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ROTATIONAL BARRIERS IN FIVE RELATED AMIDES

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Abstract

Interest in the low carbonyl infrared frequency of 2-hydroxy-*N,N*-bis(2-hydroxyethyl)acetamide (**2**) initially prompted our interest in the amide rotational barrier of this molecule and four related amides which present a variety of hydrogen-bonding possibilities. In the course of this study, a previously incorrect structural assignment was established as *N,N*-bis[2-(acetyloxy)ethyl]-acetamide (**6**). In acetonitrile- d_3 , the carbonyl IR frequencies of the five amides were all essentially normal amide frequencies. Despite very different hydrogen-bonding possibilities in the five amides, no clear trends emerged in the comparison of the rotational barriers ($\Delta G^\ddagger$), and the rotational barriers were essentially normal for amides. The rotational barrier of **2** did not vary over one order of magnitude difference in concentration.

Keywords: amides; rotational barriers; hydrogen bonding

Introduction

The classic studies of Pauling led to the rationale of the planarity and rigidity of the amide linkage through resonance structures **1A** and **1B**.¹ A more detailed analysis is provided by Wiberg and co-workers² whose computational studies demonstrated that the transition state for rotation, lacking such conjugative stabilization, lengthens the C-N bond by 0.08 Å and shortens the C-O distance by only 0.01 Å. This led these researchers to emphasize the importance of a third resonance contributor **1C**. From a frontier molecular orbital perspective they identify donation from the (planar) nitrogen lone pair toward the large carbon coefficient on the $\pi^*_{\text{C=O}}$ LUMO with back donation toward the electronegative sp^2 -hybridized nitrogen as the principle contributors toward stabilization of the linkage and its high rotational barrier. The observation that gas-phase rotational barriers³ are lower than comparable solution-phase barriers and that these increase with increasing solvent polarity led to the conclusion that the ground state structures are more polar than the transition state structures consistent with this picture.^{4,5} Amide rotational barriers are in a very convenient range for monitoring by NMR spectroscopy, and rotational barriers for numerous amides were measured starting in the 1960s.⁶⁻¹⁰

Our initial interest in the series of compounds described here was drawn by the low carbonyl IR frequency of the glycolyl amide **2** (neat, 1590 cm^{-1}), synthesized, according to published procedure,^{11,12} in the course of another study. The interest focused on the possibility of an intramolecular hydrogen

bond that might raise the rotational barrier. In order to test this possibility, the rotational barriers and carbonyl frequencies were determined for **2** as well as model compounds **3-6**. Recently, the published synthesis of **3**¹³ was demonstrated to be incorrect and inconsistent with the NMR spectroscopic properties of the true **3**.¹⁴ Interestingly, no spectroscopic study was completed by the second group of authors for the ersatz **3** and we report here the correct structure (**6**) including its rotational barrier.

Experimental

Syntheses of Amides

2-Hydroxy-N,N-bis(2-hydroxyethyl)acetamide (**2**)

This compound was synthesized according to the procedure of Daryaei et al¹¹ with an improved procedure¹² for synthesis of the acetonide starting material. ¹H-NMR (CDCl₃): δ 3.32-3.34 (2H, XX' of AA'XX'), 3.60-3.62 (2H, XX' of AA'XX'), 3.77-3.80 (2H, AA' of AA'XX'), 3.93-3.96 (2H, AA' of AA'XX'), 4.27

80 (2H, s). (See SI for ^1H - ^1H COSY) ^{13}C -NMR (CDCl_3): δ 31.15, 42.79, 50.57, 60.36, 61.15, 200.04. IR (neat):

81 3246, 2872, 1590, 1063, 844 cm^{-1} . IR (CH_3CN): 3623, 1631, 1037, 832 cm^{-1} .

82 *N,N*-bis(2-Hydroxyethyl)acetamide (**3**)

83 This compound was synthesized according to the procedure of Aitken et al.¹⁴ ^1H -NMR (CDCl_3): δ 2.16

84 (3H, s), 3.48-3.50 (2H, XX' of AA'XX'), 3.52-3.54 (2H, XX' of AA'XX'), 3.77-3.79 (2H, AA' of AA'XX'), 3.80-

85 3.82 (2H, AA' of AA'XX'). (See SI for ^1H - ^1H COSY) ^{13}C -NMR (CDCl_3): δ 22.29, 50.62, 53.39, 60.77, 61.41,

86 173.31. IR (neat): 3347, 2934, 1606, 1037 cm^{-1} . IR (CH_3CN): 3092, 1639, 1037 cm^{-1} .

87 *N,N*-Diethylacetamide (**4**)

88 Purchased from Alfa Aesar and used as is. ^1H -NMR (CDCl_3): δ 1.00 (3H, t, J = 7.1 Hz), 1.06 (3H, t, J = 7.1

89 Hz), 1.96 (3H, s), 3.19 (2H, q, J = 7.1 Hz), 3.25 (2H, q, 7.1 Hz). ^{13}C -NMR (CDCl_3): δ 13.21, 14.28, 21.54,

90 40.08, 42.98, 169.80. IR (neat): 2972, 1634, 1423, 1276 cm^{-1} .

91 *N,N*-Diethyl-2-hydroxyacetamide (**5**)

92 This compound was synthesized by reaction of 2-bromo-*N,N*-diethylacetamide with sodium hydroxide.

93 Its properties were identical with those reported by Boyko et al.¹² as well as Andreas et al.¹⁵ ^1H -NMR

94 (CDCl_3): δ 1.16 (3H, t, J = 7.2 Hz), 1.19 (3H, t, J = 7.2 Hz), 3.17 (2H, q, J = 7.2 Hz), 3.45 (2H, q, J = 7.2 Hz),

95 4.15 (3H, s). ^{13}C -NMR (CDCl_3): δ 13.08, 14.05, 40.17, 40.66, 59.87, 170.77. IR (neat): 3407, 2975, 1633,

96 1076 cm^{-1} . IR (CH_3CN): 3092, 1647, 1081, 1037 cm^{-1} .

97 *N,N*-Bis[2-(acetyloxy)ethyl]acetamide (**6**)

This compound was first reported in 1934¹⁶ and a much more recent synthesis¹⁷ included no experimental or spectroscopic details. ¹H-NMR (CDCl₃): δ 2.06 (3H, s), 2.08 (3H, s), 2.15 (3H, s), 3.60-3.65 (4H, XX' of AA'XX'), 4.20-4.23 (4H, AA' of AA'XX'). ¹³C-NMR (CDCl₃): δ 20.58, 20.69, 21.30, 45.15, 48.06, 61.60, 62.04, 170.47, 170.63, 171.02. IR (neat): 2959, 1734, 1638, 1234, 1034 cm⁻¹. IR (CH₃CN): 1739, 1643, 1234, 1037 cm⁻¹.

Instrumentation

¹H NMR and ¹³C NMR spectra were acquired with a Varian UnityINOVA 500 NMR or Varian Mercury 400 BB NMR. Samples were approximately 20-50 mg/mL of solvent. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) unless otherwise noted and coupling constants (J values) are in Hertz (Hz). Variable temperature experiments were carried out in acetonitrile-d₃ unless otherwise specified. The NMR probe was allowed to equilibrate for ten minutes at each temperature prior to recording spectra. Temperature calibrations were carried out using ethylene glycol.¹⁸ Observed temperatures (°C) were in agreement with calibrated temperatures (± 0.1 °C). Infrared spectra were recorded on a ThermoFischer Scientific Nicolet iS10 FTIR spectrometer and acquired neat unless otherwise indicated.

Dynamic ¹H-NMR Studies

Results and Discussion

Figures 1-5 depict the variable-temperature ¹H-NMR spectra for amides **2-6** respectively. Rate constants were obtained by matching experimental spectra with those calculated employing the

116 WINDNMR program of Reich.¹⁹ For 2-hydroxy-*N,N*-bis(2-hydroxyethyl)acetamide (**2**), two concentrations
117 were run (Figures 1A and 1B) with the latter run a factor of 10 more dilute. In this range, there was no
118 significant dependence of rotation rate of **2** upon concentration.

119

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Figure 1. A) 2-Hydroxy-*N,N*-bis(2-hydroxyethyl)acetamide (**2**) in acetonitrile- d_3 ; B) 2-Hydroxy-*N,N*-bis(2-hydroxyethyl)acetamide (**2**) in acetonitrile- d_3 , 1:10 dilution

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126 Figure 2. A) *N,N*-Bis(2-hydroxyethyl)acetamide (**3**) in acetonitrile-*d*₃; B) *N,N*-Bis(2-

127 hydroxyethyl)acetamide (**3**) in DMSO-*d*₆

Figure 3. *N,N*-Diethylacetamide (**4**) in acetonitrile-*d*₃

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131 Figure 4. *N,N*-Diethyl-2-hydroxyacetamide (5) in acetonitrile- d_3

Figure 5. *N,N*-Bis[2-(acetyloxy)ethyl]acetamide (**6**) in acetonitrile- d_3

Table 1 lists coalescence temperatures, rate constants at (or near) coalescence and corresponding free energies of activation (kcal/mol) determined in the present study for each of the amides **2-6**, along with carbonyl frequencies neat and in acetonitrile. The two IR carbonyl bands in **6** (1638 and 1734 cm^{-1}), as well as the ^1H and ^{13}C NMR spectra are in clear accord with structure **6** which must have arisen from diacetylation of the desired product **3** and incorrect identification of the chromatographic separation product by Al-Sehemi *et al.*¹³ In application of WINDNMR, the intrinsic line widths were those of CH_3 groups (**3**, **4**, **6**) or CH_2 groups (**2** and **5**) whose chemical shifts (environments) do not change upon amide bond rotation. Free energies of activation are calculated using a transmission

coefficient ($\kappa = 0.5$).^{5,20} Each of the five amides was monitored by at least two independent sets of exchanging protons (three in the case of amide **6**). The chemical shift difference between the exchanging NCH₂ protons in **3** and **4** were so small that coalescence was recorded some 40 °C lower than for the other exchanging protons in these molecules (see Figures 2A and 4). Thus, the rates were difficult to accurately simulate and were anomalous. Interestingly, in the case of amide **5**, the NCH₂ absorbances had a much higher chemical shift difference than the CH₃ absorbances and would have demonstrated coalescence at significantly higher temperature than practical in acetonitrile. In order to calibrate this study with that of Aitken *et al*,¹⁴ very close correspondence was observed for coalescence of both CH₂O and NCH₂ exchanging protons of **3** in DMSO-d₆, a solvent that induces greater chemical shift differences and has a higher boiling point than acetonitrile-d₃. The coalescence observed at 77 °C (see Figure 2B) is nearly identical to that reported by Aitken *et al*¹⁴ at 74 °C and should correspond even better to an interpolation at 75 °C of their spectra at 74 °C and 76 °C (see Figure 3¹⁴). Aitken *et al*¹⁴ reported $\Delta G^\ddagger$ values of 18.02 kcal/mol and 18.04 kcal/mol employing exchange of the CH₂O and CH₂N protons respectively. Although not explicitly stated in that work, it is clear that Aitken *et al* employed a transmission coefficient of 1.¹⁴ The Aitken *et al* paper¹⁴ also reported rate constants based upon a simple exchange of two singlets²¹ rather than the exchange of two triplets modelled by the WINDNMR program. Applying WINDNMR simulations to the Aitken *et al*¹⁴ 300 MHz coalescence spectrum at 77 °C, and employing $\kappa = 0.5$, the corresponding $\Delta G^\ddagger$ values for **3** in DMSO average to 18.1 kcal/mol (see Table 1, footnotes c and d), a value 0.2-0.3 kcal/mol higher than the value determined in the present study

(Table 1). What is clear is the excellent internal agreements between k_r and $\Delta G^\ddagger$ in each study of **3** in DMSO, due to the excellent separation of both sets of exchanging peaks in this solvent. The rate constants for the three sets of exchanging protons in **6** (Figure 5) are also in excellent agreement in part due to the very close agreement between the three coalescence temperatures. Although, the present work does not include systematic study of error limits, the error limit estimated here ($\Delta G^\ddagger = \pm 0.1$ to ± 0.2 kcal/mol) is based upon comparison of two (or three) sets of exchanging protons in the same molecule at comparable temperature.²²

Table 1. Coalescence temperatures (t_c , see Figures 1-5), calculated rate constants and free energies of activation ($\kappa = 0.5$) for OC-N rotation in amides **2-6** in acetonitrile- d_6 (amide **3** was also studied in DMSO in order to calibrate with the study published by Aitken *et al*¹⁴). This estimated uncertainty in $\Delta G^\ddagger$ is 0.1-0.2 kcal/mol, see text. Infrared amide carbonyl frequencies (neat and in acetonitrile) are also listed for comparison.

Amide	Protons	$t_{\text{coal.}}(^{\circ}\text{C})$	$k_r (\text{sec}^{-1})$	$\Delta G^\ddagger (\text{kcal/mol})$	$\nu_{\text{CO}} (\text{cm}^{-1})$ (neat)	$\nu_{\text{CO}} (\text{cm}^{-1})$ (CH ₃ CN)
2	NCH ₂	63 ^a	6.81	18.0	1590	1631
2	CH ₂ O	63	9.01	17.8		
2 (1/10 conc)	NCH ₂	64 ^a	7.70	18.0		
2 (1/10 conc)	CH ₂ O	64	14.2	17.6		
3	NCH ₂	35 ^b	1.21	17.5	1606	1639

180	3	CH ₂ O	72	8.41	18.4		
181	3 (in DMSO)	NCH ₂	77	25.8 ^c	17.85 ^c (DMSO)		
182	3 (in DMSO)	CH ₂ O	77	24.5 ^d	17.89 ^d (DMSO)		
183	4	NCH ₂	30 ^b	(2.5) ^e	(16.8) ^e	1634	1633
184	4	CH ₂ CH ₃	74	34.8	17.5		
185	5	NCH ₂	63 ^a	28.9	17.0	1633	1647
186	5	CH ₂ CH ₃	63	15.6	17.4		
187	6	NCH ₂	70	20.1	17.7	1638	1643
188	6	CH ₂ O	72	17.6	17.9		
189	6	COCH ₃	70	20.8	17.6		

190 a. Slightly below coalescence temperature recorded for NCH₂ protons

191 b. Coalescence temperature well below that of the CH₂O protons because chemical shift difference

192 between the two exchanging NCH₂ groups extremely small also introducing significant error into the

193 calculation of the rate constants based upon NCH₂ exchange (see Figures 2A and 4).

194 c. Employing Aitken *et al*¹⁴ ¹H-NMR spectrum at 77 °C combined with WINDNMR simulation yields $k_r =$

195 16.6 sec⁻¹ and $\Delta G^\ddagger = 18.2$ kcal/mol ($\kappa = 0.5$).

196 d. Employing Aitken *et al*¹⁴ ¹H-NMR spectrum at 77 °C combined with WINDNMR simulation yields:

(OCH₂): $k_r = 18.2 \text{ sec}^{-1}$ and $\Delta G^\ddagger = 18.1 \text{ kcal/mol}$ ($\kappa = 0.5$).

e. As noted in the SI the chemical shift difference between the exchanging NCH₂ protons in **4** (in CH₃CN) is so small as to indicate considerable inaccuracy of these data.

In addition to experimental details, spectra and WINDNMR simulations, lists and plots of calculated $\Delta G^\ddagger$ values for **2-5** are provided in Supplementary Information. Unsurprisingly,⁶ due to the limited temperature range, limited information may be gained from these plots and $\Delta H^\ddagger$, $\Delta S^\ddagger$, and E_a values are not provided here although the reader can calculate them if desired.

Conclusions

The amide incorrectly reported as **3** by Al-Sehemi¹³ *et al* is actually **6**. Amide **3** was correctly synthesized and reported by Aitken *et al*.¹⁴ Although the five amides investigated here present a significant range of hydrogen-bonding possibilities, the amide rotational barriers in **2-6** are quite similar to those of most amides. One might have anticipated enhanced rotational barriers in **2** and **3** due to potential intramolecular hydrogen bonding wherein a 7-membered ring should be superior to a 5-membered ring (i.e. **2** and **5**)²³ and might enhance the contribution of resonance structure **1B**. Although the amide carbonyl frequencies of neat **2** and **3** are low and do indicate hydrogen-bonding (possibly intramolecular), there is little difference in the amide carbonyl frequencies of all five amides in acetonitrile. There appears to be no systematic difference in the rotational free energies of these five amides. The amide rotation barrier in **2** did not vary significantly over an order of magnitude change in

concentration leading one to conclude that intermolecular association has no effect on the barrier. This study, in combination with that of Aitken *et al*,¹⁴ might initially suggest a slightly higher free energy barrier to rotation in DMSO than in acetonitrile consistent with the view that DMSO is the more polar solvent and that solvent polarity is known to raise amide rotational barriers. However, considering the uncertainty in $\Delta G^\ddagger$ (0.1-0.2 kcal/mol) it is not clear whether the difference is significant. The estimated uncertainties in these $\Delta G^\ddagger$ values is considered to be ± 0.1 kcal/mol. A comparison can be made employing Kamlet-Taft solvent parameters.²⁴ Acetonitrile itself is a weak hydrogen bond donor ($\alpha = 0.19$) and a moderate hydrogen bond acceptor ($\beta = 0.40$) whereas DMSO is not a hydrogen bond donor ($\alpha = 0.00$) and is a fairly strong hydrogen bond acceptor ($\beta = 0.76$) and is somewhat more polar ($\pi^* = 1.0$) than is acetonitrile ($\pi^* = 0.75$).

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- 254 20. See p 536 in Stewart and Siddall (ref. 6).
- 255 21. This is clear from the equation on p 173 of the Aitken *et al* paper.
- 256 22. We are grateful to one of the reviewers of this paper who suggested using at least half the
- 257 difference between the values obtained from different measurements (e.g. NCH₂ vs OCH₂ in the same
- 258 molecule) to estimate error. In order to apply this assumption, it is necessary to employ $\Delta G^\ddagger$ at identical
- 259 or very similar temperatures. Thus, the calculated $\Delta G^\ddagger$ values for **3** and **4** in acetonitrile were not
- 260 employed since in each case coalescence of the NCH₂ group occurred at temperatures 30-40°C below
- 261 the coalescence of the CH₂O group.
- 262 23. Although the interactions described here are between hydroxymethyl protons and amide carbonyls,
- 263 it is worth noting that a 9-membered ring is optimal for hydrogen bonding between terminal amides
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