135481-70-8; Z-Ala-OH, 1142-20-7; H-Ala-Glu(OtBu)-Phe-OMe, 135481-71-9; H-Phe-D-Pro-Phe-Ala-Glu(OtBu)-Phe-NHNH$_2$·2HOAc, 135481-73-1; 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine, 4515-24-6.

Supplementary Material Available: Additional six figures (parts of 250-MHz E.COSY for I and II, part of the 600-MHz TOCSY spectrum of I, parts of the 600-MHz NOESY spectra of II (NH/C$_\alpha$ region) and I (NH/NH region), and expansion of the 600-MHz HMQC-NOESY spectrum (NH/C$_\alpha$ region)) (7 pages). Ordering information is given on any current masthead page.

The Influence of Altered Amidic Resonance on the Infrared and ^{13}C and ^{15}N NMR Spectroscopic Characteristics and Barriers to Rotation about the N-C(O) Bond in Some Anilides and Toluamides

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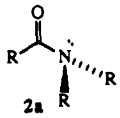
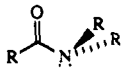
Abstract: In order to provide physicochemical evidence for or against amidic resonance, three series of anilides and toluamides have been investigated by infrared spectroscopy and ^{13}C and ^{15}N NMR, and barriers to rotation for several toluamides have been determined. Each series contains amides that are predisposed in one or more ways to disfavor resonance. These include rotation about the N–C(O) bond in a series of bicyclic anilides, N-pyramidalization in a series of *N*-toluoyl cyclic amines, and removal of N electron density in some toluamides by inductive means or by occupying the N lone pair in an aromatic sextet. The structures of the *N*-toluoyl derivatives of azetidine, pyrrole, and 2,5-dimethylpyrrole were determined by X-ray diffraction. The physicochemical data are generally consistent with the resonance model, but there are anomalies indicating that other factors are also important. When resonance is favored, the infrared $\nu_{C=O}$ and ν_{C-N} bands are respectively found at lower and higher values than in amides where resonance is disfavored. The ^{13}C NMR chemical shift for a wide variety of toluamides and anilides with different resonance abilities consistently appears between δ 167 and 172 ppm, except for the distorted bicyclic anilides (δ 180–200 ppm) or *N*-toluoylaziridine (δ 178 ppm). Since the sets include amides of considerable structural diversity, the ^{13}C=O chemical shifts are compared with the ^{13}C chemical shift of the corresponding *N*-methylamine: the $\Delta\delta(^{13}\mathrm{C})$(amide–amine) values span a range of $\sim$122–143 ppm, with amides having inhibited resonance lying at the higher values. ^{15}N chemical shifts for amides for which resonance can be invoked appear to be $\sim$80 ppm downfield from their corresponding N-methylated tertiary amines. The ^{15}N chemical shifts of amides in which resonance is impaired by rotation about the N–C(O) bond, by N-pyramidalization, or by occupying the N lone pair in an aromatic sextet move upfield by $\sim$30–40 ppm, but are still 45–50 ppm downfield from their corresponding tertiary amines. The $\Delta G^\ddagger$ for rotation about the N–C(O) bond in a series of toluamides appears to be relatively insensitive to the ability of the N to support (+)-charge as gauged by the gas-phase basicity of the corresponding amines. Where structural and $\Delta G^\ddagger$ rotational data can be compared, those amides with short N–C(O) bonds (1.34–1.37 Å) have high rotational barriers (14.5–16.5 kcal/mol), while those amides with longer N–C(O) bonds (1.40–1.42 Å) have reduced barriers to rotation (<6–8 kcal/mol).

Resonance theory[1] has enjoyed applicability in explaining various properties of amides such as the short N—C(O) bond length,[2] planar geometry,[2] barrier to N—C(O) rotation,[3] C=O IR stretching frequencies,[4] ^{15}N NMR chemical shifts,[5] and kinetic stability toward nucleophilic attack/hydrolysis.[6] However, the importance of resonance contributor **1a** has been questioned by Wiberg and Laidig[7] who have reported high-level ab initio calculations on planar and orthogonal formamides (**1**, **2**, R = H, respectively) along with Bader's electron population analysis[8] for the various atoms in each conformer. In contrast to what is expected on the basis of the resonance model, the computed electron population at N in **1**, R = H, is larger than in **2**, R = H, while the population at each O is similar. In **1**, the electron population at C is less than in **2** so that there is a net transfer of electrons from C to N in the former. The N—C(O) bond lengthens in passing from **1** to **2**, but the C=O bond length is scarcely affected. Finally, the computed barrier to N—C(O) rotation (**1** → **2b** → **1**) is similar to the experimental one of 18–19 kcal/mol.[9] Wiberg and Laidig,[7] Bader et al.[10a] and Wiberg and


1 **1a**


2a


2b

[†] Department of Chemistry.

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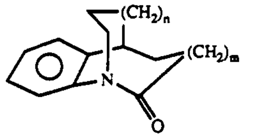
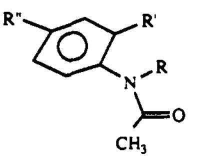
Breneman[10b] conclude that amidic resonance as is customarily invoked (involving N → O charge transfer as in **1a**) does not exist and the functional group properties stem from the hybridization changes at N (sp^2 (**1**) → sp^3 (**2**)) that accompany rotation around the N—C(O) bond.

The calculations refer specifically to the planar and rotated forms of formamide, and it remains to be established how general the conclusions are for more heavily substituted amides and how generally acceptable is the Bader electron population analysis.[8] Recently, a key report by Perrin[11] questioned this analysis and suggested that the method is flawed because it attributes unrealistically high populations to electronegative elements. In his estimation, the "fatal flaw" in the analysis precludes any conclusion other than the one that previous objections to amidic resonance[7,10] are unfounded.

Earlier reports from our laboratories[12] have provided X-ray structural support gained from **3b–d** and **4e**[12] for the predicted[7] bond length changes that accompany rotation about the N—C(O) bond. The major observed structural changes in passing from undistorted **4e** to progressively more distorted **3d** → **3c** → **3b** involve a lengthening of the N—C(O) bond (0.06–0.08 Å), a slight shortening of the C=O bond (0.02 Å), a progressive pyramidalization of the N from sp^2 to sp^3 geometry, and a rotation about the N—C(O) bond of ~30°.[12] While the structural studies provide the most relevant data for comparison with the theoretically predicted[7] structural changes that accompany N-C(O) rotation, they provide no information about atomic charges. We assume that the predicted[7] bond length changes are valid since they derive from well-accepted and reliable ab initio techniques independent of the apparently controversial[11] subsequent population[8] analysis.



3a n=m=0
b n=0; m=1
c n=1; m=0
d n=m=1



4a R=R'=R''=H
b R=CH_3; R'=R''=H
c R=R'=R''=CH_3
d R=R'=CH_3; R''=H
e R=R'=CH_3; R''=Br

A priori, we take no firm position as to whether amidic resonance exists or not, but recognize that it is an immensely powerful, albeit arbitrary, concept.[1] For the sake of caution, before abandoning such a useful device, one needs to provide acceptable alternative explanations for all the properties of amides that are currently rationalized within the context of that theory. We have provided one such explanation for the increased rate of base hydrolysis seen for distorted amides,[12] but even that rationale is not inconsistent with resonance.

The present study was undertaken to provide physicochemical data of relevance to the intriguing recent controversy[7,10,11] over amidic resonance. At present, there is a paucity of such data for amides that are predisposed in some way to disfavor resonance. We seek in this paper to provide ^{13}C, ^{15}N, $\nu_{C=O}$, and rotational barrier data for some sets of amides in which form **1a** is disfavored by one or more of three ways. These are (1) structural inhibition by progressive rotation about the N-C(O) bond in a series of anilides **3** and **4**,[12,13] (2) N-pyramidalization in a series of toluamides **5** and **6**,[14] and (3) preoccupying the N lone pair in an aromatic sextet (**7**)[15] or by inductive electron withdrawal as in **8**.

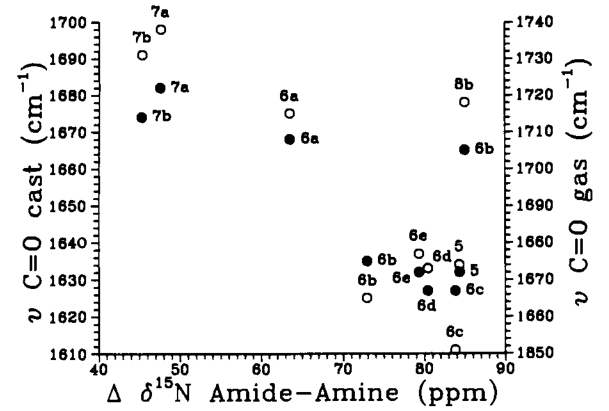
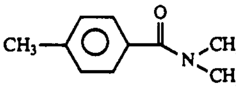


Figure 1. A graphical presentation of $\nu_{C=O}$ ($CHCl_3$ cast, left ordinate, open symbols) and $\nu_{C=O}$ (gas-phase, right ordinate, closed symbols) vs $\Delta\delta(^{15}N)$(amide–amine) chemical shifts for various amides.



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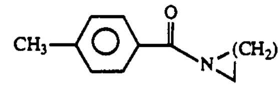
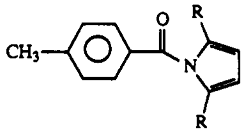
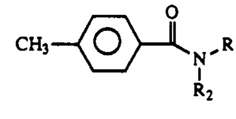


6a n=1
b n=2
c n=3
d n=4
e N-toluoylmorpholine



7a R=H
b R=CH_3



8a R_1=Et, R_2=CH_2CF_3
b R_1=R_2=CH_2CF_3

Results

Given in Table I are the infrared C=O frequencies and δ(^{13}C NMR) and δ(^{15}N NMR) chemical shifts for the various amides.[16] Each set of data was acquired under approximately equivalent conditions (e.g., solvent, temperature, concentration, phase) to facilitate comparison. The IR data were acquired from $CHCl_3$ cast spectra (Nicolet FTIR spectrophotometer) and gas-phase spectra determined on the effluent from a Hewlett-Packard 5890A gas chromatograph using a Hewlett-Packard 5965A FTIR detector. The latter so determined C=O frequencies are generally 25–50 cm^{-1} larger than the $CHCl_3$ cast frequencies, a phenomenon that has been observed before.[17] Given the structural variance, and large chemical shift range for the ^{15}N resonances, the ^{13}C=O and ^{15}N chemical shifts are most usefully compared with the

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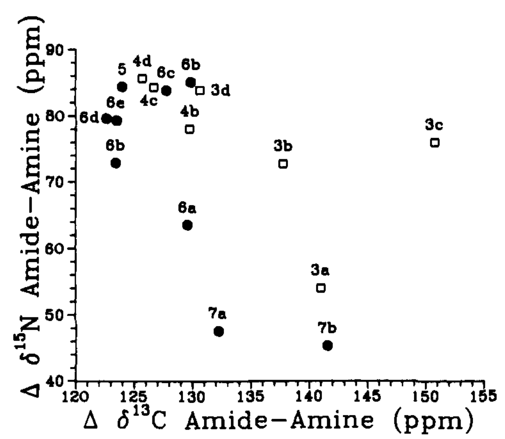


Figure 2. A graphical representation of $\Delta\delta(^{13}C)$(amide–amine) vs $\Delta\delta(^{15}N)$(amide–amine) for various amides (closed circles, toluamides; open squares, anilides).

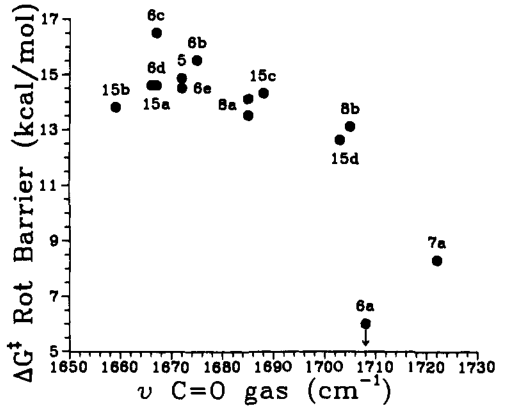
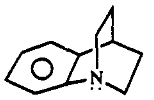


Figure 3. A graphical presentation of $\Delta G^{\ddagger}$ (rotational barrier) vs $\nu_{C=O}$ (gas-phase) for various toluamides.

corresponding amines, the structures of which are given below. The parameters of interest are the $\Delta\delta(^{13}C)$(amide–amine) and $\Delta\delta(^{15}N)$(amide–amine).



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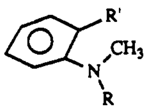
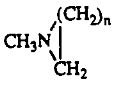
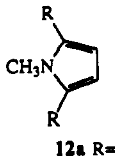


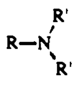
10a R=R'=H
b R=CH$_3$; R'=H
c R=R'=CH$_3$



11a n=1
b n=2
c n=3
d n=4
e N-methylmorpholine



12a R=H
b R=CH$_3$



13a R=R'=CH$_3$
b R=CH$_3$; R'=CH$_2$CF$_3$

Figures 1–3 are presented to facilitate grasping the general trends among the various data. Shown in Figure 1 is a plot of the CHCl$_3$ cast (open symbols) and gas-phase (closed symbols) $\nu_{C=O}$ IR frequencies for the amides vs the $\Delta\delta(^{15}N)$(amide–amine) chemical shifts. The plots show considerable scatter, but in general, a high ν IR value (signifying reduced amidic conjugation) correlates with a smaller $\Delta\delta(^{15}N)$; the bis(trifluoroethyl) derivative **8b** appears out of sequence. In Figure 2 is given a plot of the $\Delta\delta(^{13}C)$(amide–amine) vs $\Delta\delta(^{15}N)$(amide–amine) chemical shifts. To construct the plot, mostly the data for the toluoyl amides (and corresponding methylamines) are used, but a few tertiary anilides are shown. Of the bicyclic anilides, the only accurate NMR comparison is for **3a** and **9** since the higher homologue amines are not available. The plot shows considerable scatter, but in general a large $\Delta\delta(^{13}C)$ correlates with a small $\Delta\delta(^{15}N)$ and vice versa.

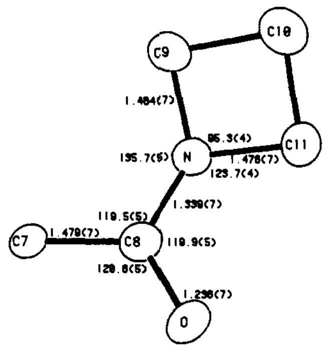


Figure 4. Perspective view of a portion of **6b** showing the atom-labeling scheme and bond lengths and angles of the amidic unit. Heavy atoms are represented by Gaussian ellipsoids at the 20% probability level.

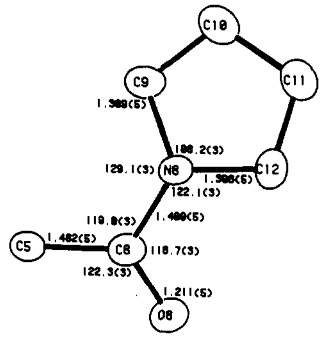


Figure 5. Perspective view of a portion of **7a** showing the atom labeling scheme and bond lengths and angles of the amidic unit. Heavy atoms are represented by Gaussian ellipsoids at the 20% probability level.

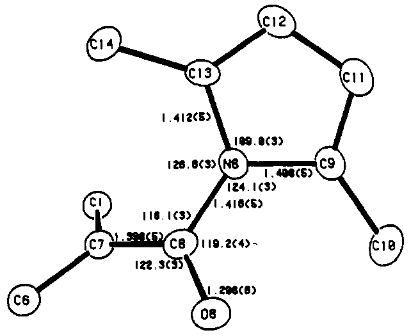


Figure 6. Perspective view of a portion of one of the three independent molecules of **7b** in the unit cell, showing the representative atom-labeling scheme, and average bond lengths and angles of the amidic unit. Heavy atoms are represented by Gaussian ellipsoids at the 20% probability level.

In order to assign the IR bands associated with the O=C—N unit ($\nu_{C=O,C-N}$), isotopic substitution of ^{13}C for ^{12}C, and ^{18}O and ^{16}O, was undertaken for amides that span the range of "good" to "poor" resonance (**5**, **6a**,**c**, and **7a**). Given in Table II are the gas-phase IR frequencies for the C=O and C—N stretching bands of these isotopically substituted amines, along with the ν_{13}/ν_{12} ratios.

Given in Table III are ^1H NMR determined N–C(O) rotational barriers ($\Delta G^{\ddagger}$) and coalescence temperatures for various toluamides in CDCl$_3$. Also given in the table, as some measure of the ability of the N to support (+)-charge, are the solution pK_a values for the corresponding ammonium ions, as well as the gas-phase basicities as measured by the literature $\Delta G°$ values for the process $NH_4^+ + HNR_1R_2 \rightleftharpoons NH_3 + H_2NR_1R_2^+$. Finally, shown in Figure 3 is a plot of the gas-phase IR $\nu_{C=O}$ values vs the $\Delta G^{\ddagger}$ rotational barriers for the toluamides. In accordance with a resonance analysis, a high $\nu_{C=O}$ value correlates with a reduced rotational barrier. There are notable deviations from the

Table I. Infrared C═O Frequencies, δ(^{13}C NMR) and δ(^{15}N NMR) Data for Various Amides and Their Comparison Amines

amides					amines				
compd	δ(^{13}C═O)^a (ppm)	$\nu_{C=O}$ (cm^{-1}) CHCl$_3$ cast	$\nu_{C=O}$ (cm^{-1}) gas	δ(^{15}N)^b (ppm)	compd	δ(^{13}C)(CH$_3$) (ppm)	δ(^{15}N) (ppm)	Δδ(^{13}C) (amide–amine, ppm)	Δδ(^{15}N) (amide–amine, ppm)
3a	190.7 (192.3)^c	1755^c	1782	−285.0	**9**	49.7^d	−339.0	141.0	54.0
3b	187.5 (189.0^c)	1705		−266.3	9	49.7^d	−339.0	137.8	72.7
3c	200.5	1711		−263.0	9	49.7^d	−339.0	150.8	76.0
3d	180.4	1677		−255.2	9	49.7^d	−339.0	130.7	83.8
4a	168.8	1663		−247.0^f	**10a**	29.9^e	−327.4^f	138.9	80.4
4b	170.1	1666		−257.6	**10b**	40.3^e	−335.6^f	129.8	78.0
4c	170.8	1653		−262.1	**10c**	44.1	−346.3^f	126.7	84.2
4d	169.8	1656		−260.7	**10d**	44.1	−346.3^f	125.7	85.6
4e	170.4	1648							
5	171.5	1634	1672	−282.6^g	**13a**	47.5^e	−366.9^f	124.0	84.3
6a	178.2	1675^h	1708	−316.0^i	**11a**	48.6^j	−379.5^f	129.6	63.5
6b	169.8	1625	1675	−275.8	**11b**	46.4^j	−348.7^f	123.4	72.9
6c	170.5	1611	1667	−256.0^g	**11c**	42.7^j	−339.8^f	127.8	83.8
6d	170.3	1633	1667	−260.9	**11d**	47.7^j	−341.3^f	122.6	80.4
6e	170.1	1637	1672	−268.4	**11e**	46.6^k	−347.7^l	123.5	79.3
7a	167.4	1698	1722	−186.1	**12a**	35.2^m	−233.7^f	132.2	47.6
7b	171.2	1691	1714	−189.2	**12b**	29.7	−234.5	141.5	45.3
8b	172.9	1678	1705	−289.2	**13b**	43.0^n	−374.2^o	129.9	85.0

^{a} In CDCl$_3$. ^{b} 10-mm broad-band probe at 30.42 MHz; δ (ppm) reported upfield from liquid CH$_3$NO$_2$; toluene d_8 lock; 293 ± 2 K. Samples of amides dissolved in CH$_2$Cl$_2$. ^{c} Data from ref 13a; ^{13}C NMR in CD$_3$CN containing 10% H$_2$^{18}O. ^{d} Chemical shift for N*C*H$_2$ of benzoquinuclidine. ^{e} Breitmaier, V.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: New York, 1987; p 237. ^{f} Data from Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; J. Wiley and Sons: New York, 1979, corrected to CH$_3$NO$_2$ reference. ^{g} $|J(^{13}C(O)^{15}N)| = 15.5$ Hz. ^{h} Neat liquid. ^{i} $|J(^{13}C(O)^{15}N)| < 2$ Hz. ^{j} English translation of the revised 2nd German ed., 1981. Pretsch, E. *Anleitungen für die Chemische Laboratoriumspraxis, BdXV Tabellen zur Strukturaufklarüng Organischer Verbindungen mit Specktroskopischen Methoden*; Springer Verlag: Heidelberg, 1981; p C45. ^{k} Jones, A. J.; Beeman, C. P.; Hasan, M. U.; Casey, A. F.; Hassan, M. M. A. *Can. J. Chem.* **1976**, *54*, 126. ^{l} Witanowski, M.; Stefaniak, L.; Webb, G. A. *Ann. Rep. NMR Spectrosc.* **1981**, *11B*, 1, Table 19. ^{m} Begtrup, M.; Claramunt, R. M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 99. ^{n} Bürger, H.; Krumm, B.; Pawelke, G. *J. Fluorine Chem.* **1989**, *44*, 147. ^{o} δ(^{15}N) for HN(CH$_2$CF$_3$)$_2$ = −375.1 ppm.

Table II. Gas-Phase Infrared Frequencies (cm^{-1}) for Isotopically Substituted Amides^a

amide		$\nu_{C=O}$	$\nu_{^{13}C(O)}/\nu_{^{12}C(O)}$	ν_{C-N}	$\nu_{^{13}C-N}/\nu_{^{12}C-N}$
5	^{12}C(^{16}O)	1672		1383	
	^{13}C(^{16}O)	1632	0.976	1373	0.993
	^{12}C(^{18}O)^b	1647		1382	
6c	^{12}C(^{16}O)	1667		1392	
	^{13}C(^{16}O)	1625	0.975	1374	0.987
	^{12}C(^{18}O)^c	1640		1392	
6a	^{12}C(^{16}O)	1708		1319	
	^{13}C(^{16}O)	1666	0.975	1308	0.992
7a	^{12}C(^{16}O)	1722		1327	
	^{13}C(^{16}O)	1681	0.976	1298	0.978
	^{12}C(^{18}O)^d	1691		1326	

^{a} Determined gy GLPC–IR using a Hewlett-Packard 5890A GC–IR with a Hewlett-Packard 5965A FTIR detector on the amide effluent passing from a Supelco Ultra 2 cross-linked 5% diphenyl, 95% dimethylpolysiloxane column; probable accuracy ±2 cm^{-1}. ^{b} $\nu_{^{12}C(^{18}O)}/\nu_{^{12}C(^{16}O)} = 0.985$; $\nu_{(C-N)^{18}}/\nu_{(C-N)^{16}} = 0.999$. ^{c} $\nu_{^{12}C(^{18}O)}/\nu_{^{12}C(^{16}O)} = 0.984$; $\nu_{(C-N)^{18}}/\nu_{(C-N)^{16}} = 1.000$. ^{d} $\nu_{^{12}C(^{18}O)}/\nu_{^{12}C(^{16}O)} = 0.982$; $\nu_{(C-N)^{18}}/\nu_{(C-N)^{16}} = 0.999$.

correlation (e.g., **6a**), and for amides that are capable of substantial resonance, steric effects seem to play a role in reducing the rotational barrier.

X-ray Crystallography. The structures of **6b**, **7a**, and **7b** were determined by X-ray diffraction. In Figures 4–6 are shown respective representations of the amidic portion showing the atom numbering along with selected bond lengths and angles.

In *p*-toluoylazetidine (**6b**), the N is pyramidalized (sum of angles at N is 354.7°, and displacement of N from C8–C9–C11 plane is 0.183 Å), and the four-membered ring is found to be planar (±0.004-Å displacement of N, C9, C10, and C11 from least-squares plane). The dihedral angle between the N–C9–C11 and C7–C8–O planes is 161.9°, with a slight twist about the N–C(O) bond of ~22° (the C7–C8–N–C9 and C7–C8–N–C11 torsion angles are 21.9 (9)° and 169.4 (5)°). The N—C(O) and C═O bond lengths are 1.339 (7) and 1.236 (7) Å, and the N—C(O)—C angle is 119.5 (5)°. As with the anilides,[12] we can define the distortions from an ideal amide unit through the use of Dunitz parameters[19] or twist and tilt parameters around the N—C bond:[12] $\chi_C = 0.7°$, $\chi_N = 32.5°$, $\tau' = 10.6°$, twist = 3.3°, tilt = 7.5°. The C═O bond length is not significantly different from the C═O bond length in undistorted amides (e.g., **4e**) or other distorted amides.[12] In addition, the N—C(O) bond length is the same as that in **4e**, (i.e., *not* significantly lengthened), and shorter than that reported for (*p*-bromobenzoyl)dimethylamine (1.37 Å).[18]

In *N*-toluoylpyrrole (**7a**), the pyrrole and toluoyl rings are planar, and are rotated from the C5–C8–O8 plane by 10.4° and 139.9° (representative torsion angles: C12–N8–C8–O8, −3.3 (6)°; C4–C5–C8–O8, −38.4 (6)°). The N—C(O) and C═O bond lengths are 1.409 (5) and 1.211 (5) Å, and the distortion parameters are $\chi_C = 0.0°$, $\chi_N = 10.1°$, $\tau' = 16.7°$, twist = 7.9°, and tilt = 2.6°; the N is displaced 0.063 Å from the C8–C9–C12 plane. The structure of toluoyldimethylpyrrole (**7b**) has also been determined, and contains three crystallographically independent molecules. Again, the pyrrole and toluoyl rings are planar, and are markedly distinct in their orientation with respect to the C—C═O plane: 145.7° and 143.0° for the dihedral angles of the pyrrole and toluoyl rings vs the C7–C8–O8 plane in molecule 1, 35.7° and 70.3° in molecule 2, and 145.7° and 113.7° in molecule 3. The average N—C(O) and C═O bond lengths are 1.416 and 1.208 Å, indistinguishable from the values quoted above for **7a**. The distortion of the amide unit is similar to that observed for **7a**: $\chi_C = 3.1°, 5.8°, 6.9°$; $\chi_N = 8.0°, 11.5°, 5.5°$; $\tau' = 69.1°, 84.9°, 84.0°$; twist = ~37°; tilt = ~1°; with average displacement of N from the plane of the three carbon substituents roughly 0.05 Å. The twist along the N–C(O) bond (37.1 (9)°, C1–C7–C8–N8 in molecule 1, 29.4 (9)° in molecule 2, 33.3 (8)° in molecule 3) clearly represents the energetic compromise between steric and electronic influences, an angle of 0° being favored electronically (cf., 13.4° for **7a**), but disfavored sterically due to unfavorable methyl –Ar—C═O interactions. The data suggest that the N—C(O) bond is markedly affected by the distortion at N and

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(18) The X-ray crystallographic structure of *p*-(bromobenzoyl)aziridine is reported to exhibit a pyramidalized N, with little twisting about the N–C(O) bond, while *N*,*N*-dimethyl-*p*-bromobenzamide contains a planar aide: Shibaeva, R. P.; Atovmyan, L. O.; Kostyanovskii, R. G. *Dokl. Akad. Nauk SSSR* **1967**, *175*, 586. English translation: *Sov. Phys.-Dokl.* (*Engl. Transl.*) **1968**, *12*, 669.

(19) Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr.* **1975**, *B31*, 251.

Table III. ^1H NMR Determined N-C(O) Rotational Barriers (Coalescence Temperatures) for Various Toluamides in $CDCl_3$, pK_a Values for Corresponding Ammonium Ions, and Gas-phase $\Delta G°$ Values for Amines

toluamide	$\Delta G^{\ddagger a}$ (kcal/mol)	T_c (K)	pK_a(25 °C)[b] ($H_2N^+R_1R_2$)	gas-phase $\Delta G°$ [c] (kcal/mol)	N–C(O) bond length (Å)
N,*N*-diethyl (**15a**)	14.6	306 ± 1	11.04	−20.2	
N,*N*-diisopropyl (**15b**)	13.8	295 ± 1	11.13	−24.1	
morpholino (**6e**)	14.5	297 ± 3	8.33	−15.6	1.343[m]
piperidine (**6d**)	14.6	310 ± 1	11.12	−21.2	
5	14.86[d]	*d*	10.73	−15.5	1.37[n]
6c	16.5	330 ± 1	11.27	−20.1	
6b	15.5	310 ± 1	11.29	−18.0	1.339 (7)[o]
6a	<6[e]	*e*	8.01	−11.2	1.41[n]
7a	8.3[f]	183 ± 1	<−3.8[g]	−4.8[h]	1.409 (5)[o]
3,3,4,4-tetrafluoropyrrolidine (**15c**)	14.3	290 ± 1	4.05[i]		1.324 (9)[p]
8a	13.5, 14.1[j]	283 ± 1	6.3[j]	−6.7[l]	
8b	13.1	278 ± 3	~2[k]	+7.1[l]	
N,*N*-dicyanomethyl (**15d**)	12.6	262 ± 0.5	0.2		

[a] Accuracy ±0.2 kcal/mol for barriers determined in this work. [b] From *CRC Handbook of Tables for Organic Compound Identification*, 3rd ed.; CRC Press: Boca Raton, FL, 1967 unless otherwise noted. [c] From Aue, D. H.; Bowers, M. T. In *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1980; Vol. 11, pp 1–51, or Taft, R. W. In *Proton Transfer Reactions*; Calden, E., Gold, V., Eds.; Chapman and Hall: London, 1975; unless otherwise noted; defined as free energy change ($\Delta G°$) for $HNR_1R_2 + H_4N^+ \rightleftharpoons H_2N^+R_1R_2 + NH_3$. [d] Fong, C. W.; Lincoln, S. F.; Williams, E. H. *Aust. J. Chem.* **1978**, *31*, 2614. [e] From data for *N*-benzoylaziridine, ref 30, in freon 2,2. [f] Solvent $CFCl_3/CD_2Cl_2$; 1:1. [g] Reference 36. [h] Lau, Y. K.; Saluja, P. P. S.; Kebarle, P.; Alder, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 7328. [i] Roberts, R. D.; Ferran, H. E., Jr.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054. [j] Exists as two unequally populated conformers with NCH_2CF_3 group syn and anti to C=O, ref 43a. [k] Approximate value based on an additive factor of 3.7 pK_a unit drop for replacement of CH_2CH_3 by CH_2CF_3 in passing from diethylamine to **8a**. [l] Calculated from data for $\Delta G°$ changes (footnote *c*) for $H_2NEt \rightarrow H_2NCH_2CF_3$ ($\Delta\Delta G°$ = 13.8 kcal/mol) and $H_2NEt \rightarrow NHEt_2$ ($\Delta\Delta G°$ = −8.2 kcal/mol) assuming an additivity of effects. [m] From X-ray diffraction of *N*-benzoylmorpholine; Arte, E.; Feneau-Dupont, J.; Declercq, J. P.; Germain, G.; van Meersoche, M. *Cryst. Struct. Commun.* **1977**, *6*, 767. [n] From X-ray diffraction of *N*-benzoylaziridine and *N*,*N*-dimethylbenzamide; ref 18. [o] This work. [p] Slebocka-Tilk, H.; Bennet, A. J.; Brown, R. S.; Ball, R. G. To be published.

the twist along the N—C(O) bond, unlike the C=O bond, which appears to be largely insensitive.

Discussion

a. IR(C=O) Frequencies. Amide carbonyl stretching frequencies ($\nu_{C=O}$) are generally analyzed in terms of the resonance model.[4,16] For bicyclic lactams, it is argued that structurally imposed deconjugation of the N and C=O groups is reflected in increasing $\nu_{C=O}$ relative to an appropriate bicyclic ketone.[16] Undistorted tertiary anilide **4e** by X-ray analysis[12] has a planar amidic unit that is nearly perpendicular to the plane of the aromatic ring. Anilides **4c**,**d** are also likely to have similarly disposed geometries of **4e**, and all three $\nu_{C=O}$ lie in the range of 1648–1656 cm^{-1} (column 3, Table I). Amidic distortion increases in the bicyclic anilides in the order **3d**[12] < **3c**[13d] ≃ < **3b**[13c] < **3a**, and the $\nu_{C=O}$ values increase more or less regularly from 1677 to 1755 cm^{-1}.

A similar trend of increasing $\nu_{C=O}$ is seen for nonbicyclic toluamides **5**–**8**. The values for planar **5**[18] and **6c** appear at ($CHCl_3$ cast (gas-phase)) 1634 (1672) and 1611 (1667) cm^{-1} while that in N-pyramidalized[18] **6a** appears at 1675 (1708) cm^{-1}. *N*-Toluoylazetidine (**6b**), which possesses a pyramidal N in the crystalline state, and probably in solution as based on evidence for *N*-benzoylazetidine,[20a] has a $\nu_{C=O}$ 1625 (1675) cm^{-1}. The similarity of these values to those of planar **5** and **6c** suggests N-pyramidalization alone is not particularly important in determining the $\nu_{C=O}$.

In *N*-toluoylpyrrole (**7a**), the N lone pair is said to be delocalized away from the C=O in order to maintain an aromatic sextet in the pyrrole,[15] and the same must be true for **7b** in which the 2- and 5-methyls cause rotation of the plane of the amine relative to the N—C=O plane. The $\nu_{C=O}$ values for **7a** and **7b** at 1698 (1722) and 1691 (1714) cm^{-1} are the highest for any toluamide in Table I, and are consistent with the notion that decreased resonance leads to an increased stretching force constant, and a higher observed frequency. Inductively withdrawing substituents that should decrease the nitrogen's conjugating ability also raise the gas-phase $\nu_{C=O}$ values (**8b**, 1705; *N*,*N*-dicyanomethyltoluamide (not shown in the table), 1703 cm^{-1}); this is consistent with resonance arguments.

Within a series of amides, the attribution of a charge in $\nu_{C=O}$ to a single dominant effect is subject to uncertainty due to the complex nature of the molecular deformation that accompanies the vibration. What is normally assigned as a C=O group frequency is actually a highly coupled motion of the molecule as a whole constrained in such a way that the center of mass does not change. Normal coordinate analysis for even such simple tertiary amides as dimethylformamide,[21a] or dimethylacetamide,[21b] indicates that the C=O and C—N stretches are actually heavily coupled vibrations having complex character. Thus, in a given case, the change in an amide $\nu_{C=O}$ can be caused by changes in the C=O stretching force constant and/or changes in the interaction between the C=O groups and other groups such as C—N or R—C(O).

Wiberg and Breneman[10b] have computed the C=O and C—N force constants and the C=O/C—N interaction terms for planar, and 90° rotated, formamide (**1**, **2**). Analysis of the computed[10b] vibrational data for formamide suggested that the increase in $\nu_{C=O}$ in nonconjugated **2** arises from changes in the C=O force constant, and from significant changes in the coupling of the C=O and C—N stretching modes.

Changes in coupling of the C(O) and C—N modes might be expected for amides whose resonance is precluded by means other than rotation about the N—C(O) bond. We have sought to identify unambiguously the C=O and C—N stretching bands of such amides by investigating the gas-phase IR spectra of isotopically substituted derivatives (Table II). Substitution of ^{18}O for ^{16}O, or $^{13}C(O)$ for $^{12}C(O)$, allows one to identify the isotopically sensitive vibrations. Moreover, comparison of the isotope shift of the C=O or C—N band with the theoretical value expected for an isolated noncoupled bond allows some assessment of the extent to which the atom in question contributes to the vibration and of other kinetic (energy) coupling that also contributes to the vibration. A priori, kinetic coupling of the local oscillators will lead to a mixing that is strongest for the stretching modes of adjacent bonds (e.g., C=O, N—C(O)) but will also be significant for the $N(R_1)R_2$ symmetric bending modes with $\nu_{N-C(O)}$.[17] Such mixing increases the separation of two coupled bands over what it would be in the absence of mixing, and the effect should be

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(20) a. Fong, C. W.; Grant, H. G. *Aust. J. Chem.* **1981**, *34*, 2307 and references therein. b. Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; pp 279–306.

(21) a. Durgaprasad, G.; Sathyanarayana, D. N.; Patel, C. C. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 316. b. Durgaprasad, G.; Sathyanarayana, D. N.; Patel, C. C.; Randhawa, H. S.; Goel, A.; Rao, C. N. R. *Spectrochim. Acta* **1972**, *28A*, 2311.

largest when the bands have similar frequencies.

From Table II, those amides that are expected to be highly resonance-capable (**5**, **6c**) have lower $\nu_{C=O}$, and higher ν_{C-N}, values than do resonance-impaired amides **6a** and **7a**. The theoretical $\nu_{C(^{18}O)}/\nu_{C(^{16}O)}$ ratio is 0.976 for an isolated C=O stretch. The observed ratios for **5**, **6c**, and **7** are significantly different: 0.985, 0.984, and 0.982. This suggests the oxygen atom movement in that mode is reduced from the theoretical maximum, and that other vibrational components contribute to what is assigned as the C=O stretch. A similar situation exists for the $\nu_{C=O}$ in diisopropyl ketone (^{16}O → ^{18}O, -31 cm^{-1}),[22] which has been interpreted[17] to indicate that significant mixing of the C=O stretch with other vibrational modes does occur. From the data in Table II, the ^{18}O for ^{16}O substitution gives (within the experimental uncertainty) no detectable changes in the ν_{C-N} bands for any of **5**, **6c**, or **7**, which signifies little apparent involvement of the oxygen in the C–N mode. In DMF,[17] the same ^{16}O → ^{18}O substitution gives a shift in the C=O band of -25.2 cm^{-1}, and a shift in the ν_{C-N} of -5.2 ± 0.4 cm^{-1}, signifying some mixing of the two modes. Surprisingly, isotopic substitution of ^{15}N for ^{14}N in DMF produces no observable change in the $\nu_{C=O}$,[23] despite the expectation that some shift would be evident if these two modes were coupled.

Isotopic substitution of ^{13}C(O) for ^{12}C(O) shifts all the C=O frequencies by -41 ± 1 cm^{-1}, so that as judged by the $\nu_{^{13}C(O)}/\nu_{^{12}C(O)}$ ratio, each amide in the series, regardless of its degree of resonance, exhibits an isotope shift very close to that theoretically expected for an isolated C=O stretch (0.9778).[17] This magnitude is also very close to that observed for $\nu_{C=O}$ of DMF (-39 cm^{-1})[23] or diisopropyl ketone (-37 cm^{-1}).[22] This might indicate either that the C atom moves maximally in the C=O stretch, or that it moves to a lesser extent but contributes to other modes involving the C—N or C—toluoyl units that are coupled to the C=O stretch. On the other hand, the $\nu_{^{13}C-N}/\nu_{^{12}C-N}$ ratio for the series varies from 0.993 to 0.978, signifying appreciable changes in the nature of the vibration but in no particular order that is consistent with changes in resonance. Since the theoretical value for the $\nu_{^{13}CN}/\nu_{^{12}CN}$ ratio is 0.979, it can be simplistically computed that the C–N bands reported in Table II are comprised of varying percentages of C–N stretching character (33%, **5**; 62%, **6c**; 38%, **6a**; 100%, **7a**) admixed with other modes as is the case for dimethylformamide itself.[17,23]

More detailed isotopic substitution (e.g., ^{14}N → ^{15}N) of amides **5**, **6a**,**c** and **7a** would be required to evaluate mixing of the C=O/C—N modes. The ^{18}O isotopic data at hand indicate that the C=O stretching mode is coupled with some other modes in **5**, **6c**, and **7a** but there is a disturbing insensitivity of ν_{C-N} to that isotopic substitution that could be taken as evidence for changes in the C=O/C—N interaction resulting from resonance. What can be ascertained from the peak positions given in Table II is some evidence consistent with a resonance model. Thus, for the good resonance amides **5** and **6c**, the C=O and C—N bands are closer together than is the case for the poor resonance amides **6c** and **7c**. This is in accordance with expectations based upon changes in the amount of double bond character. Also, the $CHCl_3$ cast or gas-phase $\nu_{C=O}$ data for **4a**, and **3a–d** given in Table I appear quite consistent with the resonance model, but they are not inconsistent with the Wiberg[7,10b] and Bader[10b] model, which also indicates $\nu_{C=O}$ should increase with rotation around the N—C(O) bond.

b. ^{13}C=O NMR Chemical Shifts. It has been suggested[20,24,25] that resonance contributors such as **1a** lead to a reduced electron deficiency of the carbonyl C, thereby producing an increased nuclear shielding and a corresponding upfield shift in the ^{13}C=O resonance of an amide relative to an aldehyde or ketone. Thus, the ^{13}C=O resonances of a wide variety of primary, secondary, and tertiary amides generally appear in the range of 150–175 ppm,[24] with benzamides being in the range of 166–173 ppm.[25] ^{13}C chemical shifts are governed by a complex mixture of electronic effects that influence the nuclear shieldings.[20b] Application of the resonance argument to amides predicts that reduced conjugation should produce a downfield shift for the ^{13}C=O.[26] The δ(^{13}C=O) data in Table I for **4a–d**, **5**, **6b–e**, **7**, and **8b** indicate an essentially invariant chemical shift of 167.4–172.9 ppm despite large structural and substituent effects. Only the aziridine derivative **6a** and the bicyclic anilides **3a–d** appear at lower field.

Because of the large structural variations, it is difficult to dissect the changes to the δ(^{13}C=O) resulting from differences in resonance from those due to structural variations within the amines. An attempt to do so relates the change in δ(^{13}C) in passing from a corresponding *N*-methylamine to the amide, e.g., $\Delta\delta$(^{13}C)(N*C*(O)–N*C*H_3). For the bicyclic anilides **3**, the corresponding comparison utilizes benzoquinuclidine. (This comparison is only valid for **3a**, because the larger homologues vary the orientation of the C=O relative to the aromatic ring, and furthermore possess opportunities for different γ-gauche interactions[27] that are also known to affect the ^{13}C chemical shifts.) In the toluamide series, the $\Delta\delta$(^{13}C)(amide–amine) is observed to be 122.6–127.8 for the amides expected to exhibit resonance, while the range for nondistorted tertiary anilides is 125.7–129.8 ppm. Of the remaining toluamides, **6a** and **8b** (129.6, 129.9) and the pyrroles **7a**,**b** (132.2, 141.5) exhibit a $\Delta\delta$(^{13}C) outside the normal range for toluamides. The bicyclic anilides, despite considerable scatter that may be due to the choice of **9** as a comparison amine, are also outside the tertiary anilide range, consistent with the notion that inhibiting resonance deshields the C=O.

In sum, the toluamide data for the absolute δ(^{13}C=O) shows a surprising insensitivity to the amide structure (except for **6a**); it is only by comparing the amide/amine $\Delta\delta$(^{13}C) values in the manner outlined above that the poor resonance amides **7a**,**b** and **8b** can be shown to fall outside the normal range. Even so, the difference is not dramatic, which leads one to suggest that the resonance contribution to the chemical shift of the amide C=O group probably is not as important as is generally[19b] believed.

The only amides in the series of relevance to the Wiberg[7,10b]/Bader[10a] studies concerning the effects of bond rotation in formamide are anilides **3a–d**, which do show marked downfield shifts of their ^{13}C=O relative to **4c**,**d**. In the theoretical study,[7] rotated formamide (**2**) possesses a C with more electron density than the planar form **1**. If the electron density is related to the degree of nuclear shielding, and this is a major effect in determining chemical shifts, then progressive rotation about the N—C(O) bond is expected to lead to an *upfield* shift in the δ(C=O). The fact that the δ(^{13}C=O) data for **3d–a** show a progressive *downfield* shift on N—C(O) rotation suggests other factors than the computed[7] C charge density must control the chemical shift.

c. ^{15}N NMR Chemical Shifts. It has been suggested[5] that the N lone pair delocalization with the π-system of an adjacent C=O deshields the nitrogen nucleus and thus leads to a downfield shift of an amide relative to some comparison amine. ^{15}N chemical shifts are generally considered to be dominated by the paramagnetic term in the Ramsey equation.[28] This term can be influenced by a complex mixture of inductive, steric and conjugation effects, substituent-induced distortions of the α–β bonds, and substituent-induced polarization of the lone pair electrons.[29]

Gluska et al.[30] have suggested that, to a first approximation, large deviations of a peptide bond angle (ω) away from 180° should be associated with upfield ^{15}N shifts due to decreased double bond $>N^{+}=C-O^{-}$ character. However, comparison of

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[22] Karabatsos, G. J. *J. Org. Chem.* **1960**, *25*, 315.

[23] Steele, D.; Quatermain, A. *Spectrochim. Acta* **1987**, *43A*, 781.

[24] Reference 4c, pp 267–269.

[25] In ref 20a, it is quoted that some 40 benzamides have C=O resonances from 166 to 173 ppm.

[26] The resonance argument has been invoked in ref 16 to explain the downfield shifts of the ^{13}C resonance of bicyclic lactams relative to normal amides.

[27] Beierbeck, H.; Saunders, J. K.; ApSimon, J. W. *Can. J. Chem.* **1977**, *55*, 2813.

[28] a. Ramsey, N. F. *Phys. Rev.* **1950**, *78*, 699. b. Webb, G. A. In *NMR of Nuclei other than Protons*; Axelrod, T., Webb, G. A., Eds.; Wiley: New York, 1974; Chapter 4.

[29] For a compendium of references, see: Nakanishi, H.; Roberts, J. D. *Org. Magn. Reson.* **1981**, *15*, 7.

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the ^{15}N chemical shifts for the various amides in bovine pancreatic trypsin inhibitor with their distortion (as determined by X-ray diffraction) revealed no systematic trends.[30]

In Table I are the observed $\delta(^{15}N)$ chemical shifts for various amides and their comparison amines. For a planar anilide (**4a–d**) or toluamide (**5**, **6c**, **6e**), the ^{15}N signal is 78–86 ppm downfield of the comparison amine. As the anilide becomes progressively more distorted, the $\delta(^{15}N\text{–}C(O))$ moves upfield by ~25–30 ppm (e.g., **4d** → **3d** → **3a**). Despite the near orthogonality in **3a**, the ^{15}N resonance appears 54 ppm downfield from benzoquinuclidine. Of the toluamides, **6a**, **7a**,**b**, and **8b** should have diminished resonance capabilities, and all but the latter exhibit ^{15}N resonances that move toward the comparison amines. Toluamide **8b**, however, is among the furthest away from its comparison for reasons that are unclear: Apparently inductive withdrawal from the N is not a major factor in determining the $\Delta\delta(^{15}N)$, at least for this derivative.

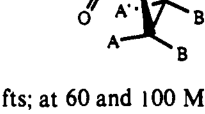
In sum, with the exception of **8b**, the available data support the resonance model in that removal of conjugation by rotation about the N–C(O) (**3a–d**), N-pyramidalization (**6a**,**b**), or occupying the lone pair in an aromatic sextet leads to an upfield shift toward the comparison amine. However, the data also indicate that at least as important an effect in rationalizing why an amidic N is downfield from its comparison amine in a deshielding of the N attributable to an inductive substituent effect.

Of relevance to the Wiberg[7,10b]/Bader[10a] model of rotated formamide are the ^{15}N NMR data for anilides **4d** and **3a–d** in which progressive rotation leads to an upfield shift of $\delta(^{15}N)$. Rotated formamide is said to have *less* electron density on N than its planar form. If, as has been proposed,[5,20,24,25] charge density contributes a large effect to the ^{13}C and ^{15}N chemical shifts, then all things being equal, the $\delta(^{15}N)$ should move *downfield* in response to rotation about the N–C(O) bond. That the data are in opposition to this expected trend suggests other factors than those computed[7,10] charges must be more prominent in determining $\delta(^{15}N)$.

Since the IR and ^{13}C and ^{15}N NMR data each show trends consistent with resonance, correlations between these are expected. In Figure 1, is a depiction of the IR $\nu_{C=O}$ and $\Delta\delta(^{15}N)$ data for the toluamides. The better relationship obtains for the gas-phase IR $\nu_{C=O}$ (right $\nu_{C=O}$ scale), and **8b** is out of sequence with the others. The graphical depiction of $\Delta\delta(^{13}C)$ vs $\Delta\delta(^{15}N)$ for the toluamides shown in Figure 2 exhibits considerable scatter. Although **8b** again is out of sequence (its $\Delta\delta(^{15}N)$ value is high), a loose correlation exists wherein large $\Delta\delta(^{15}N)$ values are associated with small $\Delta\delta(^{13}C)$ values.

d. Barriers to N–C(O) Rotation. It has been concluded that *N*-acylaziridines possess N inversion and rotational barriers of <6 kcal/mol.[19a,31] The upper limit to this value is based on the expectation that the syn and anti protons (A, B, A′, B′) in **14** would

14



have different chemical shifts; at 60 and 100 MHz, the aziridine protons appeared as a singlet even at −155 °C in freon 2,2.[31a] To check for a possible near chemical shift equivalence (unresolvable at 60 or 100 MHz), we have determined the ^{13}C and ^1H NMR for **6a** at 100 and 400 MHz in 1:1 $CH_2Cl_2/CFCl_3$. No evidence for two sets of signals is apparent, confirming the low barrier for aziridine rotation/inversion.[31a]

The process of rotation about the N–C(O) bond is likely to be a complex coupled motion involving N-pyramidalization, N–C(O) bond lengthening, and rotation; factors influencing each component will alter the $\Delta G^‡$, connecting the ground-state planar form with its transition-state rotated form. Although substituents on N are believed to affect rotational free energies ($\Delta G^‡$) by a combination of steric and electronic effects, the relative importance has been investigated in only a few instances.[32] With simple N substituent changes, the following generalities are discerned: (a) an increase in N substituent size reduces $\Delta G^‡$ for acetamides,[32a] less so for formamides,[32b,33] but produces irregular results with ortho-substituted benzamides,[34] (b) surprisingly, inductively electron withdrawing substituents were said to increase, and electron donors decrease, the $\Delta G^‡$, but the trends were based on too few examples to be general.[32] Yoder and Gardner[32a] have established that steric parameters are most important for tertiary acetamides and formamides. In that interpretation,[32a] increasing the substituent size sterically destabilizes the planar amide and leads to a reduced rotational barrier.

Amidic resonance implies a partial double bond character to the N–C(O) unit that must be broken in the rotational transition state.[3] Implicit in the argument is the expectation that those amides in which the N is most capable of sustaining a (+)-charged sp^2 configuration should have the highest rotational barriers (as measured by $\Delta G^‡$). For substituted tertiary formanilides as the remote substituent varies from p-NO_2 to p-$N(CH_3)_2$, $\Delta G^‡$ increases by 2–3 kcal/mol.[32b] In that series, the steric requirements are constant, but the basicity of the N, as judged by the pK_a[35,36] of the corresponding anilinium ion (a measure of its ability to support (+)-charge, at least as an sp^3 hybrid in H_2O), varies by 6–7 pK_a units.

Given in Table III are the ^1H NMR determined rotational barriers for several toluamides, along with the corresponding pK_a for their ammonium ions in H_2O.[34,35] Also in the table are the gas-phase free energies ($\Delta G°$) for the equilibrium $NH_4^+ + HNR_1R_2 \rightleftharpoons NH_3 + H_2NR_1R_2^+$: The more negative the $\Delta G°$, the more basic is the amine.[37] The gas-phase free energies span a greater range than do the solution-phase pK_a values, and moreover are free from the entropic effects of solvation.[38] The pK_a values span a range of >11 units, while the $\Delta G°$ values span a range of ~30 kcal/mol.

With the exception of **6a** and **7a**, the rotational barriers lie between 12.6 and 16.5 kcal/mol. The former two amides are considered anomalous because of the low barrier for **6a** (possibly because the rotated form gains from stabilization by conjugation of the Walsh-type orbitals in the three-membered ring with C=O), and because the site of protonation on pyrrole is not N but C.[39] Although a very loose correlation between amine basicity and rotational barrier exists (a plot (not shown) of $\Delta G^‡$ vs $\Delta G°$ (except for **6a** and **7a**) has a slope of -0.06 ± 0.03 ($r = 0.604$)), other factors such as steric ones are important. For example, although *N*,*N*-diethylamine and pyrrolidine have essentially equal gas-phase $\Delta G°$ values, the rotational barrier of diethyltoluamide (**15a**) is 2 kcal/mol less than that of **6c**. Similarly, the diisopropyl derivative (**15b**) has the lowest rotational barrier of any of the first seven entries in the table, despite its having the most basic amine.

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(36) In practice, the terms to be compared would be the $\Delta H^‡$ for rotation and $\Delta H°$ for the acid dissociation since each of these is free from differences in solvation entropies, and is temperature independent. The $\Delta G^‡$ values available in Table III were determined at the coalescence temperatures, which vary between the amides; full line shape analysis would be required to separate the $\Delta H^‡$ and $T\Delta S^‡$ terms.

(37) Whether one uses $\Delta G°$ for the gas-phase proton transfer or the preferable $\Delta H°$ makes little difference since the values are similar. The entropic contribution to the $\Delta G°$ at 25 °C (~1 kcal/mol) is dependent upon the changes in rotational symmetry numbers: Aue, D. H.; Bowers, M. T. In *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1980; Vol. 11, pp 1–51.

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Where the amine portions have approximately equivalent steric demands (e.g., **15a**, **8a**, **8b**, **15d** or **6b**,**c** **15c**), reduced basicity leads to a lower $\Delta G^{\ddagger}$, but the effect is a highly attenuated one.

From Figure 3, there is some relationship between a high solution-phase $\Delta G^{\ddagger}$ rotation, and low $\nu_{C=O}$ (gas-phase) for the toluamides. Within the series, certain sets of data appear to correlate linearly (e.g., **6c**,**b**, **15c**; **15a**, **8a**, **8b**, **15d**), but substantial variations exist wherein the $\Delta G^{\ddagger}$ is lower than predicted from $\nu_{C=O}$. In the data that form the upper left portion of the Figure, this could arise from steric interactions as previously discussed, or from the use of the conditional $\Delta G^{\ddagger}$ derived from the coalescence temperature rather than $\Delta H^{\ddagger}$.[36] Also quite out of sequence are the data for **6a**, which has an unusually low $\Delta G^{\ddagger}$ value; **7a** appears to have a somewhat low barrier, but it is structurally unlike the others.

It is of interest to consider the relationship between N–C(O) bond length and rotational barrier since each of these is said to be influenced by resonance. Since the rotational transition state exhibits an elongated N–C(O) bond, and pyramidalized N,[7] any amidic distortion of the ground state involving bond elongation and N rehybridization should be expected to reduce the barrier. The extant structural data available are given in Table III. Three of the data are taken from the *N*-benzoyl derivatives of **6a**, **5**,[18] and **6c**,[40] and these N–C(O) bond lengths are assumed to be relevant to the toluoyl series. The other bond lengths were determined for this study except for that of **15c**, the structure of which was determined by Dr. R. G. Ball of Merck, Sharp and Dohme Research Laboratories, Rahway, NJ.[41] A short bond is anticipated to correspond to a high barrier and vice versa; however, the shortening of the bond introduces steric interaction between the N- and C=O substituents, which as shown above could destabilize the planar form and reduce the barrier. The exact situation is determined by energetic compromise, and it is of note that the amides with short N—C(O) bonds (**6b**, **6e**, **15c**) contain sp^3-like nitrogens where the rehybridization moves the N substituents out of the destabilizing eclipsing interaction with Ar—C=O. These amides, and **5**, have high rotational barriers while reduced barriers are seen for **7a** and **6a**, which have longer N—C(O) bonds. (The structural data pertaining to **5** and **6a** are suggestive, but not as precise as one would like since the esd's are ~0.02 Å.[18]) Of these distortions, N-pyramidalization is probably not particularly important since each of **6b**, **6a**,[18] and **6e**[40] have pyramidal nitrogens but only **6a** has a markedly reduced barrier.

Conclusions

Prompted by the intriguing theoretical analysis[7,10] of planar and rotated formamide, and the subsequent report[11] of a deficiency in the latter charge analysis methodology, the present study was undertaken to provide physicochemical data for three series of amides exhibiting different potential for resonance. It was hoped that the data for these amides could provide support for or against the resonance model. In sum, the data seem generally consistent with that model, but there are indications that other factors can modify or offset the resonance effects. The main differences between the resonance and Wiberg[7,10b]/Bader[10a] models stem from the changes in the charge densities of the N and C=O in the rotated and planar form of the amide. Of the amides used in this study, only the anilide series (**3**, **4**) is directly relevant to the question of amidic rotation, but it is not easy to analyze the physicochemical data in terms of atomic electron populations. Many of the physical properties of these anilides and the toluamides ($\nu_{C=O}$, $\Delta G^{\ddagger}$ rotation, N–C(O) bond lengths) are not uniquely consistent with either model, and so cannot be used to distinguish between them. If, as has been suggested,[5,20,24–26] atomic charge densities contribute in a major way to the ^{13}C or ^{15}N chemical shifts in amides, then the two models predict opposite trends in response to attenuated resonance. The NMR data herein ($\Delta\delta(^{13}C)\uparrow$, $\Delta\delta(^{15}N)\downarrow$ accompanying reduced resonance) are in direct opposition to the trend expected on the basis of the Wiberg/Bader computed changes, and in the simplest analysis support the resonance model. Nevertheless, given the large number of competing factors contributing to the NMR chemical shifts, the so-computed[17] charge densities could represent a minor effect.

Experimental Section

a. Instrumental Details. Liquid/cast infrared spectra were determined with a Nicolet FTIR spectrophotometer using $CHCl_3$ casts or thin films of the amide. Gas-phase IR spectra were determined on the effluent of a Hewlett-Packard 5890A gas chromatograph using a Hewlett-Packard 5965A FTIR detector. In general, a sample of amide was dissolved in CH_2Cl_2 and injected onto Supelco Ultra 2 cross-linked 5% diphenyl, 95% dimethylpolysiloxane column at T_0 = 100 °C, ramped at 20 °C/min to a final temperature of 250 °C.

^{1}H NMR and ^{13}C NMR spectra were determined a Brucker WH-400 FT NMR spectrometer with ~0.02 M amide solutions in $CDCl_3$ (TMS as internal standard). Barriers to rotation were determined on the above machine in $CDCl_3$ or in some cases a 1:1 mixture of freon 1,1 and CD_2Cl_2. Natural abundance ^{15}N NMR spectra were recorded on a Brucker AM-300 FT-NMR spectrometer equipped with a 10-mm broad-band probe at 30.42 MHz. Chemical shifts (δ, ppm) given in Table I are reported upfield from CH_3NO_2 (liquid, 18.4 M) with toluene-d_8 as a lock solvent in a concentric 5-mm tube supported with PTFE O-rings. All reported shifts are at 293 ± 2 K and are uncorrected for magnetic susceptibility. Measurement of ^{15}N shifts of other reference standards such as acetonitrile(liq) and DMF(liq) under the above conditions gave values within ±0.2 ppm of the reported chemical shifts.[42] Samples of amides (as concentrated as possible) were dissolved in CH_2Cl_2, and 250 μL of toluene-d_8 was added. In all measurements, a short pulse (10–12 μs, 30–36°) followed by a long relaxation delay (15–30 s) was used. Data were obtained with a typical spectral width of 100 ppm and 16 384 points. Actual spectra were obtained after a line broadening of 2–4 Hz depending upon the signal intensity.

b. Materials. Previously synthesized amides were prepared as reported: **3ab**,[13a] **3c**,[13d] **3d**.[12] Standard Schotten–Bauman procedures (1 equiv of amine plus 1 equiv of toluoyl chloride in aqueous NaOH plus benzene) were used to prepare **5**,[14] **6a**,[14] **6c**,[14] **6d**,**e**, **4a–e**, and **8a**.[43] The toluoylpyrroles **7a** and **7b** were prepared analogously to procedures reported for the preparation of substituted benzoylpyrroles[44] by reacting with potassium anion of the pyrrole with *p*-toluoyl chloride in THF at reflux. ^{18}O-labeled toluamides were prepared by general methods previously described.[45] ^{13}C-enriched derivatives were prepared by the general Schotten–Bauman procedure but by using ^{13}C-enriched toluoyl chloride (from MSD, lot no. D-291, 90.25 atom % [^{13}C]toluic acid).

Bis(trifluoroethyl)-*p*-toluamide (8b). A solution of 4.0 g (0.022 mol) of bis(trifluoroethyl)amine (PCR Inc.) in 8 mL of dry THF was added to 0.583 g (0.024 mol) of NaH, and the mixture was heated to reflux under an Ar atmosphere overnight. The mixtue was cooled, and to it was added 2.9 mL (0.022 mol) of *p*-toluoyl chloride in 8 mL of dry THF. The resulting mixture was heated at reflux for 5 days, and then terminated by cooling and pouring the reaction mixture onto 20 g of ice. The basic solution was neutralized by the addition of 1 M HCl and then extracted with ether (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and filtered and the volatiles removed by rotary evaporation. The residue was vacuum distilled (73 °C (0.15 Torr)) to yield 1.5 g (23%) of a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 4.25 (q, J = 8.8 Hz, 4 H), 7.27 (m, 4 H); IR ($CHCl_3$ cast) 1678.77 cm^{-1}; exact mass calcd for $C_{12}H_{11}F_6NO$ 299.0745, found 299.0746. Anal. C, H, N.

***p*-Toluoylazetidine (6b).** This amide was prepared from azetidine, which was in turn prepared by a slight modification of the procedure of White and McGillivray.[46] *N*-Tosyl-*O*-tosyl-3-aminopropanol[47] (14.57 g, 0.038 mol) was suspended with mechanical stirring in 1.6 L of H_2O. The solution was heated to reflux, and a solution of 1.02 N NaOH (37.5 mL, 0.038 mmol) was added via a high-dilution dropping funnel over a period of 2 h, followed by heating at reflux for an additional 3 h. The hot solution was treated with activated charcoal and filtered through a

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Table IV. Summary of Crystallographic Information

	6b	**7a**	**7b**
formula	$C_{11}H_{13}NO$	$C_{12}H_{11}NO$	$C_{14}H_{15}NO$
formula weight	175.23	185.23	213.28
crystal size (mm)	0.10, 0.25, 0.38	0.05, 0.20, 0.35	0.12, 0.30, 0.36
a (Å)	7.690 (5)	6.136 (6)	7.588 (5)
b (Å)	10.754 (3)	20.448 (7)	13.466 (7)
c (Å)	11.442 (4)	7.610 (2)	19.694 (10)
α (deg)			69.19 (4)
β (deg)			79.14 (5)
γ (deg)			74.39 (5)
V (Å^3)	946	954	1802
Z	4	4	6
space group (no.)	$P2_12_12_1$ (19)	$P2_12_12_1$ (19)	$P\bar{1}$ (2)
μ (cm^{-1})	0.72	0.50	0.69
scan rate (deg min^{-1})	1.0	0.5–1.0	2.0
2θ(max) (deg)	56	56	40
θ scan width (deg)	1.0	0.5	0.6
no. of reflns (total)	1363	2304	3371
no. of reflns (used)	628	1334	1914
R_1	0.068	0.059	0.070
R_2	0.062	0.065	0.068
goodness of fit	1.62	1.46	1.82

Celite pad and the filtrate cooled to allow crystals to form. The mixture was then filtered to afford 6.74 g (84%) of *N*-tosylazetidine.[46] Detosylation of this material was effected as reported,[47] and the amide **6b** was prepared by using the standard Schotten–Bauman reaction.

c. X-ray Crystallography. Experimental details on each of the determinations are summarized in Table IV. Single-crystal X-ray diffraction intensities were collected at ambient temperatures on an Enraf-Nonius CAD4 diffractometer with Mo Kα radiation (λ = 0.7107 Å) and Zr filter. The structure solution and refinement were carried out on a SUN Microsystems 3/160 workstation. Complete details, including listings of atomic coordinates, displacement parameters, all interatomic bond lengths and angles, torsional angles, least-squares plane information, and structure factor amplitudes have been deposited as supplementary material.

Acknowledgment. We thank the University of Alberta and Natural Sciences and Engineering Research Council of Canada for financial support of this work. In addition, we are grateful to Professor J. E. Bertie (Department of Chemistry, University of Alberta) for helpful discussions concerning infrared analysis, to Ms. B. A. Kellogg for the preparation of **8b** and *N*,*N*-dicyanomethyltoluamide, and to Dr. H. Slebocka-Tilk for the preparation of **8a** and *N*-toluoyl-3,3,4,4-tetrafluoropyrrolidine. Finally, Professor E. Knaus, Faculty of Pharmacy, University of Alberta, is acknowledged for his generosity in making available the Bruker AM300 FT NMR spectrometer to V.S. for determining the ^{15}N chemical shifts.

Registry No. 3a, 76059-52-4; **3b**, 102586-88-9; **3c**, 128732-45-6; **3d**, 128732-46-7; **4a**, 103-84-4; **4b**, 579-10-2; **4c**, 6332-98-5; **4d**, 573-26-2; **4e**, 128732-47-8; **5**, 14062-78-3; **5**-^{13}C, 135469-61-3; **5**-^{18}O, 113109-79-8; **6a**, 2453-33-0; **6a**-^{13}C, 135469-64-6; **6b**, 51425-91-3; **6c**, 59746-40-6; **6c**-^{13}C, 135469-62-4; **6c**-^{18}O, 135469-63-5; **6d**, 13707-23-8; **6e**, 63833-44-3; **7a**, 70971-70-9; **7a**-^{13}C, 135469-65-7; **7a**-^{18}O, 135469-66-8; **7b**, 135469-59-9; **8b**, 135469-60-2; bis(trifluoroethyl)amine, 407-01-2; *p*-toluoyl chloride, 874-60-2; azetidine, 503-29-7; *N*-tosyl-*O*-tosyl-3-aminopropanol, 51425-88-8; *N*-tosylazetidine, 7730-45-2.

Supplementary Material Available: Experimental details and tables of atomic coordinates, displacement parameters, all interatomic bond lengths and angles, torsional angles, and least-squares plane information for **6b**, **7a**, and **7b** (47 pages); tables of calculated and observed structure factors for **6b**, **7a**, and **7b** (39 pages). Ordering information is given on any current masthead page.

Tracing Indications of Anomalous Diffusion in Adsorbent–Adsorbate Systems by PFG NMR Spectroscopy

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Abstract: PFG (pulsed field gradient) NMR spectroscopy is applied to measure the molecular mean square displacement in various adsorbent–adsorbate systems in dependence on the observation time. Irrespective of the fact that the pore size distribution yields fractal properties, for the investigated active carbons over the accessible space scale ($\gtrsim 1$ μm), mass transfer of the adsorbed molecules is found to obey the laws of ordinary diffusion. When molecular mass transfer in beds of zeolite crystallites is investigated, deviations from ordinary diffusion are found. They are to be attributed, however, to the influence of the crystallite boundary and/or the intercrystalline space. It is most likely that the recently observed indication of anomalous diffusion in polycrystalline grains of zeolite ZSM-5 may be attributed to analogous microdynamic processes.

In the last few years, mass transfer in disordered media has attracted the interest of a large number of researchers.[1-6] As yet, the major part of these investigations has been devoted to purely geometrical models, so that there is a remarkable deficiency in our knowledge of mass-transfer phenomena in real systems reflecting the properties predicted by the theory. PFG (pulsed field gradient) NMR spectroscopy has been repeatedly proposed as a most sensitive tool for detecting deviations from ordinary diffusion during mass transfer in adsorbent–adsorbate systems.[5-7] In comparison to other techniques, the PFG NMR method provides a most direct way to measure molecular mean square displacements without any interference with the intrinsic mass transfer phenomena.[8,9]

In the case of ordinary, three-dimensional diffusion, according to Einstein's relation

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