Solvent Effects on Barrier to Rotation of Enaminonitriles Using Inversion Transfer ^{1}H NMR Spectroscopy and FTIR Spectroscopy

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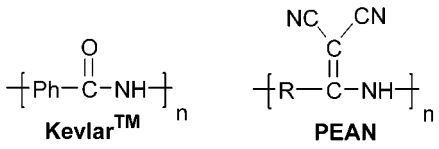
Abstract: The barrier to rotation and hydrogen bonding interactions of 2,2-dicyano-1-(*N*,*N*′-dimethylamino)vinylbenzene (**1**) were studied in a range of solvents. The barrier to rotation of **1** in chloroform was 14.8 kcal/mol and increased by 1.7 kcal/mol in a protic solvent, trifluoroethanol. FTIR studies showed a shift in the cyano stretch of **1** to a higher wavenumber in trifluoroethanol, which is consistent with **1** participating in a hydrogen bonding interaction at the vinyl carbon (C_v) of the enaminonitrile group.

The chemical properties of the amide bond make a significant contribution to the formation of protein structure and bulk properties of commercially important polymers such as Kevlar. In both of these examples, the amide properties of interest include the ability to participate in hydrogen bonding interactions and the "slow" rotation observed about the C−N bond. Decades of studies have revealed that Pauling's resonance theory explains much of the behavior of amides,[1] and in the design of novel amide mimics, these properties are important features to be considered. In this study, we report our findings on the characterization of the amide-like character of enaminonitriles to evaluate its potential as a peptidomimic. The enaminonitrile group was first described by Wallenfel[2] who suggested that the $C(CN)_2$ group is inductively equivalent to an oxygen atom. Moore et al. developed synthetic approaches to make high molecular weight poly(enaminononitriles) (PEANs) where the oxygen atom of the amide bond was replaced with the $C(CN)_2$ moiety to give the enaminonitrile group (Chart 1).[3] PEANs were originally developed to overcome the inherent insolubility of a commercially important aromatic polymer, Kevlar, that otherwise exhibits excellent thermal and mechanical properties. With the incorporation of enaminonitrile linkages, PEANs became significantly more soluble in polar aprotic solvents than their aromatic polyamide counterparts. The improved solubility of PEANs is believed to be the result of lower crystallinity and/or weaker hydrogen bonding interactions caused by the presence of the bulkier and more polarizable dicyanovinylidene group in the polymer.[3] Thus, unlike the strong intermolecular amide associations in polyamides, PEANs may be less self-associated and solvents are able to compete for hydrogen bonding sites in PEANs, leading to solubilization.

Chart 1



The enaminonitrile linkage retains many of the features of the amide linkage, including a high barrier to rotation about the C−N bond and the ability to participate as both a hydrogen bond donor and acceptor. It is our interest to study more closely the amide-like character of enaminonitriles. Solvent effects on the barrier to rotation for amides have been previously reported[4,5] and will be compared to enaminonitriles. The barrier to rotation in enaminonitriles has been measured using dynamic NMR spectroscopy, but these studies have a ±1.0 kcal/mol margin of error.[6] As a result, subtle differences in the barrier to rotation between the amide and enaminonitrile groups have been difficult to discern. Previous studies on amide compounds have shown that both electronic effects and sterics influence the barrier to rotation, with a decrease in the barrier to rotation being observed with the increasing bulk of amide substituents.[7] Molecular modeling studies on enaminonitriles, however, suggest that the presence of the bulkier $(CN)_2C$ moiety is not likely to impact the barrier to rotation to any significant extent, and electronic effects are expected to be the predominant factor in determining the barrier to rotation.[8]

Compound **1** was selected as the enaminonitrile model compound for this study because it can participate as a hydrogen bond acceptor but not as a hydrogen donor (Scheme 1). The barrier to rotation about the C−N bond for **1** was determined in solvents using inversion transfer ^{1}H NMR spectroscopy. FTIR spectroscopy was used to follow changes in the cyano vibrational mode of **1** in aprotic and protic solvents of varying polarity.

The behavior of enaminonitriles in solvents of different polarity can be evaluated using resonance theory. The expected resonance structures for an enaminonitrile group are outlined in Scheme 2, with three primary structures illustrated because of the extended conjugation possible with the cyano groups. Two of these resonance structures indicate potential hydrogen acceptor sites: the

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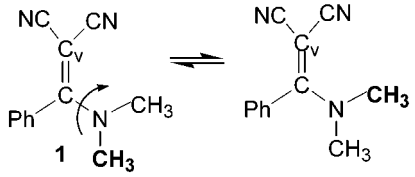
Scheme 1



Scheme 2. Primary Resonance Structures of Enaminonitrile

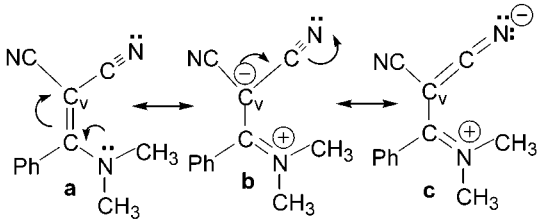


Table 1. Solvent Effects on the Activation Parameters of Compound 1

solvent	ϵ_r[a]	$\Delta G^{\ddagger}$[b]	$\Delta H^{\ddagger}$[c]	$\Delta S^{\ddagger}$[d]
$CDCl_3$	4.81	14.8	19.9	17
CD_2Cl_2	8.93	14.9	18.6	12
CD_3CN	35.94	15.1	16.9	6
DMF-d_6	36.71	15.1	18.4	11
TFE[e]	25.41	16.5	19.7	11

[a] Dielectric constants.[11] At 25 °C: [b] At 25 °C: ±0.2 kcal/mol. [c] At 25 °C: ±0.3 kcal/mol. [d] At 25 °C: ±4 cal/(mol K). [e] See ref 12.

negatively charged carbon in resonance structure **b** and the negatively charged nitrogen in resonance structure **c**. With protic polar solvents, both dielectric constant effects and hydrogen bonding interactions are possible, although the latter are expected to predominate.[9] Hydrogen bonding should lead to a higher contribution from the more polar resonance structures **b** and **c**, and, accordingly, a higher barrier to rotation is expected. There is some controversy in the literature about the validity of using the resonance model to describe amides.[10] One contention is that the resonance description does not adequately explain changes in the bond length determined experimentally and from theoretical calculations. This controversy also has been considered for enaminonitriles where the overall charge density distribution for an enaminonitrile compound has been determined using *ab initio* quantum mechanical calculations. In the case of enaminonitriles, the theoretical calculations appear to be in agreement with the resonance description outlined in Scheme 2.[8]

The barrier to rotation ($\Delta G^{\ddagger}$) around the C−N bond in **1** was determined using inversion transfer ^{1}H NMR spectroscopy. Table 1 reports the $\Delta G^{\ddagger}$ for **1** in solvents of different polarity, along with the thermodynamic data for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ calculated using a linear least-squares fit of the Eyring plots (see Figure 1 in Supporting Information).

A significant barrier to rotation is observed for **1** (14.8 kcal/mol in $CDCl_3$). This value is slightly lower than the barrier to rotation reported for its amide counterpart, *N*,*N*-dimethylbenzamide (15.3−15.6 kcal/mol in $CDCl_3$),[13] suggesting that the $C(CN)_2$ group may have a slightly lower electron-withdrawing effect than the oxygen atom in amides. These results, however, demonstrate that enaminonitriles, like amides, have a fairly high barrier to rotation and that there is significant double-bond character about the C−N bond in enaminonitriles, as predicted by the resonance delocalization description (Scheme 2). Also like amides, Eyring plots of different solvents showed a linear relationship, an indication that there is no significant heat capacity of activation for this isomerization reaction.

The data presented in Table 1 report the barrier to rotation for **1** in solvents of different polarity. The activation parameters show that the barrier to rotation is mostly enthalpic in origin with a minor entropic contribution. This thermodynamic signature is similar to that reported for amides[4] and carbamates.[14] In the absence of hydrogen bonding, the barrier to rotation appears to increase slightly with increasing polarity of aprotic solvents; there is a small 0.3 kcal/mol increase in the barrier to rotation as the dielectric constant of the solvent goes from 4.81 in chloroform to 35.94 in acetonitrile. While this change is subtle, the trend is consistent with the expectation that greater polarity of the solvent should stabilize the resonance structures **b** and **c** that have dipolar character (Scheme 2). Acyclic tertiary amides also respond to solvents of greater polarity with a higher barrier to rotation, with increases on the order of 0.3−1.0 kcal/mol reported in the literature.[4] Thus, the enaminonitrile group appears to respond to solvent polarity in a fashion similar to that of amides, albeit with a smaller change in the barrier to rotation. The barrier to rotation of **1** increased significantly when studied in TFE (trifluoroethanol), most likely the result of hydrogen bonding interactions between the protic polar solvent and the enaminonitrile group. A similar increase in the rotational barrier was observed for tertiary amides in the presence of a protic solvent.[4]

While the barriers to rotation of amides and enaminonitriles show similar trends in protic polar solvents, the barrier to rotation for *N*,*N*-dimethylaminoacrylonitrile, $NC-CH=CH-N(CH_3)_2$, in methanol or water was reported to be insensitive to hydrogen bonding interactions.[9] Also, the barrier to rotation of 12.6 kcal/mol in chloroform for *N*,*N*-dimethylaminoacylonitrile is significantly lower than that observed for **1**. This result is not unexpected because one cyano group in *N*,*N*-dimethylaminoacrylonitrile is likely to have a lower inductive effect than $C(CN)_2$ in enaminonitriles. This observation is supported by the difference in ^{13}C NMR chemicals shifts observed for the two vinyl carbons in the enaminonitrile group (a difference of 110−120 ppm).[5] The vinyl carbons of *N*,*N*-dimethylaminoacrylonitrile show a smaller difference (95 ppm), which is consistent with a smaller charge separation that can be expected for a lower inductive effect and may explain the insensitivity of the barrier to rotation for *N*,*N*-dimethylaminoacrylonitrile to the presence of protic solvents.

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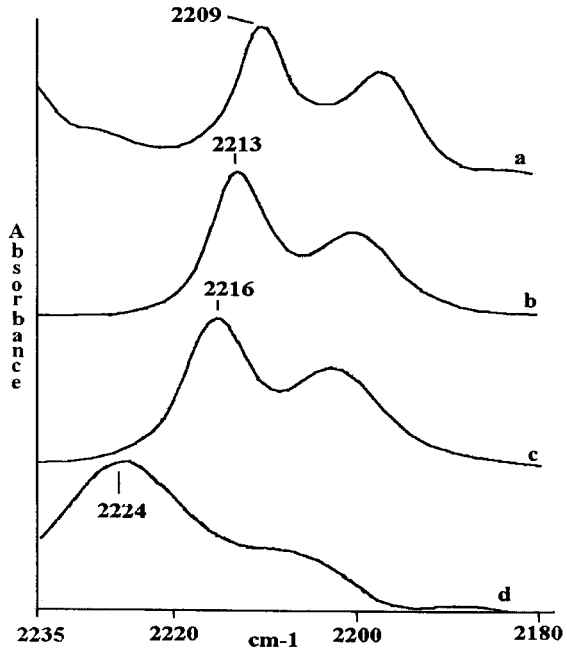

Figure 1. FTIR spectra of compound **1** in (a) CH_3CN, (b) CH_2Cl_2, (c) $CHCl_3$, and (d) TFE.

Table 2. Solvent Effects of the Cyano Vibrational Modes of 1

solvent	ϵ_r	CN vibrational mode A (cm^{-1})	CN vibrational mode B (cm^{-1})
$CHCl_3$	4.81	2216	2202
CH_2Cl_2	8.93	2213	2200
CH_3CN	35.94	2209	2196
TFE	25.41	2224	2209

FTIR spectroscopy was used to follow changes in the frequency of the cyano vibrational mode for **1** in several solvents of different polarity at concentrations of 2, 5, and 10 mM. No aggregation behavior was observed over these concentrations. Figure 1 shows the FTIR spectrum of the cyano region for compound **1** in solvents of different polarity. Two cyano stretches were observed, and the results are summarized in Table 2. Changes in the cyano bond order provide information about the electronic redistribution that occurs as the enaminonitrile group interacts with its dielectric environment. A gradual decrease in the wavenumber of the CN band is observed as the polarity of the solvent changes from the relatively nonpolar $CHCl_3$ solvent to the aprotic polar solvent, CH_3CN. These results are consistent with a reduction in the cyano bond order as the polarity of the solvent increases and can be explained by the resonance picture depicted in Scheme 2. Increasing the polarity of the solvent is expected to favor resonance structures **b** and **c** that have dipolar character; this interpretation is consistent with the subtle increase in the barrier to rotation observed with increasing solvent polarity. A further distinction between resonance structures **b** and **c** can be made on the basis of changes in the cyano bond order. The slight decrease in the cyano bond order with increasing solvent polarity is best explained by contribution from resonance structure **c**. If only structure **b** was involved, no changes at the cyano band would have been observed. Overall, the resonance description of enaminonitriles shown in Scheme 2 provides an adequate explanation of the behavior of the enaminonitrile group when polarity of the solvent is increased.

When **1** was studied in TFE, the frequency of the cyano vibrational mode increased by 15 cm^{-1} relative to CH_3CN. This shift corresponds to an increase in the bond order of the cyano band in the presence of a protic solvent, which is in contrast to the trend observed in polar aprotic solvents. TFE is both a polar solvent and a strong hydrogen bond donor. Since the trend is not consistent with polarity effects, where a shift to lower wavenumbers would be anticipated, hydrogen bonding interactions are likely to be the dominant effect observed here where the solvent is the proton donor to **1**. The increase in the barrier to rotation of **1** in trifluoroethanol implies that resonance structures **b** and **c** are favored. The accompanying increase in the bond order of the cyano band further suggests that resonance structure **b** is the more important of the two resonance structures when hydrogen bonding interactions are present. If the contribution from structure **c** was significant, a shift to lower wavenumbers in the cyano band would have been the result. Therefore, these results suggest that the hydrogen acceptor site in enaminonitriles is the vinyl carbon atom labeled C_v in Scheme 2. The fact that the hydrogen bonding apparently occurs at the C_v atom suggests that the vinyl C_v is more basic than the nitrogen atom of the cyano group.

Our findings suggest that the enaminonitrile group may serve as an amide mimic. The amide-like properties include resonance that leads to a barrier to rotation about the C−N bond and the capacity to participate in hydrogen bonding. In particular, **1** shows a barrier to rotation that follows the same trends in protic polar solvents as do acyclic tertiary amides. While these properties demonstrate the amide-like character of enaminonitriles, there are some subtle differences. First, the barrier to rotation of **1** is 0.6 kcal/mol lower than that of the amide equivalent. Second, the hydrogen acceptor site in enaminonitrile is proposed to be a vinyl carbon atom (C_v) in contrast to an oxygen atom in amides, and third, enaminonitriles are believed to exhibit weaker intermolecular interactions than amides.[3] In our future work, we plan to study how these differences play a role in the structure and properties of peptides containing the enaminonitrile linkage, with the long-term goal of applying this knowledge toward the synthesis of a novel class of synthetic proteins.

Experimental Section

Materials. 1-Chloro-2,2-dicyanovinylbenzene was synthesized using reported procedures[3]; diazabicylo[2.2.2]octane (DABCO) was sublimed under vacuum (5 mmHg) between 60 and 65 °C. Dimethylamine HCl, acetonitrile (CH_3CN), methylene chloride (CH_2Cl_2), chloroform ($CHCl_3$), dimethylformamide (DMF), dimethylacetamide (DMAC), and trifluoroethanol (TFE) were purchased commercially and used as received (HPLC grade).

Synthesis of 2,2-Dicyano-1-(*N*,*N*′-dimethylamino)vinylbenzene (1). Dimethylamine HCl (0.65 g, 8.0 mmol), DABCO (1.82 g, 16.0 mmol), and 6 mL of DMAC were placed in a dried 50 mL three-necked flask, equipped with a nitrogen inlet and a magnetic stirrer. 1-Chloro-2,2-dicyanovinylbenzene (1.5 g, 8 mmol) was added slowly as a solid, and a light yellow solution was obtained. After 24 h at room temperature, water was added to the reaction mixture and a light yellow solid was obtained upon filtration. The product was purified by recrystallization from chloroform (0.81 gm, 50% yield), followed by sublimation at 100 °C under vacumn (1 Torr) to give yellow crystals. Mp: 120−122 °C. FTIR (KBr pellet): 2920, 2216, 2202 (CN), 1540,

1440, 1365, 1285, 1268, 1010, 885 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.44−7.57 (m, 3H), 7.333 (d, 2H, J = 9 Hz), 2.87, 3.52 (broad singlets, CH_3). ^{13}C NMR ($CDCl_3$): δ 171.8 (N−*C*═C), [133.0, 131.8, 129.4, 128.6], 116.6, 117.1 (CN), 53.3 (N−C═*C*), 43.1, 44.6 (CH_3). GC/MS (EI): *m*/*e* 197 (M^+), 156, 131, 91,77. Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.10; H, 5.58; N, 21.32. Found: C, 73.17; H, 5.66; N, 21.42.

FTIR Spectroscopy. FTIR spectra were recorded on a spectrophotometer using CaF_2 cells with a 1 mm path length. Each spectrum was collected for 32 or 64 scans with a resolution of within 2 cm^{-1}. Concentrations of 2, 5, and 10 mM of **1** in CH_2Cl_2, $CHCl_3$, CH_3CN, and TFE were studied. No concentration effects were observed.

Inversion Transfer NMR Spectroscopy. The isomerization rates of **1** were determined using the method described by Led and Gessmar.[15] These ^1H NMR inversion transfer experiments were conducted on a spectrometer using a 5 mm broadband probe. Each enaminonitrile sample was prepared at 10 mM concentrations of **1** in the highest quality solvents available. Doubling or halving the concentration of **1** in the sample did not alter the rates. Experiments were performed using temperatures of 270−299 K. Temperature settings of the spectrometer were calibrated to within 1 °C by reference to a glycol standard. Further experimental and calculation details are available in Supporting Information.

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Supporting Information Available: Eyring plots for model compound **1** (Figure 1), and further details on treatment of experimental data for inversion transfer ^1H NMR spectroscopy experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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