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Amide Conformational Switching Induced by Protonation of Aromatic Substituent

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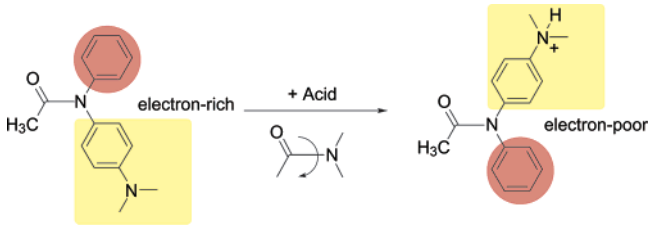
ABSTRACT



Introduction of an electron-withdrawing group on the aromatic ring of *N*-methylacetanilide decreased the ratio of the cis conformer, and the ratio correlates well with the Hammett σ values of the substituents. These steric properties can be applied to achieve amide conformational swiching by protonation at the aromatic substituent of 4-[bis(dimethylamino)]-*N*-methylacetanilide or *N*-[*p*-(dimethylamino)phenyl]-*N*-phenylacetamide.

The amide bond structure of amide derivatives often plays a key role in functions such as molecular recognition events or biological activities.[1] In contrast to the extended trans structures of most secondary amides, such as acetanilide (**1a**) and benzanilide (**2a**),[2,3] the corresponding *N*-methylated compounds, **3a** and **4a**, respectively, exist in cis form in the crystals and predominantly in cis form in various solvents (Figure 1).[4] The cis conformational preference is useful as a building block to construct aromatic molecules with unique crystal or solution structures.[5] In the present study, we demonstrate that the conformational properties of **3a** can be applied to achieve amide conformational switching by protonation at a remote substituent.[6]

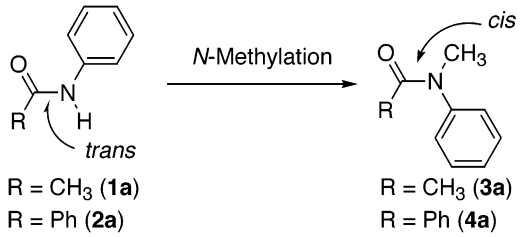


Figure 1. Cis-conformational preference of *N*-methylated anilides.

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(2) In this paper, cis and trans are defined as shown in Figure 1 in order to describe the molecular conformations consistently, since *E* and *Z* can be interconverted simply by a change of the substituents.

(3) (a) Stewart, W. E.; Sidwell, T. H., III. *Chem. Rev.* **1970**, *70*, 517−551. (b) Kashino, S.; Ito, K.; Haisa, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 365−369.

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Ab initio calculations for **1a** and **3a** showed that the phenomenon can be understood in terms of destabilized trans structure of **3a** with a large torsion angle of the Ph−N bond, due to the steric hindrance between the two methyl groups and to electronic repulsion between the carbonyl and the phenyl groups.[7] From this result, it seems reasonable that the electronic properties of the *N*-aromatic ring would affect the stability difference between cis and trans conformers. Substituent effects on amide rotational barriers have been well studied by using dynamic NMR techniques,[8,9] while no significant dependency of cis/trans equilibrium on the aromatic substituents was found.[10] Our ab initio calculations with the HF/6-31G* basis set showed that the relative stability of the cis conformer of **3a** was decreased by introduction of a *p*-nitro group (data not shown). This result led us to investigate the cis/trans energy differences ($\Delta G°$, $[\Delta G°_{cis} - \Delta G°_{trans}]$) of various *N*-methylacetanilides. All monosubstituted *N*-methylacetanilides (**3b**−**o**) exist in two conformers at low temperature.[11] In each case, the major conformer was assigned as cis ($\Delta G° < 0$), based on the chemical shifts, and the ratio of the cis conformer decreases as the group on the aromatic ring of **3** becomes more electron-withdrawing. Significantly, the change of $\Delta G°$ shows a good correlation ($R = 0.978$) with the Hammett's σ values,[12] with a slope of 1.01 (Figure 2). Considering this

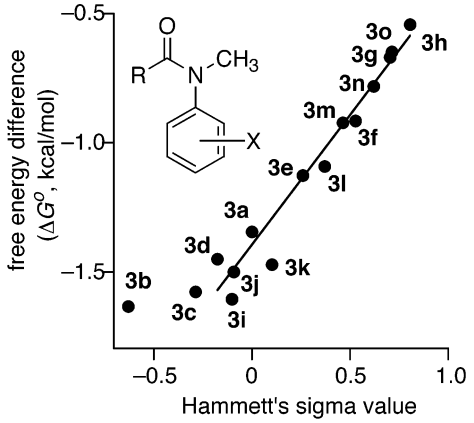
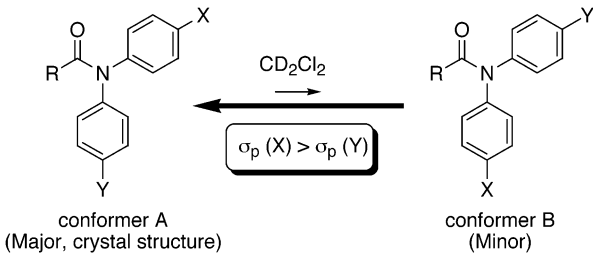


Figure 2. Plot of $\Delta G°$ vs Hammett's substituent constant (σ). The substituent (X) is H (**3a**), *p*-$N(CH_3)_2$ (**3b**), *p*-OCH_3 (**3c**), *p*-CH_3 (**3d**), *p*-Br (**3e**), *p*-CF_3 (**3f**), *p*-CN (**3g**), *p*-NO_2 (**3h**), *m*-$N(CH_3)_2$ (**3i**), *m*-NH_2 (**3j**), *m*-OCH_3 (**3k**), *m*-Cl (**3l**), *m*-CF_3 (**3m**), *m*-CN (**3n**), and *m*-NO_2 (**3o**). In the calculation of the fitting line ($\Delta G° = -1.40 + 1.01\ \sigma$, $R = 0.978$), the data of **3b**, **3c**, and **3i**, having less than 2% of the minor conformer, were excluded.

linearity, *N*-methylacetanilide bearing an electron-withdrawing group ($\sigma > 1.39$) was expected to prefer the trans conformation. Indeed, *N*-methyl-*m*,*m*-dinitroacetanilide (**3p**, $\sigma = 0.71$ for one *m*-nitro group) exists in trans form as the major conformer ($\Delta G° = 0.28$ kcal/mol).

In contrast to the above results, the introduction of substituents on the *N*-phenyl ring of benzanilides (**4**) only slightly affects the cis conformational preference. The $\Delta G°$ value for **4a** or **4b** with a *p*-methoxy group is −1.55. Compound **4c** with a *p*-nitro group showed an ^{1}H NMR spectrum at 193 K corresponding to a single conformer, assigned as the cis form.[2]

The substituent effects on the confomation of *N*-methylacetanilides (**3**) indicate that the electronic character of the *N*-phenyl group contributes at least partially to cis conformational preference. This means that the more electron-deficient aromatic ring would prefer the cis relationship to the carbonyl oxygen when the amide bears two different *N*-aromatics. In fact, such conformations (named conformer A, Figure 3) are observed in the crystals and in the



	R	X	Y	ΔG^o (kcal / mol)	
5	CH_3	NO_2	OCH_3	1.13	(183 K)
6	CH_3	H	$N(CH_3)_2$	0.56	(233 K)
7	Ph	NO_2	OCH_3	0.45	(183 K)

Figure 3. Solution equilibrium of *N*,*N*-diarylamides **5**−**7** in CD_2Cl_2.

predominant solution structures of *N*,*N*-diarylacetamides **5** and **6**.[13] The free energy difference between the two conformers A and B of **5** ($\Delta G° = 1.13$ kcal/mol) is larger than that of **6** ($\Delta G° = 0.56$ kcal/mol), as would be expected

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(10) Waisser, K.; Palat, K., Jr.; Exner, O. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1295−1306.

(11) The structures **3** and the rotational barrier ($\Delta G^‡$) are shown in the Supporting Information. The $\Delta G^‡$ value of the para-substituted compounds correlates well with the Hammett σ value, while the meta substitution affects less on the $\Delta G^‡$ value.

(12) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structures*, 5th ed.; John Wiley & Sons: New York, 1999; p 370.

(13) The ratio of the conformers of **6** was determined by using **6**-d_5 in which all hydrogen atoms on the unsubstituted phenyl group were replaced by deuterium atoms, since the methyl group signals did not show complete separation.

from the difference in the Hammett's σ values of the two substituents (R_1 and R_2). Interestingly, the benzamide **7** also showed a crystal structure with the electron-poor nitrophenyl group cis to the amide oxygen atom, like **5**. The result that the energy difference ($\Delta G° = 0.45$ kcal/mol) is less than half that of **5** is in accordance with the fact that the preferred conformation of *N*-methylbenzanilide (**4**) was little affected by the aromatic substituent.

The substituent effects observed in acetamides can be applied to achieve amide conformational switching induced by acid; that is, the conformation of acetamides having a basic amino group on the aromatic ring is expected to be altered by protonation on the amino group. In the case of **3b** with a *p*-dimethylamino group, the addition of TFA-*d* (excess over **3b**) decreased the percentage of cis conformer from 97.2% to 82.6% at 233 K. This small change is reasonable, considering the σ value (0.60) of the NH_3^+ group.[12] In the case of **3q** with two dimethylamino groups, the major conformation (>99.9% cis in CD_2Cl_2) dramatically changed to trans (76.1%) upon addition of TFA-*d* (Figure 4). The fact that the percentage of the cis conformer of **3a** (95.5% in CD_2Cl_2) was not affected (95.3%) by the addition of TFA-*d* indicated that the amide conformational alteration did indeed result from protonation on the dimethylamino group. The percentage of cis conformer in CD_3OD (>99.9%) also decreased to 71.6% by the addition of DCl, but the extent of the change was small. This indicates that the cis/trans ratio of **3q** depends significantly on the acidity of the solvent. The estimated σ value of the *m*,*m*-bis(dimethylamino) group using the correlation line shown in Figure 2 is 1.92 in CD_2Cl_2−TFA-*d* or 0.89 in CD_3OD−DCl.

Similar amide conformational switching was observed in the *N*,*N*-diarylacetamide **6**. The amide **6** has a major conformer A (76.9%) with the electron-rich *p*-dimethylaminophenyl group trans to the amide oxygen atom in CD_2Cl_2. Upon addition of TFA-*d*, the conformer B-H^+ became predominant (84.7%). In the case of **6**, conformational switching from conformer A (72.6%) to B-H^+ (83.5%) was also observed in the experiment using CD_3OD and DCl as solvent and acid, respectively.

The results shown here are simple examples, but should be applicable to the construction of pH-dependent aromatic architecture. Recently the development of functional molecular devices that undergo reversible conformational interconversion between two or more stable states when exposed to an external stimulus, such as light, electricity or a chemical reaction, has received much attention.[6] The molecular conformational change of aromatic amides caused by remote protonation may be applicable as a solvent acidity-dependent molecular switch.[14]

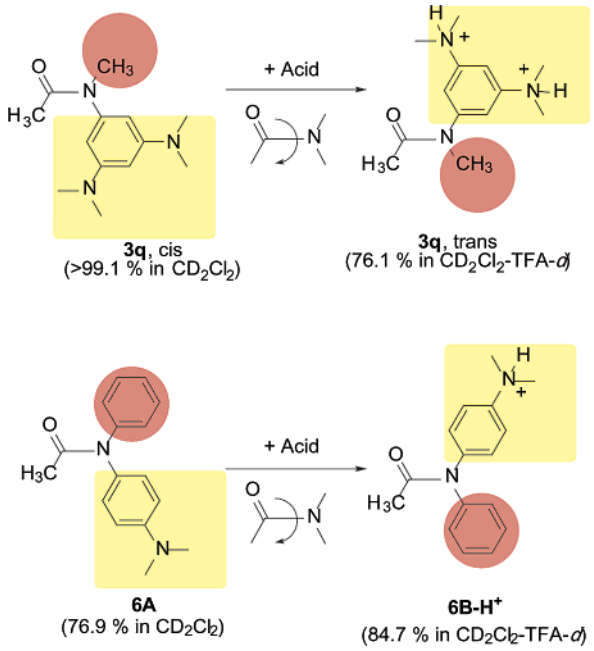

Figure 4. Amide conformational switching by acid. The amount of acid is 3% w/w to solvent. Further addition of acid did not affect the conformational ratio.

Supporting Information Available: Experimental details, ^{1}H NMR data, and crystal structures (**5** and **6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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