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Structures of *N,N*-Dialkoxyamides: Pyramidal Anomeric Amides with Low Amidicity

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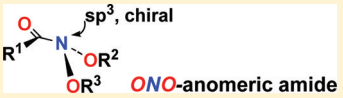
Supporting Information

ABSTRACT: The first X-ray structures of two anomeric *N,N*-dialkoxyamides (**2** and **3**) have been obtained, which confirm that they are highly pyramidalized at nitrogen and have long N−CO bonds, a characteristic of other anomeric amides and a consequence of drastically reduced amidicity. The crystals also demonstrate chirality at the amide nitrogen in the solid state. The structures are well-predicted by density functional calculations using *N,N*-dimethoxyacetamide as a model. The amidicity of *N,N*-dimethoxyacetamide has been estimated by two independent methods, COSNAR and a new transamidation method, which give almost identical resonance stabilization energies of −8.6 kcal mol^{-1} and only 47% that of *N,N*-dimethylacetamide computed at the same level. The total destabilization is composed of a resonance and an inductive contribution, which we have evaluated separately. The electronegative oxygens at nitrogen are responsible for localization of the nitrogen lone pair on the amide nitrogen, a factor that contributes to a loss of resonance over and above the impact of pyramidalization at nitrogen, as well as the fact that *N,N*-dimethoxyacetamide is predicted to protonate on the carbonyl oxygen in preference to nitrogen.

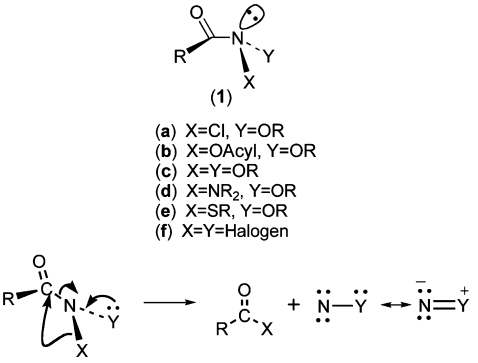


INTRODUCTION

Anomeric amides (**1a**−**f**) are defined as amides that are substituted at nitrogen with two electronegative atoms.[1] This configuration at nitrogen radically alters the amide characteristics since the electronegative requirements of the heteroatoms are best satisfied if the nitrogen assumes sp^3 hybridization in which the nitrogen lone pair becomes localized in a hybrid orbital. The reduced p-character results in vastly reduced amide resonance. In addition, by analogy with bis-heteroatom-substituted carbon, such amides usually exhibit ground-state anomeric effects through the amide nitrogen, which influence their conformation and reactivity. With a good leaving group at nitrogen (**1a** and **1b**), $n_Y-\sigma^*_{NX}$ overlap weakens the N−X bond and they can undergo both S_N1 and S_N2 reactions at the amide nitrogen.[2−10] With weaker leaving groups (**1d** or with **1b** in nonpolar solvents), the anomeric effect drives the unusual HERON reaction[11] in which anomeric destabilization results in migration of a substituent, X, from nitrogen to the carbonyl carbon with attendant formation of a Y-atom-stabilized nitrene (Scheme 1).[9,12−18]

Spectroscopic, theoretical, and structural evidence has been presented for a range of such amides (**1a**−**f**).[1,9,17] Notably, theoretical calculations on model structures predict a high degree of pyramidality at nitrogen (Winkler−Dunitz pyramidality indices[19,20] vary from χ = 32° for **1e** to 58° for **1b**), long C−N bonds that range between 1.40 Å for **1d** and 1.43 Å for **1a**, but relatively small twist angles about the C−N bond (τ ranges between 2 and 9°),[17] and these predictions are borne out by structural properties where these are available and by spectroscopic data.[1,9,17,21,22] While there is a significant lengthening of the C−N bond in anomeric amides, theoretical and structural data predict relatively small changes in the carbonyl bond lengths. However, this is well-known for many amides in which amide resonance is reduced by twisting about the amide bond[23−28] and reflects the contemporary view that amide resonance is best described as a HOMO−LUMO interaction between the lone pair on nitrogen and carbonyl antibonding orbital, which has its major contributor on carbon rather than oxygen (Figure 1a).[29] Reduction in amide resonance therefore impacts more upon the N−C bond than the C═O bond. The contribution of resonance form II to the hybrid (Figure 1b) is small. However, all anomeric amides exhibit relatively high carbonyl stretch frequencies in their infrared spectra (typically 1710−1770 cm^{-1}), and force constants appear to be more sensitive to the presence of electronegative substituents at nitrogen. While anomeric amides

Scheme 1



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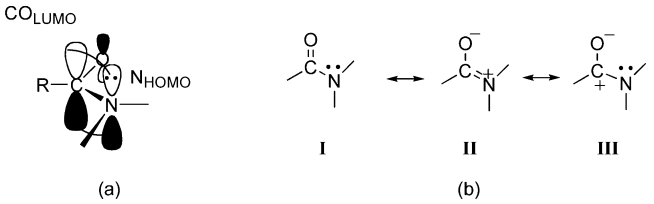


Figure 1. (a) Frontier orbital interaction and (b) resonance in simple amides.

exhibit greatly reduced amide resonance, the carbonyls are not ketonic as the ^{13}C NMR carbonyl resonances are some 30 ppm upfield of ketones and aldehydes and are more typical of esters or acid chlorides.[1,17] The triad of electronegative atoms adjacent to the carbonyl destabilizes the polar resonance form III (Figure 1b), and the best resonance representation of an anomeric amide is I in Figure 1b.

Anomeric amides **1** exhibit very different spectroscopic properties to those of amides with one heteroatom at nitrogen. For instance, the hydroxamic ester precursors to **1a−d** exhibit much lower carbonyl stretch frequencies (typically between 1650 and 1690 cm^{-1}), and unlike **1a−d**, many exhibit line broadening in their NMR spectra on account of high barriers to *E*−*Z* isomerization.[1,9,17,30−32]

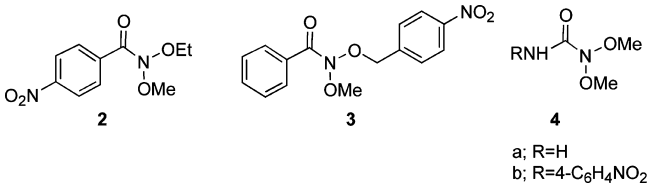
While theoretical, spectroscopic, and structural data for ONCl, ONOAc, and ONN systems have been reported, the properties of dialkoxyamides (**1c**) are less well-known. The spectroscopic properties of a limited number have been reported to date,[1,17,33] and the only crystallographic data available are for two urea analogues, *N*,*N*-dimethoxyurea (**4a**) and, very recently, its *N*′-4-nitrophenyl analogue (**4b**)[34,35] both of which possess a highly pyramidal dimethoxylated nitrogen attached by a long N−C bond but, on account of the competing α-amino group, are not fully representative of a pure anomeric amide.

In this paper, we report the first crystal structures of two *N*,*N*-dialkoxyamides and demonstrate that they exhibit all the hallmarks of true anomeric amides. In addition, we have determined computationally the extent of amide resonance in the model *N*,*N*-dimethoxyacetamide and show that *N*,*N*-dialkoxyamides are likely to have amidicity <50% that of *N*,*N*-dimethylacetamide.

RESULTS AND DISCUSSION

A limited number of *N*,*N*-dialkoxyamides have been synthesized by solvolysis of *N*-alkoxy-*N*-chloroamides in aqueous alcohol[1,13] or by the reaction of *N*,*N*-dialkoxyamines with acyl halides or isocyanates.[36] Following the recent discovery that hydroxamic esters can be readily oxidized to *N*-acyl-*N*-alkoxynitrenium ions by hypervalent iodine reagents,[37−42] we have found that, upon oxidation of hydroxamic esters in the presence of alcohols, either as solvents or as reagents in acetonitrile, *N*,*N*-dialkoxyamides can be made in synthetically useful yields and with short reaction times. We recently reported the synthesis, spectroscopic properties, and radical decomposition reactions of a number of congeners.[33]

While almost all *N*,*N*-dialkoxyamides made to date are oils at room temperature, we found that *N*-ethoxy-*N*-methoxy-4-nitrobenzamide (**2**) and *N*-methoxy-*N*-(4-nitrobenzyloxy)-benzamide (**3**), which were synthesized directly from *N*-ethoxy-4-nitrobenzamide and *N*-(4-nitrobenzyloxy)benzamide in methanol with phenyliodine[III]bistrifluoroacetate (PIFA),



were low-melting solids. **2** could be crystallized as colorless prisms by solvent displacement at low temperature using ethylacetate/hexane, while **3** crystallized as colorless needles directly from cold methanol at 10 °C. Both exhibited relatively high carbonyl stretch frequencies at 1708 (**1**) and 1709 cm^{-1} (**2**) in their chloroform IR spectra and some 20 wave numbers higher than their hydroxamic acid precursors. Their ^{13}C NMR carbonyl resonance frequencies were at 172 and 174 ppm, respectively, and at similar shifts to the analogous *N*-acyloxyl substrates, **1b**.[1,9,17]

X-ray structures of both *N*,*N*-dialkoxyamides are illustrated in Figure 2, and selected data are presented in Table 1.

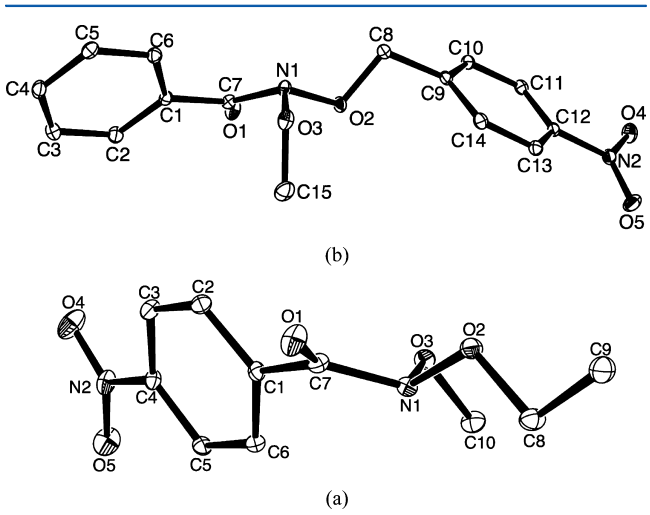


Figure 2. X-ray structures of (a) *N*-ethoxy-*N*-methoxy-4-nitrobenzamide **2** and (b) *N*-methoxy-*N*-(4-nitrobenzyloxy)benzamide **3**.

Table 1. Selected Structural Properties of *N*-Ethoxy-*N*-methoxy-4-nitrobenzamide 2, *N*-Methoxy-*N*-(4-nitrobenzyloxy)benzamide 3, and B3LYP/6-31G(d) Minimum Energy Structure for *N*,*N*-Dimethoxyacetamide 5 (Figure 4a)

parameter	2	3	5
$r_{C(7/1)O(1)}$ (Å)	1.206(3)	1.211(2)	1.212
$r_{C(7/1)N(1)}$ (Å)	1.409(4)	1.421(2)	1.417
$r_{N(1)O(2)}$ (Å)	1.393(3)	1.402(2)	1.391
$r_{N(1)O(3)}$ (Å)	1.418(3)	1.408(2)	1.406
$C_{(7/1)}-N_{(1)}-O_{(2)}$ (°)	111.7	111.5	114.2
$O_{(3)}-N_{(1)}-O_{(2)}$ (°)	109.4	109.4	111.9
$O_{(3)}-N_{(1)}-C_{(7/1)}$ (°)	110.1	113.7	116.9
$\langle\beta\rangle$ (°)[a]	110.4	111.5	114.3
τ (°)[b]	6.7	13.9	8.5
χ_N (°)[c]	58.3	55.6	48.1
$C_{(8/2)}-O_{(2)}-N_{(1)}-O_{(3)}$ (°)	−114.1	−101.6	66.6
$C_{(10/15/3)}-O_{(3)}-N_{(1)}-O_{(2)}$ (°)	95.9	−63.8	83.8

[a] $\langle\beta\rangle = \Sigma(\beta)/3$. [b] Angle subtended by the axes of the nitrogen lone pair and the carbonyl carbon $2p_z$ orbital. [c] Amide distortion parameters defined in accordance with Winkler−Dunitz.[19,20]

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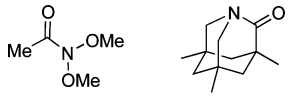
Both amides exhibit a high degree of pyramidality at nitrogen. The Winkler–Dunitz pyramidality indices, χ_N, are



5 6

58 and 56° for **1** and **2**, respectively.[19,20] Though highly pyramidalized at nitrogen, they are less pyramidal than *N*-acyloxy-*N*-alkoxyamides, which have χ_N of 65°.[17,22] The N–C bonds are typical of bis-oxo-substituted amides and much longer than those for primary, secondary, and tertiary amides (average bond length 1.359 Å with median 1.353 Å[22]). The bonds are slightly shorter than the corresponding bonds in *N*-acyloxy-*N*-alkoxyamides (**1b**), where crystallographic evidence gives the N–C bond length at 1.44 Å.[9,17,22] In keeping with previous findings for twisted[23−28,43] and anomeric amides,[17,21,22] the carbonyls undergo relatively little contraction.

Like other anomeric amides, there is relatively little twist about the N–C bonds (τ = 7 and 14° for **1** and **2**, respectively) and the nitrogen lone pair is in reasonably good alignment with the neighboring carbon $2p_z$ orbital. In common with all structures of anomeric amides, there appears to be a conformational preference enabling some overlap with the carbonyl carbon $2p_z$ orbital. This general feature of anomeric amides is rational. Though the lone pair on nitrogen is contracted on account of electron demand of both nitrogen substituents, alignment with the carbonyl is still a stabilizing influence, albeit much more weakly than in conventional primary, secondary, or tertiary amides. However, low-temperature NMR studies failed to detect isomerization processes down to −90 °C in support of a low *E*/*Z* isomerization barrier.[1]

In *N*-methoxy-*N*-(4-nitrobenzyloxy)benzamide **3**, the methoxyl group is *endo* to the nitrogen pyramid while both alkoxyl alkyl groups in *N*-ethoxy-*N*-methoxy-4-nitrobenzamide **2** are *exo*. On account of the similar electron demand of the nitrogen substituents, anomeric effects are expected to be weaker in these systems than in *N*-acyloxy-*N*-alkoxyamides (**1b**) or *N*-alkoxy-*N*-chloroamides (**1a**).[1,9,17] In both structures, the conformation at the nitrogen appears to be dictated by two anomeric effects. However, one anomeric effect is stronger than the other in both structures, based on orbital overlap considerations. Thus in compound **2**, the CH_3–O–N–OCH_2 dihedral angle is 96° and the CH_2–O–N–OCH_3 is −114°, while in compound **3**, the CH_3–O–N–OCH_2 dihedral angle is −64° and the CH_2–O–N–OCH_3 is 102° The N–O bond distances would appear to be dictated by other geometrical factors in addition to the anomeric effect; the N–O bonds *syn* to the carbonyl oxygen are shorter in each structure.

Both molecules are chiral at nitrogen, but in solution, enantiomers can interconvert by inversion at nitrogen. While acyclic pyramidal *N*,*N*-dialkoxyamines are known to have high nitrogen inversion barriers and are configurationally stable,[44−47] in anomeric amides, inversion at nitrogen is a low-energy process on account of the fact that the planar inversion transition state is stabilized by resonance delocalization of the nitrogen lone pair.[1,17,30,48] However, chiral amide nitrogens are clearly evident in the unit cells in both crystals, which comprise two pairs of enantiomers (Figure 3a,b).

In an earlier paper, we reported in detail theoretical properties of *N*,*N*-dimethoxyformamide.[30] B3LYP/6-31G(d) calculations predicted a long N–C bond of 1.396 Å and a relatively unchanged carbonyl at 1.21 Å. The methoxyl *syn* to carbonyl was *endo* relative to the nitrogen pyramid, though the *exo*/*exo* structure analogous to *N*-ethoxy-*N*-methoxy-4-nitrobenzamide was only 1 kcal mol^{-1} higher in energy. Anomeric effects were computed to be weaker in *N*,*N*-dimethoxyformamide relative to *N*-chloro-*N*-methoxyformamide or *N*-chloro-*N*-dimethylaminoformamide and *N*-dimethylamino-*N*-methoxyacetamide.[48] A theoretical amide rotational barrier of some 12 kcal mol^{-1} was reported. This level of theory successfully predicts structural properties, barriers to conformational change, as well as the activation energies for reactions of a range of anomeric amides.[8−10,14,16−18,30,48,49]

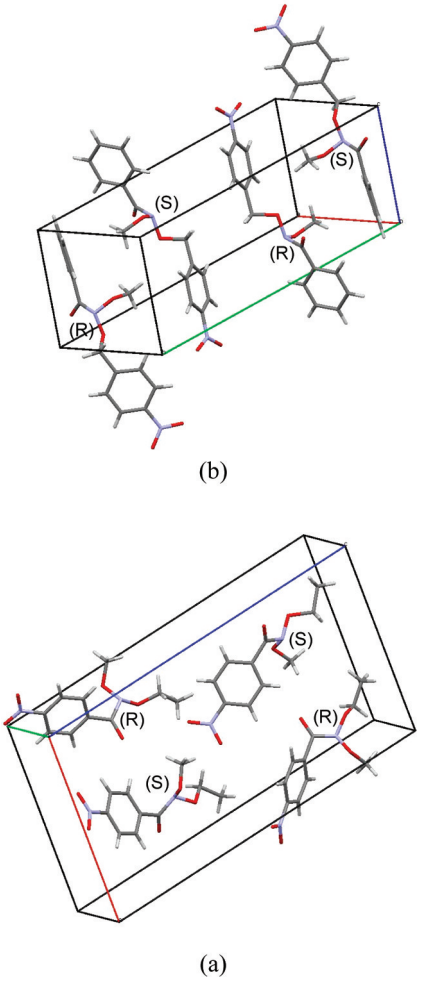


Figure 3. Crystal packing for (a) *N*-ethoxy-*N*-methoxy-4-nitrobenzamide **2** and (b) *N*-methoxy-*N*-(4-nitrobenzyloxy)benzamide **3**.

The structure of *N*,*N*-dimethoxyacetamide has been computed at the same level in this study and is depicted in Figure 4a with selected data given in Table 1. Its properties are very similar to those computed for the formamide, and predicted properties of *N*,*N*-dimethoxyacetamide correspond well to the crystallographic data for **2** and **3**. In the lowest energy conformer, the methoxyl group *syn* to the carbonyl is *endo* to the nitrogen pyramid and this form is 1.8 kcal mol^{-1} lower in energy than the *exo*/*exo* structure. The amide nitrogen in the most stable conformer has a χ_N of 48° and angle, τ, of only 8°. The N–C bond length of 1.42 Å is long when compared to *N*,*N*-dimethylacetamide computed at the B3LYP/6-31G(d) level (1.38 Å), while the carbonyl bond length of 1.21 Å was similar to the computed length in

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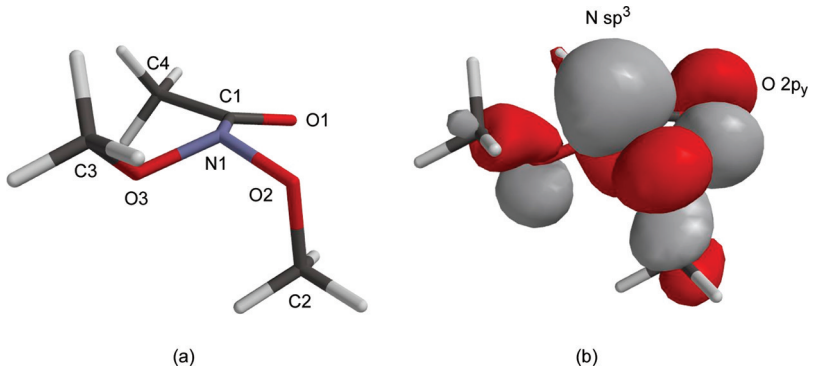
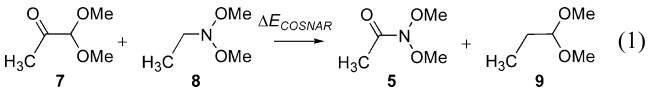


Figure 4. (a) B3LYP/6-31G(d) optimized geometry and (b) HOMO of the lowest energy conformer of *N,N*-dimethoxyacetamide.

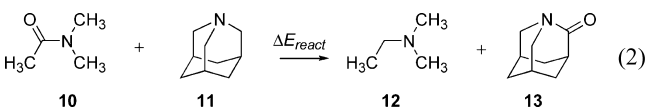
N,N-dimethylacetamide (1.23 Å). In the theoretical structure, the $C_{(3)}-O_{(3)}-N_{(1)}-O_{(2)}$ twist angle is close to 90°, and the $n_{O_{(3)}}-\sigma^*_{NO_{(2)}}$ anomeric interaction appears to be favored over the alternative overlap.

The N−C bonds in **2** and **3**, though much longer than those of *N,N*-dialkylamides, are shorter than that found in the 1-aza-2-adamantanone **6**, Kirby's most twisted amide, which has a N−C bond length of 1.455 Å.[26,50−52] This, together with the low twist angle in *N,N*-dimethoxyacetamide suggests that these highly pyramidalized amides might still possess a degree of amide resonance. We have computed the residual amide resonance in *N,N*-dimethoxyacetamide by two independent isodesmic methods: by COSNAR[53−55] and by a transamidation method we have developed. COSNAR measures directly the resonance stabilization when a carbonyl and an amino nitrogen are proximate in the same scaffold. Thus, for *N,N*-dimethoxyacetamide, **5**, eq 1 applies.The transamidation



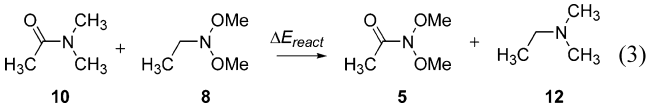
(1)

method computes the total destabilization of an amide relative to dimethylacetamide **10** and the maximum possible loss of resonance can be estimated isodesmically from eq 2 for fully



(2)

twisted 1-aza-2-adamantanone **13**. The total destabilization of *N,N*-dimethoxyacetamide **5** relative to *N,N*-dimethylacetamide **10** can be determined from eq 3. However, this energy is



(3)

composed of a resonance and an inductive destabilization, since in the product *N,N*-dimethoxyacetamide **5**, the polar carbonyl is further destabilized by the inductive effect of two oxygen substituents. We estimated this inductive contribution from the difference between ΔE_{react} of 1-aza-2-adamantanone **13** and its hypothetical *N,N*-dioxo analogue **15** or from the isodesmic reaction in eq 4. After correction for the inductive destabilization, the residual resonance stabilization can be estimated from eqs 2, 3, and 4. Table 2 gives B3LYP/6-31G(d)

(4)

energies for the optimized geometries of **7**, **9** and various amides and amines used in eqs 1−4. Since isodesmic reactions were used, ΔE_{COSNAR}, ΔE_{react}, and $\Delta E_{inductive}$ were calculated without incorporation of zero-point energies (ZPE) or thermodynamic quantities, which largely cancel. The residual resonance stabilization computed by COSNAR (from eq 1) is −8.59 kcal mol^{-1}. By our method, ΔE_{react} for 1-aza-2-adamantanone from eq 2 yields a maximum destabilization due to complete loss of resonance of 18.17 kcal mol^{-1}. For *N,N*-dimethoxyacetamide **5**, ΔE_{react} is computed from eq 3 to be 13.87 kcal mol^{-1}, the sum of destabilization due to both loss of resonance as well as the inductive influence of dimethoxyl substitution. $\Delta E_{inductive}$ from eq 4 measures the additional destabilization of *N,N*-bis-oxa-substitution in the fully twisted amide **15** at 4.27 kcal mol^{-1}, and the residual resonance stabilization in *N,N*-dimethoxyacetamide given by eq 5 is thus −8.58 kcal mol^{-1} and essentially identical to the COSNAR stabilization energy.

$$-18.17 + (\Delta E_{react} - E_{inductive}) \quad (5)$$

The resonance stabilization in *N,N*-dialkoxyacetamide is therefore likely to be about 47% that of *N,N*-dimethylacetamide. With this reduction in resonance, the barriers to rotation away from the ground state in *N,N*-dialkoxyamides are likely to be below the normal detection limits of NMR spectroscopy.

This represents the first estimation of amidicity in an anomeric amide. The loss of resonance in untwisted *N,N*-dimethylacetamide due to complete pyramidalization at nitrogen and localization of the lone pair in an sp^3 rather than a 2p$_z$ orbital is estimated to be about 6.5 kcal mol^{-1} from the difference in energies between pyramidal **10** (χ_N = 60°, τ = 0°) and planar **10** (χ_N = 0°, τ = 0°) (Table 2). Since the degree of twist in *N,N*-dimethoxyacetamide **5** is relatively small, the loss of a further 3−4 kcal mol^{-1} worth of resonance interaction over and above the loss attributable to sp^3 hybridization at nitrogen can be accounted for by localization of the lone pair on nitrogen. As a consequence of the combined electronegativity of both oxygens, the sp^3 hybrid lone pair orbital must be lowered in energy, resulting in a much greater reduction in π overlap with the carbonyl carbon.

The HOMO of **5** is shown in Figure 4b and clearly has a N sp^3 lone pair, as well as some O 2p$_y$ character, and protonation could occur at both atoms. In keeping with this lowering in energy of the lone pair on nitrogen, computed proton affinities

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Table 2. B3LYP/6-31G(d) Energies of Minimum Energy Conformations of 5, 7−15, Reaction Energies from Equations 1−5 and Proton Affinities of *N,N*-Dimethoxyacetamide 5 and *N,N*-Dimethylacetamide 10

structure	energy (au)	energy (kcal mol^{-1})
N,N-dimethoxyacetamide **5**	−438.150456 (−438.001676)[a]	
1,1-dimethoxypropanone **7**	−422.190691	
N,N-dimethoxyethylamine **8**	−364.131007	
1,1-dimethoxypropane **9**	−348.184927	
N,N-dimethylacetamide **10** ($\chi_N = \tau = 0°$)	−287.830189 (−287.690489)[a]	
N,N-dimethylacetamide **10** ($\chi_N = 60°$, $\tau = 0°$)	−287.819817	
1-azaadamantane **11**	−406.744846	
N,N-dimethylethylamine **12**	−213.788638	
1-aza-2-adamantanone **13**	−480.757454	
2,6-dioxo-1-azaadamantane **14**	−478.462685	
2′,6′-dioxo-1-aza-2-adamantanone **15**	−552.468467	
5 COH^+	−438.498605 (−438.336389)[a]	
5 NH^+	−438.482551(−438.320598)[a]	
10 COH^+	−288.189375(−288.037134)[a]	
10 NH^+	−288.170972(−288.017956)[a]	
eq 1	−0.013685	−8.59
eq 2	0.028957	18.17
eq 3	0.022102	13.87
eq 4	0.006812	4.27
eq 5	−0.013667	−8.58
pyramidal **10** − planar **10**	0.010372	6.51
PA−**5** COH^+	0.348149 (0.334713)[a]	218.46 (210.03)[a]
PA−**5** NH^+	0.332095 (0.318922)[a]	208.39 (200.12)[a]
PA−**10** COH^+	0.359178 (0.346644)[a]	225.38 (217.52)[a,b]
PA−**10** NH^+	0.340776 (0.327467)[a]	213.84 (205.49)[a]

[a]ZPE and enthalpy corrected values in parentheses. [b]Experimental proton affinity at oxygen is 217 kcal mol^{-1}.[56]

(Table 2) predict that protonation of *N,N*-dimethoxyacetamide would still be more favorable at the carbonyl oxygen, rather than on nitrogen, by some 10 kcal mol^{-1}. This contrasts markedly with highly twisted *N,N*-dialkylamides with low amidicity where PAs indicate that localization of the lone pair results in a more basic nitrogen than oxygen lone pair.[54,55] The PAs of both the carbonyl oxygen and the nitrogen of **5** are significantly lower than those computed for *N,N*-dimethylacetamide (**10**) at B3LYP/6-31G(d), which with enthalpy corrections predicts a PA at oxygen close to the experimental value of 217 kcal mol^{-1}.[54−57]

In this regard, a comparison with *N*-acylaziridines is supportive. In these, the nitrogen is also pyramidal on account of the three-membered ring, and the lone pair is conjugaed with the carbonyl.[43,58] However, in contrast with *N,N*-dimethoxyacetamide, the lone pair is not subject to electronegative tightening and calculations on *N*-formylaziridine at both the MP2/6-31G(d,g)[59] and more recently at the MP2/6-311++G(d,g) level[43] predicted a small preference for protonation at nitrogen (by 2 kcal mol^{-1} in the gas phase and 5 kcal mol^{-1} in water,[59] and 1 kcal mol^{-1} in the gas phase[43]). The resonance stabilization in *N*-formylaziridine has also been estimated to be some 15 kcal mol^{-1} at HF/3-21G(d) level,[58] and we calculate it to be 14 kcal mol^{-1} by the same method at B3LYP/6-31G(d).[60] The reversal of proton affinities in *N,N*-dimethoxyacetamide, as well as its lower resonance stabilization, is entirely consistent with the electron demand of the alkoxyl oxygen atoms.

CONCLUSION

The structures of two *N,N*-dialkoxyamides have been obtained that demonstrate they are true anomeric amides. The nitrogen lone pair resides in an sp^3 hybrid orbital on the nitrogen atom, which is highly pyramidalized like that of the other bis-heteroatom-substituted amides. Evidence for radically reduced resonance can be found in a substantial lengthening of the N−CO bond, but in keeping with previous findings for amides with impaired resonance, the carbonyl bond length is little affected. The lone pair, while largely aligned with the carbonyl carbon $2p_z$ orbital, undergoes very limited delocalization on account of its localization on nitrogen, a consequence of the electron demand of the two oxyl substituents. The crystal packing exhibits enantiomerism due to chirality at the nitrogen, a property that cannot be detected in solution studies of these or other chiral anomeric amides.

Density functional theory reproduces the structural properties observed in the crystalline forms of amides **2** and **3**. In addition, the model *N,N*-dimethoxyacetamide **5** is computed to have less than half the resonance of planar *N,N*-dimethylacetamide. Pyramidalization at nitrogen cannot alone account for this loss of resonance, which is also impaired by localization of the lone pair on nitrogen due to the electronegativity of the methoxyl substituents. Computed PAs of the carbonyl oxygen and nitrogen accord with this localization. Protonation on the carbonyl oxygen of **5** is preferable to the reaction at nitrogen.

The correspondence between COSNAR and our transamidation method for computing residual amide resonance is reproduced with other similar systems, and we will shortly demonstrate that the resonance in this unusual class of amides, as well as in mono-heteroatom-substituted amides, varies largely in line with the total electronegativity of substituents at the amide nitrogen. We have found that these two approaches to determining amidicity (relative to *N,N*-dimethylacetamide [100%] and 1-aza-2-adamantanone [0%]) are more reliable than the heat of hydrogenation method

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recently published by Csizmadia and co-workers,[61−63] particularly when strained lactams are involved.

EXPERIMENTAL SECTION

Synthetic Details. The synthesis of *N*-ethoxy-*N*-methoxy-4-nitrobenzamide **2** and *N*-methoxy-*N*-(4-nitrobenzyloxy)benzamide **3** by PIFA oxidation of *N*-ethoxy-4-nitrobenzamide and *N*-(4-nitrobenzyloxy)benzamide in methanol together with their characterization has recently been reported.[33]

X-ray Crystallography. Intensity data were collected with an Oxford Diffraction SuperNova CCD diffractometer using Mo Kα radiation (graphite crystal monochromator λ = 0.7107); the temperature during data collection was maintained at 130.0(1) K using an Oxford Cryosystems cooling device.

The structures were solved by direct methods and difference Fourier synthesis.[64] Thermal ellipsoid plots were generated using the program ORTEP-3[65] integrated within the WINGX[66] suite of programs

Crystal Data for **2**: $C_{15}H_{14}N_2O_5$, M = 302.28, T = 130.0(1) K, λ = 0.7107, monoclinic, space group $P2_1/c$, a = 10.9575(3), b = 17.3679(5), c = 7.9564(2) Å, β = 108.867(3)°, V = 1432.82(7) Å^3, Z = 4, D_c = 1.401 mg M^{-3} μ(Mo Kα) 0.107 mm^{-1}, F(000) = 632, crystal size 0.6 × 0.3 × 0.1 mm; 7060 reflections measured, 2522 independent reflections (R_{int} = 0.0221); the final R was 0.0348 [$I > 2\sigma(I)$], and $wR(F^2)$ was 0.0863 (all data).

Crystal Data for **3**: $C_{10}H_{12}N_2O_5$, M = 240.22, T = 130.0(1) K, λ = 0.7107, orthorhombic, space group *Pca*21, a =12.2038(7), b = 4.1403(3), c = 22.3872(16) Å, V = 1131.17(13) Å^3, Z = 4, D_c = 1.411 mg M^{-3} μ(Mo Kα) 0.115 mm^{-1}, F(000) = 504, crystal size 0.6 × 0.5 × 0.4 mm; 3203 reflections measured, 1854 independent reflections (R_{int} = 0.0321); the final R was 0.0490 [$I > 2\sigma(I)$], and $wR(F^2)$ was 0.1268 (all data).

Computational Details. B3LYP/6-31G(d) calculations were carried out using SPARTAN 08.[67] Energies of global minima of structures **5** and **7**−**15** for use in isodesmic eqs 1−4 were computed directly without ZPE and enthalpy corrections. B3LYP/6-31G(d) energies for *N*,*N*-dimethoxyacetamide **5** and planar *N*,*N*-dimethylacetamide **10** and their carbonyl oxygen- and nitrogen-protonated structures for determination of proton affinities were computed together with enthalpy corrections using frequency calculations.

ASSOCIATED CONTENT

Supporting Information

Geometries and energies of minimum energy structures listed in Table 2. Calculation of the B3LYP/6-31G(d) resonance energy for *N*-formylaziridine using the method of Greenberg and co-workers.[58] CIF's for crystal structures of *N*-ethoxy-*N*-methoxy-4-nitrobenzamide **2** and *N*-methoxy-*N*-(4-nitrobenzyloxy)benzamide **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Glover, S. A. *Tetrahedron* **1998**, *54*, 7229−7272.
(2) Campbell, J. J.; Glover, S. A.; Hammond, G. P.; Rowbottom, C. A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 2067−2079.
(3) Bonin, A. M.; Glover, S. A.; Hammond, G. P. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1173−1180.
(4) Glover, S. A.; Hammond, G. P.; Bonin, A. M. *J. Org. Chem.* **1998**, *63*, 9684−9689.
(5) Campbell, J. J.; Glover, S. A. *J. Chem. Res. (S)* **1999**, *8*, 474−475.
(6) Glover, S. A. *ARKIVOC* **2001**; part xii, issue in honor of O.S. Tee, ms. OT-308C, 143−160.
(7) Glover, S. A.; Mo, G. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1728−1739.
(8) Cavanagh, K. L.; Glover, S. A.; Price, H. L.; Schumacher, R. R. *Aust. J. Chem.* **2009**, *62*, 700−710.
(9) Glover, S. A. In *Advances in Physical Organic Chemistry*; Richard, J., Ed.; Elsevier: London, 2008; Vol. *42*, pp 35−123.
(10) Glover, S. A.; Adams, M. *Aust. J. Chem.* **2011**, *64*, 443−453.
(11) **H**eteroatom **R**earrangements **O**n **N**itrogen.
(12) Buccigross, J. M.; Glover, S. A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 595−603.
(13) Buccigross, J. M.; Glover, S. A.; Hammond, G. P. *Aust. J. Chem.* **1995**, *48*, 353−361.
(14) Glover, S. A.; Mo, G.; Rauk, A. *Tetrahedron* **1999**, *55*, 3413−3426.
(15) Mo, G. Ph.D. thesis, University of New England, 1999.
(16) Glover, S. A.; Rauk, A.; Buccigross, J. M.; Campbell, J. J.; Hammond, G. P.; Mo, G.; Andrews, L. E.; Gillson, A.-M. E. *Can. J. Chem.* **2005**, *83*, 1492−1509.
(17) Glover, S. A. In *The Chemistry of Hydroxylamines, Oximes and Hydroxamic, Acids, Part 2*; Rappoport, Z., Liebman, J. F., Eds.; Wiley: Chichester, UK, 2009; pp 839−923.
(18) Johns, J. P.; van Losenoord, A.; Mary, C.; Garcia, P.; Pankhurst, D. S.; Rosser, A. A.; Glover, S. A. *Aust. J. Chem.* **2010**, *63*, 1717−1729.
(19) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169−182.
(20) Dunitz, J. D. *X-ray Analysis and Structure of Organic Molecules*; Cornell University Press: London, 1979.
(21) Glover, S. A.; Mo, G.; Rauk, A.; Tucker, D.; Turner, P. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2053−2058.
(22) Gillson, A.-M. E.; Glover, S. A.; Tucker, D. J.; Turner, P. *Org. Biomol. Chem.* **2003**, *1*, 3430−3437.
(23) Yamada, S. *J. Org. Chem.* **1996**, *61*, 941−946.
(24) Yamada, S. *Rev. Heteroat. Chem.* **1999**, *19*, 203−236.
(25) Yamada, S. In *The Amide Linkage. Structural Significance in Chemistry, Biochemistry and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; John Wiley & Sons, Inc.: New York, 2000; p 215.
(26) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522−529.
(27) Duspara, P. A.; Matta, C. F.; Jenkins, S. I.; Harrison, P. H. M. *Org. Lett.* **2001**, *3*, 495−498.
(28) Cow, C. N.; Britten, J. F.; Harrison, P. H. M. *J. Chem. Soc., Chem. Commun.* **1998**, 1147−1148.
(29) Wiberg, K. B. In *The Amide Linkage. Selected Structural Aspects in Chemistry, Biochemistry and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; John Wiley & Sons, Inc.: New York, 2000.
(30) Glover, S. A.; Rauk, A. *J. Org. Chem.* **1996**, *61*, 2337−2345.
(31) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376−384.
(32) Brown, D. A.; Glass, W. K.; Mageswaran, R.; Mohammed, S. A. *Magn. Reson. Chem.* **1991**, *29*, 40−45.
(33) Digianantonio, K. M.; Glover, S. A.; Johns, J. P.; Rosser, A. A. *Org. Biomol. Chem.* **2011**, *9*, 4116−4126.
(34) Shtamburg, V. G.; Shishkin, O. V.; Zubatyuk, R. I.; Kravchenko, S. V.; Tsygankov, A. V.; Shtamburg, V. V.; Distanov, V. B.; Kostyanovsky, R. G. *Mendeleev Commun.* **2007**, *17*, 178−180.
(35) Shtamburg, V. G.; Tsygankov, A. V.; Gerasimenko, M. V.; Shishkin, O. V.; Zubatyuk, R. I.; Mazepa, A. V.; Kostyanovsky, R. G. *Mendeleev Commun.* **2011**, *21*, 50−52.
(36) Rudchenko, V. F.; Ignatov, S. M.; Kostyanovskii, R. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 2384−2395.
(37) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1188−1189.
(38) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053−1056.
(39) Wardrop, D. J.; Landrie, C. L.; Ortiz, J. A. *Synlett* **2003**, *9*, 1352−1354.
(40) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582−6587.

(41) Correa, A.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem.* **2005**, *70*, 2256−2264.
(42) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, *68*, 5429−5432.
(43) Alkorta, I.; Cativiela, C.; Elguero, J.; Gil, A. M.; Jiménez, A. I. *New J. Chem* **2005**, *29*, 1450−1453.
(44) Rudchenko, V. F.; Ignatov, S. M.; Chervin, I. I.; Nosova, V. S.; Kostyanovskii, R. G. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1986**, 1153−1160.
(45) Shustov, G. V.; Zolotoi, A. B.; Kostyanovsky, R. G. *Tetrahedron* **1982**, *38*, 2319−2326.
(46) Kostyanovsky, R. G.; Rudchenko, V. F.; Shtamburg, V. G.; Chervin, I. I.; Nasibov, S. S. *Tetrahedron* **1981**, *37*, 4245−4254.
(47) Rudchenko, V. F.; Chervin, I. I.; Kostyanovskii, R. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 924−925.
(48) Glover, S. A.; Rauk, A. *J. Org. Chem.* **1999**, *64*, 2340−2345.
(49) Glover, S. A.; Rauk, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1740−1746.
(50) Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785−786.
(51) Kirby, A. J.; Komarov, I. V.; Kowski, K.; Rademacher, P. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1313−1316.
(52) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Am. Chem. Soc.* **1998**, *120*, 7101−7102.
(53) **C**arb**o**nyl **S**ubstitution **N**itrogen **A**tom **R**eplacement.
(54) Greenberg, A. In *The Amide Linkage. Structural Significance in Chemistry, Biochemistry and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; John Wiley & Sons, Inc.: New York, 2000; p 47.
(55) Greenberg, A.; Moore, D. T.; DuBois, T. D. *J. Am. Chem. Soc.* **1996**, *118*, 8658−8668.
(56) Hunter, E. P.; Lias, S. G. *J. Phys. Chem. Ref. Data* **1998**, *27*, 413−656.
(57) Abboud, J.-L. M.; Canada, T.; Homan, H.; Notario, R.; Cativiela, C.; Diaz de Villegas, M. D.; Bordeje, M. C.; Mo, O.; Yanez, M. *J. Am. Chem. Soc.* **1992**, *114*, 4728−4736.
(58) Greenberg, A.; Chiu, Y.-Y.; Johnson, J. L.; Liebman, J. F. *Struct. Chem.* **1991**, *2*, 117−126.
(59) Cho, S. J.; Cui, C.; Lee, J. Y.; Park, J. K.; Suh, S. B.; Park, J.; Kim, B. H.; Kim, K. S. *J. Org. Chem.* **1997**, *62*, 4068−4071.
(60) This study. See Supporting Information.
(61) Mucsi, Z.; Chass, G. A.; Csizmadia, I. G. *J. Phys. Chem. B* **2008**, *112*, 7885−7893.
(62) Mucsi, Z.; Tsai, A.; Szori, M.; Chass, G. A.; Viscolcz, B.; Csizmadia, I. G. *J. Phys. Chem. A* **2007**, *111*, 13245−13254.
(63) Mucsi, Z.; Chass, G. A.; Csizmadia, I. G. *J. Phys. Chem. B* **2009**, *113*, 10308−10314.
(64) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112−122.
(65) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
(66) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837−838.
(67) *Spartan '08 for Macintosh*, 1.2.1; Wavefunction Inc.: Irvine, CA, 2008.