$]
Br	—	—	0.65	5.3	−0.30
MeO	−0.55	3.39	—	3.6	−0.47
Cl	−0.97	2.84	0.55	0.2	−1.72
Me	−1.24	2.82	0.52	0.1	−2.03
F	−0.46	1.22	0.27	3.2	−0.52
H	0.00	—	0.00	10.6	0.00

[a] Average of at least triplicate runs. Maximum standard deviation: DAA ≈ 0.1; [b] Concentration ≈ 0.045M. [c] For values see refs 7 and 8.

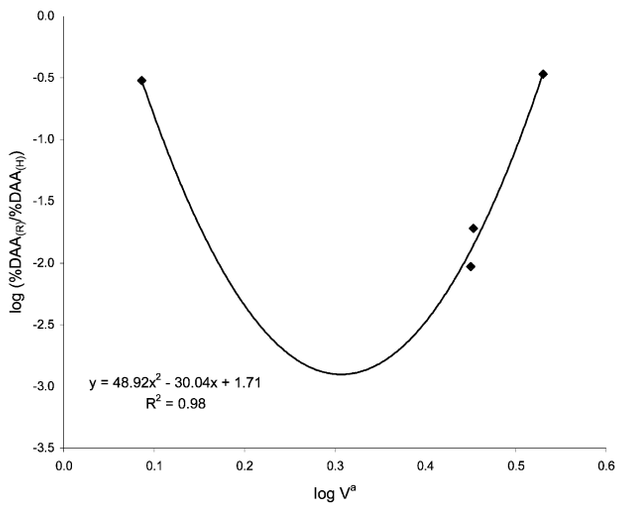


Fig. 4 Plot of log[%$DAA_{(R)}$/%$DAA_{(H)}$] *vs.* log V^a for the decomposition of *N*-benzyl-*N*-nitrosopivalamide in 2-R-benzonitriles.

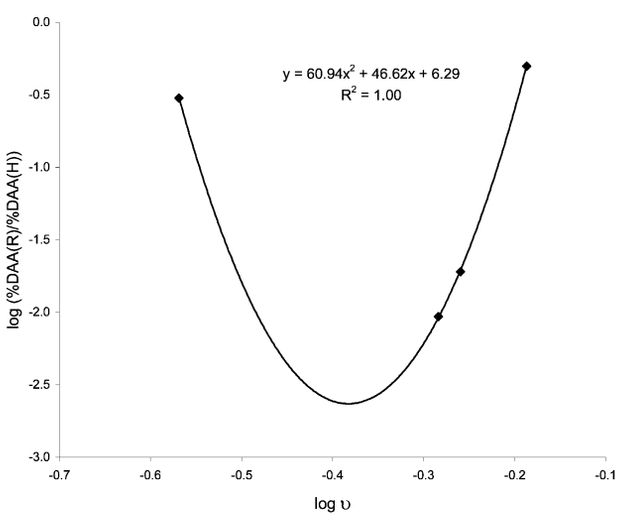


Fig. 5 Plot of log[%$DAA_{(R)}$/%$DAA_{(H)}$] *vs.* log *v* for the decomposition of *N*-benzyl-*N*-nitrosopivalamide in 2-R-benzonitriles.

term (but not the other two) is evidently quite insensitive to the influence of non-steric factors in the reaction (*vide infra*).

It is possible that this additional effect that results in the deviations from linearity in Figs. 3–5 is indeed π*-acceptor agostic interactions (*vide supra*) as proposed above for R = Me. Although a case can be made for the forbidden stereoelectronic requirements for σ ⟶ π* donation in that case, the question arises, however, as to its origin in the other cases. One other important question is why, even though Br is the largest group attached to the *ortho* position, it allows the formation of the second largest yield of DAA (Table 2, Fig. 5)?

We believe that the answers to both of these questions stem from agostic interactions involving not only σ ⟶ π* donation

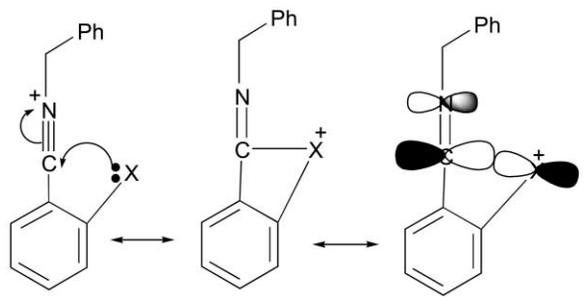


Fig. 6 Curved arrow and orbital representations of n to π* through space hyperconjugation between electron-rich 2-R substituents and the nitrilium carbon in the 2-R-benzonitrilium ions.

as for R = Me, but also from n ⟶ π* donation for substituents that have lone pairs on the atoms attached to the ring (Fig. 6). The ability of the heteroatom to effect n ⟶ π* donation would appear to depend upon its size and electronegativity (although these are not independent variables). Thus the large p-orbitals of Br possess poor complementarity of fit (due to dissimilar sizes and energies) with the C-based π* orbital of the C–N bond. Thus it is the least involved in agostic interactions resulting in an electronically unhindered nucleophilic attack at the distal position. The presence, however, of steric hindrance to nucleophilic attack from the face proximal to the Br as well as some steric crowding in the transition state due to mandatory rehybridization of the *ipso* carbon, serve to lower the yield below that of R = H.

The excellent complementarity between C–O and C–F orbital systems (C, O, and F are all mid to late second period elements) suggests the presence of significant n ⟶ π* agostic interactions in the R = MeO and F cases. Conversely, one would expect relatively poor p_{Cl}/p_C fit and diminished hyperconjugation in the R = Cl case. If this were the major operating factor, larger yields of DAA would have been observed in the R = Cl case. However, O and F are extremely electronegative atoms and are less adept at donating electron density than the larger Cl and so the potential for n ⟶ π* donation in the R = F, MeO cases is diminished leading to a relatively electronically uncompromised nitrilium ion and enhanced yield of DAA in the R = F, MeO cases relative to the R = Cl one.

It would appear then that the yield of DAA in these Ritter-type reactions is a complex function of the nature and position of the R group on the aromatic nucleus. Although a steric factor is operational, an electronic one made possible by π*-acceptor agostic interactions may also be involved.

A note on steric parameters[9d,e]

Taft's original E_s term has been shown by Charton to be a linear function of Van der Waals radii.[9f] There appears to be universal consensus on the validity of E_s as a steric parameter;[9e] the validity of the dozen or so terms that are derivatives of E_s (*e.g.*, E_s°, E_s^*, E_s', E_s^e, *etc.*,) remains in question, however.[9e] Another measure of steric effects that has been widely accepted

is Charton's ν term which, like E_s is a linear function of Van der Waals radii. Indeed, E_s and ν are related through:

$$\nu = \delta E_s + C$$

and excellent correlations between the two terms have been demonstrated.[9j] It would appear from the inversion of the shapes of the quadratic plots in Figs 4 and 5 that the δ term is negative under these circumstances.

Meyer's V^a values are derived from molecular mechanics calculations and are based upon the structure of the molecule and specifically upon the volume of the portion of the substituent that is within 0.3 nm of the reaction center.[9k] Like ν and E_s, it is also a function of van der Waals radii and Fig. 4 shows excellent correlation amongst these various steric terms. It would appear that a general equation of the type

$$a = \text{const.}_1(b) + \text{const.}_2$$

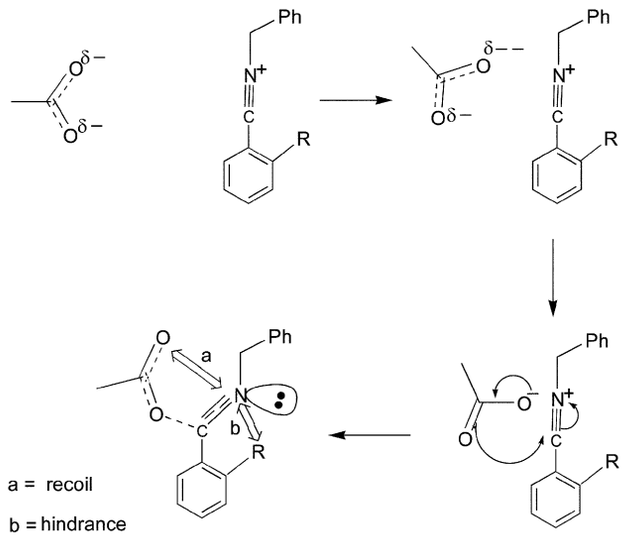
where a and b are steric terms is valid for the interrelationships among ν, E_s, and V^a. It is noteworthy again that of the three terms employed in these analyses, the E_s term is the least sensitive to non-steric effects operational in this reaction (*vide supra*).

The relative yields of amides versus mixed diacylamines

Despite large variation of the electronic effects of the R-group at the 4-position of the benzonitriles,[1a,b] the yield of amide relative to DAA (the SDPs) changes by a relatively small amount (Table 1).[1a,b] Thus the term (Δ%amide/$\Delta\sigma$) for the entire range ≈ 9.†† [1a,b] In the present case, however, where the R group is varied in the 2-position, not only are the yields of amide relative to SDP generally much higher, but the sensitivity of the %amide (with respect to the SDPs only) is also greater [(Δ%amide/$\Delta\sigma$) ≈ 72; Table 2).†† ‡‡

It can be easily argued that the smaller water molecule is sterically more adept than its bulkier competitor, pivalate, at scavenging the nitrilium ion. Consequently, larger yields of amides would be expected from this attack. The problem with this argument, however, is that the water molecules are present only in trace amounts in the medium (*i.e.*, external to the solvent cage) whereas the pivalate ion (from the first generation benzyl cation) is present in the solvent cage with the nitrilium ion (the second generation electrophile). Consequently, pivalate ions would appear to be both positionally and electronically favored over water to consume the nitrilium ions.

It has been previously argued [1a,b] that while still in the solvent cage, the nitrilium and pivalate ions must undergo significant relative motion to achieve the stereoelectronic requirement for the ion pair collapse to imidic anhydride.[1b,c] This delay before ion pair collapse allows adventitious water molecules to enter into bimolecular reaction with the nitrilium ion leading to enhanced yields of amides.[1a,b] Interestingly, however, with the *para* substituent the amide yields are relatively insensitive to significant variation in the electronic nature of the R group.[1a,b] Here, however, the amide yields are generally larger and more sensitive to the nature of R. The larger amide yields, as well as the wider range in amide yields, can be accounted for in terms of the docking trajectories of the nucleophiles attacking the distal face of the nitrilium ion.



Scheme 2 Trajectory of approach of a carboxylate ion to the nitrilium ion in formation of an electronically and sterically strained activated complex.

Scheme 2 depicts the likely approach of the negatively charged pivalate ion to the nitrilium ion. It is likely that the early approach of the anion to the cation would be dominated by electronic effects resulting in a reapportioning of the charge density on the carboxylate oxygens to maximize the electrostatic attraction between this anion and the positively charged nitrilium N (Scheme 2). Thus strong ionic forces are operational in defining the trajectory of approach of the pivalate ion. At some point the lagging O (with the initially smaller negative dipole), comes into bonding range of the p-orbital of the nitrilium carbon and a transfer of electron density (that is, bonding) occurs between the lagging O and the nitrilium C.

During this phase of the reaction, the originally positively charged N which has drawn the more negatively charged O closely to it, becomes electron rich again and the ensuing repulsion between the close, electron rich O and the now electron-rich N causes both atoms to recoil away from each other. The result is that with carboxylate attack on the nitrilium (leading to DAA formation) the transition state experiences significant electronic (electron rich O/N repulsion) and steric (close nitrilium/iminyl group to 2-R substituent) interactions that destabilize the activated complex and thus slow the reaction.

Conversely, in the advance of the electrically neutral water molecule upon the nitrilium ion, the water is probably initially more attracted to the nitrilium N, by virtue of ion–dipole interactions, but since no reasonable reaction can occur between these two sites, the water molecule (probably while still in the encounter complex with the nitrilium ion) may "slide" toward the receptive nitrilium C to begin reaction. Upon such reaction there will be no residual electron-rich particle near the rehybridizing and polarity reversing N (*vide supra*) and so no companion recoil occurs. Consequently, the transition state for aqueous interception of the nitrilium ion experiences neither the electrostatic nor the steric discomfort that is likely in the pivalate case.

The result is that carboxylate interception of the nitrilium ion (and hence DAA formation) is disfavored both on the proximal face of the 2-R substituent (a steric effect) as well as on the distal face (both an electronic and a steric effect). Here again, steric factors apparently exert an effect on the product distribution. Note that this persisteric effect was previously invoked to account for diminutions in DAA yield between the 2-R- and 4-R-benzonitriles (an "intermolecular electrophilic" selectivity). In the present incarnation, it is being used to

†† For groups that are ERGs *via* resonance σ_p^+values [12] are used; for those that are EWG *via* induction σ_p values [12] are employed.[1,2b]

‡‡ σ_p, σ_p^+ values [12] were used here assuming that the pure electronic effects of the substituents are similar in both the *o*- and *p*-positions. Although this assumption is dubious at best, it is clear from the data (Table 2 and Table 1 in ref. 1*a*) that the range of amide yields is larger in the 2-R case (Table 2) over a smaller range of what organic chemists generally understand as electron releasing to electron withdrawing ability.

account for differences in the yields of water-derived and carboxylate-derived product (an "intermolecular nucleophilic" selectivity).

Conclusion

2-R-Benzonitriles give rise to significantly diminished yields of solvent-derived products than do their 4-R-counterparts. The role of the 2-R-group in diminishing the formation of SDP is evidently an intriguing marriage of steric and electronic effects as well as orbital interactions. A novel kind of steric effect has been suggested in which a given group sterically affects a given reaction in both the near-ground and transition states by diminishing reactions at multiple sites of the same reagent in different ways. The terms "persistent steric" or "persisteric" effect have been coined to describe this apparently novel phenomenon. The nonlinearity of Taft and related plots of $\log[\%DAA_{(R)}/\%DAA_{(H)}]$ *vs.* appropriate steric terms (E_s, V_a and ν) based upon Van der Waals radii suggest, however, that the effect is not purely steric but that electronic/orbital factors may also be operational. Interestingly, the Taft-like plot is the least sensitive to non-steric modulation of the reaction kinetics since the data give a good fit to a straight line.

A novel kind of π*-acceptor agostic-type interaction is proposed in which $\sigma \longrightarrow \pi^*$ or $n \longrightarrow \pi^*$ donation of electron density between the *ipso* atom of the 2-R-substituent (or a bond from it) and the nitrilium C occurs. Such an interaction (a marriage between electronic and orbital effects) in which non-π electron density is delocalized through space over a π-system deactivates the nitrilium species toward reaction with external nucleophiles. The extent of this agostic effect ostensibly depends upon the size and electronegativity of the *ipso* atom (and the nature of the *ipso* atom–X bond).

Finally, the charge, charge distribution, and size of the nucleophile attacking the nitrilium ion appear to play a significant role in the former's docking trajectory with respect to the nitrilium C/N system. Consequently, both the yields and range of yields of amide from aqueous interception of the nitrilium ion are larger than the corresponding pivalate ion/nitrilium ion reactions.

Experimental section

Materials and methods

All commercial reagents were reagent grade and were used without further purification. Chemical shifts in the ^{1}H NMR spectra are reported in parts per million downfield from internal tetramethylsilane. Spectra were recorded on JEOL Eclipse$^+$ 300 MHz FT-NMR, Perkin Elmer 1600 Series FT-IR, and Beckman Model 25 UV–Vis spectrometers.

Stability of *N*-4-R-benzyl-*N*-nitrosopivalamides; handling and storage

N-Benzyl-*N*-nitrosopivalamide is thermolabile and unstable in the presence of acids, bases, and moisture; being photolabile it was handled in the dark. The dry, neutral oil was 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[10a] and carcinogenicity (local and systemic).[10b] Efficient fume hoods and appropriate personal protection (chemical-resistant gloves, safety glasses, lab coat, etc.) are recommended when handling these compounds.

N-Benzylpivalamide

N-Benzylpivalamide was prepared from the method of Heyns and von Bebenburg;[11] for physical data see ref. 2*b*.

N-Benzyl-*N*-nitrosopivalamide (1)

N-Benzyl-*N*-nitrosopivalamide was prepared from the method described in ref. 2a; for physical data see ref. 2a.

Decomposition of *N*-benzyl-*N*-nitrosopivalamide (1) in 2-, and 4-R-benzonitriles

In a typical run, ~75 μl of **1** was added to 750 mg of the appropriate nitrile in an opticlear™ vial. The sample was then placed in an oven at 60 °C for 1h (~ 12 half lives). The sample was taken out of the oven and 200 μl were removed and added to 400 μL of $CDCl_3$ in an NMR tube and NMR spectra were recorded. The products observed were benzyl pivalate (δ 5.10), N-aryl-N-pivaloylbenzylamine (~ δ 4.82), benzyl 2-R-benzamides (δ 4.65), and benzyl alcohol (δ 4.56). The methyl signals of the pivaloyl groups of the compounds in this study are indistinguishable from each other.

Acknowledgements

Acknowledgement is made to the Calcasieu Parish Industrial and Development Board Endowed Professorship administered by the McNeese State University Foundation, the Shearman Research Initiative administered by the Office of Research Services, MSU, The Louisiana Alliance for Minority Participation (LS-LAMP) & The National Science Foundation (NSF)/ Louisiana Education Quality Support Fund (LEQSF), and to the Chemistry Department, MSU for partial support of this research. The authors also wish to acknowledge the contributions of Dr George F. Mead, Jr., Dr August Gallo (Chemistry Department, University of Louisiana at Lafayette), Mrs Nyla R. Darbeau, and Ms Joan E. Vallee.

References

1 (*a*) R. W. Darbeau, R. E. Gibble, R. S. Pease, D. E. Bridges, L. M. Siso and D. E. Heurtin, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1084; (*b*) Rebecca E. Gibble, MS Thesis, McNeese State University, Lake Charles, LA, USA, 2001; (*c*) R. W. Darbeau, E. H. White, N. Nunez, B. C. Coit and M. J. Daigle, *J. Org. Chem.*, 2000, **65**, 1115.
2 (*a*) R. W. Darbeau, E. H. White, F. Song, N. R. Darbeau and J. C. Chou, *J. Org. Chem.*, 1999, **64**, 5966; (*b*) R. W. Darbeau, R. S. Pease and R. E. Gibble, *J. Org. Chem.*, 2001, **66**, 5027; (*c*) E. H. White, R. W. Darbeau, D. Chen, S. Chen and Y. Chen, *J. Org. Chem.*, 1996, **61**, 7986; (*d*) R. W. Darbeau and E. H. White, *J. Org. Chem.*, 1997, **62**, 8091; (*e*) R. W. Darbeau, M. S. Delaney, U. Ramelow and K. R. James, *Org. Lett*, 1999, **1**(5), 796; (*f*) R. W. Darbeau and E. H. White, *J. Org. Chem.*, 2000, **65**, 1121; (*g*) F. Song, R. W. Darbeau and E. H. White, *J. Org. Chem.*, 2000, **65**, 1825.
3 (*a*) E. H. White, J. T. De Pinto, A. J. Polito, I. Bauer and D. F. Roswell, *J. Am. Chem. Soc.*, 1988, **110**, 3708; (*b*) E. H. White, K. W. Field, W. H. Hendrickson, P. Dzadzic, D. F. Roswell, S. Paik and P. W. Mullen, *J. Am. Chem. Soc.*, 1992, **114**, 8023; (*c*) E. H. White, R. H. McGirk, C. A. Aufdermarsh, H. P. Tiwari and M. J. Todd, *J. Am. Chem. Soc.*, 1973, **95**, 8107.
4 (*a*) R. Huisgen and C. Ruchardt, *Justus Liebigs Ann. Chem.*, 1956, **601**, 1; (*b*) E. H. White and L. A. Dolak, *J. Am. Chem. Soc.*, 1966, **88**, 3790.
5 (*a*) T. Fujita and T. Nishioka, *Prog. Phys. Org. Chem.*, 1976, **12**, 49; (*b*) M. Charton, *Prog. Phys. Org. Chem.*, 1971, **8**, 235; (*c*) P. Segura, *J. Org. Chem.*, 1985, **50**, 1045; (*d*) C. N. Robinson, J. L. Horton, D. O. Foshee, J. W. Jones, S. H. Hanissian and C. D. Slater, *J. Org. Chem.*, 1986, **51**, 3535; (*e*) M. Charton, *Can. J. Chem.*, 1960, **38**, 2493.
6 (*a*) M. Brookhart and M. L. H. Green, *J. Organomet. Chem.*, 1983, **250**, 395; (*b*) R. H. Crabtree and D. G. Hamilton, *Adv. Organomet. Chem.*, 1988, **28**, 299; (*c*) C. Elschenbroich; A. Salzer, in *Organometallics: A Concise Introduction*, 2nd edn. VCH, New York. 1992, pp. 267–8; (*d*) R. H. Crabtree, in *The Organometallic Chemistry of the Transition Metals*, 3rd Ed. Wiley-Interscience, New York, 2001, p. 74; (*e*) R. H. Crabtree, in *The Organometallic Chemistry of the Transition Metals*, 3rd edn. Wiley-Interscience, New York, 2001, p. 303.
7 (*a*) J. W. Baker, *Hyperconjugation*, Oxford University Press: Oxford, 1952; (*b*) M. J. S. Dewar, *Hyperconjugation*, Ronald Press: NY, 1962;

(*c*) P. B. D. de la Mare, *Pure Appl. Chem.*, 1984, **56**, 1755; (*d*) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 1935, 1840; (*e*) W. J. Hehre, R. T. McIver Jr., J. A. Pople and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1974, **96**, 7162; (*f*) E. M. Arnett and J. M. Aboud, *J. Am. Chem. Soc.*, 1975, **97**, 3865; (*g*) B. T. Cooney and D. A. R. Happer, *Aust. J. Chem.*, 1987, **40**, 1537; (*h*) T. Laube and T. Ha, *J. Am. Chem. Soc.*, 1988, **110**, 5511.

8 For reviews of quantitative treatments of steric effects see. (*a*) R. Gallo, J. Roussel and U. Berg, *Adv. Heterocycl. Chem.*, 1988, **43**, 173; (*b*) R. Gallo, *Prog. Phys. Org. Chem.*, 1983, **14**, 115; (*c*) S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, 1976, **12**, 91.

9 (*a*) M. Charton, *J. Am. Chem. Soc.*, 1975, **97**, 1552; (*b*) M. Charton, *J. Org. Chem.*, 1976, **41**, 2217; (*c*) D. F. DeTar, *J. Org. Chem.*, 1980, **45**, 5166; (*d*) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th edn., John Wiley and Sons, New York. 2001, pp. 374–5; (*e*) For an excellent review, see R. Gallo, *Prog. Phys. Org. Chem.*, 1983, **14**, 115; (*f*) M. Charton, *J. Am. Chem. Soc.*, 1969, **91**, 615; (*g*) H. Mager, P. P. Mager and A. Barth, *Tetrahedron*, 1979, **35**, 1953; (*h*) H. Mager, *Tetrahedron*, 1981, **37**, 509; (*i*) H. Mager, *Tetrahedron*, 1981, **37**, 523; (*j*) M. Charton, *J. Org. Chem.*, 1972, **37**, 3684; (*k*) A. Y. Meyer, *J. Chem. Soc.; Perkin Trans. 2*, 1986, 1567.

10 (*a*) K. Lee, B. Gold and S. Mirvish, *Mutat. Res.*, 1977, **48**, 131; (*b*) R. Preussman, B. W. Stewart *Chemical Carcinogenesis*, ed. C. Searle, ACS Monograph No. 182, American Chemical Society, Washington, DC, 1984, pp. 643.

11 K. Heyns and W. v. Bebenburg, *Chem. Ber.*, 1953, **86**, 278.

12 M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th edn., John Wiley and Sons, New York. 2001, p. 370.