Proton NMR Spectroscopic Studies on 5-(Acylamino)oxazoles. Rotameric Mixtures of Amides at Ambient Temperatures

Bruce H. Lipshutz,* Keith E. McCarthy, and Randall W. Hungate

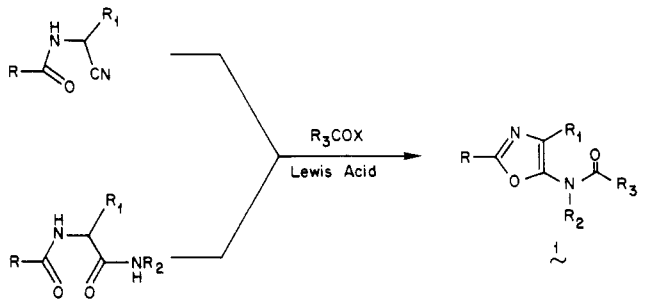
Department of Chemistry, University of California, Santa Barbara, California 93106

Received August 30, 1983

The ^1H NMR spectra of numerous 5-(acylamino)oxazoles resulting from the cyclization of diamides or α-amide nitriles are discussed. Depending upon the nature of the substituents at the C-4 and C-5 positions of the oxazole ring, both rotameric forms of secondary amides may be seen at ambient temperatures. These examples represent one of the few systems known where isomers of secondary amides are readily observed.

Introduction

During the course of our studies on the use of heterocycles as latent diamide/dipeptide equivalents en route to the cyclopeptide alkaloids,[1] we prepared a variety of 5-(acylamino)oxazoles (1) as illustrated. Routine NMR



spectral analysis at 60 or 80 MHz of compounds **1**, derived from acetyl halides ($R_3 = CH_3$), rather than leading to an expected singlet for the acetamide CH_3, clearly afforded, in many cases, two distinct signals associated with this group. Likewise, for **1**, $R = CH_3$, the methyl moiety would concurrently appear as two separate singlets, although the differences in chemical shifts ($\Delta\delta$ ca. 0.05 ppm) were noticeably smaller than those arising from the acetamide absorptions ($\Delta\delta$ ca. 0.16 ppm). The occurrance of multiple resonances for each oxazole appendage is not, however, characteristic of all **1**, as it is sensitive to the substitution pattern at both the C-4 and C-5 positions. These data suggest that rotameric mixtures of *E* and *Z* isomers exist in solution at room temperature, a most uncommon phenomenon with, specifically, secondary acetamides.[2,3] Based on these initial findings and in light of the potential synthetic value of these heteroaromatic nuclei, a more complete study on the unusual solution properties of **1** has been undertaken, the details of which are reported herein.

Results and Discussion

^1H NMR Spectra. 5-Acetamidooxazoles. From close examination of a variety of 5-acetamidooxazoles at 300 MHz a pattern emerged indicating that oxazoles which are either (a) C-4 substituted, C-5 secondary amides or (b) C-4 unsubstituted, C-5 tertiary amides give rise to more than one resonance for substituents on the ring. On the other hand, (c) C-4 substituted, C-5 tertiary amides and (d) C-4 unsubstituted, C-5 secondary amides in all cases give only a single set of resonances per oxazole substituent. Representative examples are illustrated in Table I.

Insofar as a is concerned, the methylene group of an isobutyl residue in a C-4 isobutyl-containing, C-5 secondary acetamide (e.g., entry 1) appears as an imperfect triplet due to overlapping doublets ($\Delta\delta$ 0.026) of unequal intensities. The two methyl signals are also split into what appears as a triplet (overlapping doublets, $\Delta\delta$ 0.021). The same type of observations have been made where a benzyl group is present at C-4 (entry 4), in this case the individual methylene protons being discernable albeit only at high field. Switching to a C-5 secondary benzamide (entry 6) likewise gave the same indication of two species being present.

Removing the substituent at C-4 and generating an N-alkylated acetamide (entry 11) also gives rise to a rotameric mixture of oxazoles (ratio 3.5–4:1). This presumably reflects the s-trans to s-cis equilibrium mixture of tertiary amides spatially uncomplicated by the lack of a substituent at C-4. Thus, the proton at C-4, as well as the C-2 and acetamide methyl groups, each appear as two sharp singlets.

With regard to c, formation of a C-4 substituted tertiary acetamidooxazole (either by direct ring closure or N-alkylation of the corresponding secondary acetamide) results in a conformationally fixed product. Due to steric constraints, amide isomerization is strongly discouraged (entry 5). As for C-4 unsubstituted secondary amides, presumably removal of steric congestion at the 4 position (entry 10) significantly favors the *E* isomer.

Insofar as secondary acetamides are concerned, it is clear that substitution at C-4 is the key factor responsible for generating an observable rotameric mixture at ambient temperatures. Drieding models suggest that a relatively bulky substituent at this location significantly inhibits rotation about the C-5 carbon–nitrogen bond. This steric interaction may force the amide moiety out of plane with respect to the oxazole nucleus. As a result, the *E* and *Z* isomers may become similar in energy and the relative populations of their ground states become such that each isomer is detectable by NMR.[4,5]

These findings parallel those reported by Kessler and Riecker for substituted acetanilides.[5] Acetanilide itself shows only the *E* isomer at room temperature, while increasing the steric bulk at the 2 and/or 6 position of the aromatic ring (i.e., replacing H for some alkyl group) increases the amount of *Z* conformer present. In fact these authors were able to isolate both isomers of 2,4,6-tri-*tert*-butylacetanilide by thin layer chromatography performed at +5 °C.

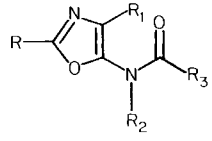
An alternative, although less appealing, explanation for the presence of multiple resonances in the ^1H NMR

* A. P. Sloan Foundation Fellow, 1984–1986.

(1) Lipshutz, B. H.; Hungate, R. W.; McCarthy, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 7703.
(2) Siddall, T. H.; Steward W. E. *Chem. Rev.* **1970**, *70*, 517.
(3) LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337.
(4) This rationale has been expounded by a number of authors; see ref 2, p 543 and references therein.
(5) (a) Kessler, H.; Riecker, A. *Liebigs Ann. Chem.* **1967**, *708*, 57. (b) Kessler, H.; Riecker, A. *Z. Naturforsch.* **1967**, *22*, 456.

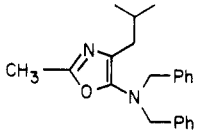
0022-3263/84/1949-1218$01.50/0

Table I. Selected IR and NMR Spectral Data for 5-(Acylamino)oxazoles

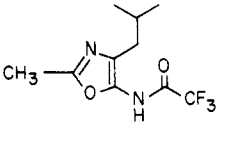


entry	R	R_1	R_2	R_3	^{1}H NMR, δ	^{13}C NMR, δ	IR$_{(\nu C=O)}$, cm^{-1}
1	CH_3	$CH_2CH(CH_3)_2$	H	CH_3	0.91 (6 H, overlapping d, $CH(CH_3)_2$), 1.90 and 2.10 (3 H, s, CH_3CO), 2.24 (2 H, overlapping d; CH_2-$CH(CH_3)_2$), 2.37 and 2.40 (3 H, s, CH_3-)		1695
2	CH_3	CH_2-C_6H_5	H	CH_3	1.80 and 1.96 (3 H, s, CH_3CO), 2.33 and 2.39 (3 H, s, CH_3), 3.75 (2 H, s, CH_2-C_6H_5)	18.9, 19.8, 20.1, 22.3, 31.3, 31.8	1710
3	PhCH=CH	CH_2-C_6H_5	H	CH_3	1.87 and 2.03 (3 H, s, CH_3CO), 3.87 (2 H, s, CH_2-C_6H_5)		1710
4	C_6H_5	CH_2-C_6H_5	H	CH_3	1.85 and 2.00 (3 H, s, CH_3CO), 3.89 and 3.91 (2 H, s, CH_2-C_6H_5)	20.5, 23.0, 31.8, 32.5	1715
5	CH_3	CH_2-C_6H_5	$BrC(CH_2)=CH_2$	CH_3	1.84 (3 H, s, CH_3CO), 2.41 (3 H, s, CH_3-), 3.78 (2 H, s, CH_2-C_6H_5)		1690
6	CH_3	$CH_2CH(CH_3)_2$	H	C_6H_5	0.89 (6 H, d, J = 7 Hz), 1.90 (1 H, m), 2.25 (2 H, d, J = 5.7 Hz, CH_2-CH), 2.36 and 2.37 (3 H, s, CH_3)	14.11, 22.34, 27.60, 34.52	1675
7	CH_3	$CH_2CH(CH_3)_2$	CH_2-C_6H_5	CF_3	0.77 (6 H, d, J = 7 Hz, $CH(CH_3)_2$), 1.86 (3 H, m, $CH_2CH(CH_3)_2$), 2.26 (3 H, s, CH_3), 4.70 (2 H, s, CH_2-C_6H_5)		1722
8	CH_3	$CH_2CH(CH_3)_2$	H	CF_3	0.88 (6 H, d, J = 6.6 Hz, $CH(CH_3)_2$), 2.00 (1 H, m, $CH(CH_3)_2$), 2.20 (2 H, d, J = 7 Hz, CH_2-CH), 2.40 (3 H, s, CH_3)	13.73, 22.03, 27.39, 34.14	1765
9	H	$CH_2CH(CH_3)_2$	H	$C(CH_3)_3$	0.89 (6 H, d, J = 6.6 Hz, $CH(CH_3)_2$), 1.30 (9 H, s, t-Bu), 2.00 (1 H, m, $CH(CH_3)_2$), 2.27 (2 H, d, J = 6.9 Hz, CH_2-$CH(CH_3)_2$)	26.36, 27.10, 27.46, 34.26, 39.04	1700
10	PhCH=CH	H	H	CH_3	2.22 (3 H, s, CH_3CO), 7.14 (1 H, s, 4-H)		1705
11	CH_3	H	$C_6H_5CH_2$	CH_3	1.80 and 1.95 (3 H, s, CH_3CO), 2.35 and 2.40 (3 H, s, CH_3-), 4.27 (2 H, s, C_6H_5-CH_2-), 6.40 and 6.75 (1 H, s)		1710

spectrum for each oxazole appendage involves restricted rotation about the oxazole C-5–nitrogen bond. Preparation of a hindered tertiary amino derivative **2** followed by



2



3

spectral analysis at 300 MHz does not afford a pattern similar to that seen with amide-containing derivatives.

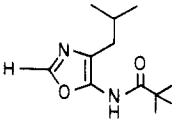
Further evidence for the existence of rotamers was secured from a variable temperature NMR study in toluene-d_8. Typical barriers to rotation about an amide C–N bond range between ca. 16–22 kcal/mol,[6] while those for C–N single bonds are expected to be considerably lower.[7] 2-Methyl-4-isobutyl-5-acetamidooxazole (Table I, entry 1) dissolved in toluene-d_8 showed the 2:1 ratio of isomers at ambient temperature. Increasing the temperature in intervals of approximately 10 °C resulted in the coalescence of (a) the C-2 methyl, (b) the acetamide methyl, and (c) the methyl resonances of the C-4 isobutyl residue, until the spectrum at 90 °C showed a first-order pattern for each group. The barrier to rotation was determined by estimating the coalescence temperature for each moiety, using the following equation:[8] $\Delta G^{\ddagger} = [22.96 + \ln (Tc/\delta\nu)]/RTc$ (kcal/mol). The frequency differences, the coalescence temperatures, and the calculated barriers are as follows: (a) $\delta\nu$ = 10.19 Hz, Tc = 306 °K, $\Delta G^{\ddagger}$ = 16.02 kcal/mol; (b) $\delta\nu$ = 12.28 Hz, Tc = 316 °K, $\Delta G^{\ddagger}$ = 16.48 kcal/mol; (c) $\delta\nu$ = 31.56 Hz, Tc = 335 °K, $\Delta G^{\ddagger}$ = 16.80 kcal/mol. The results indicate a barrier to rotation of ca. 16.5 kcal/mol.[9] The spectrum obtained upon cooling the sample back to room temperature reveals the same initial ca. 2:1 ratio of isomers.

The assignment of the major isomer for this 5-acetamidooxazole as *E* had been assumed, on the basis of this preferred orientation in secondary amides. While this seems quite reasonable, more definitive data was desired. We anticipated that an NOE difference spectroscopy experiment, should it be successful, would clarify this issue.[11] In principle, presaturation of the acetamide methyl resonance which corresponds to the *E* isomer would lead to enhancement. The *Z* isomer, on the other hand, should not lead to any observable increase in the N–H peak. In setting up the experiment, initial irradiation of either acetamide methyl resonance at ambient temperature resulted in the disappearance of both singlets. This effect of saturation transfer is a rather common occurrance in systems which interconvert quickly relative to their relaxation times (i.e., $k_1 > 1/T_1$). To prevent rapid interconversion of the isomers on the NMR time scale, the solution was cooled to −20 °C. Presaturation of the singlet at δ 2.15 (i.e., the methyl resonance corresponding to the major rotamer) led to an 8.4% enhancement, in this case, of the downfield N–H signal. As expected, no effect was seen upon irradiation of the methyl peak at δ 1.93. These results demonstrate that (1) for this NOE phenomenon to have occurred, *Z–E* isomerism about the amide portion of the molecule must exist and (2) the *E* rotamer is indeed the major isomer in solution.[12]

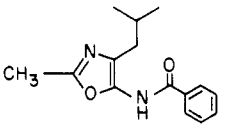
Other 5-(Acylamino)oxazoles. In marked contrast to the data obtained in the acetamido series, analysis of the corresponding 5-trifluoroacetamides (e.g., **3**) gives only a single observable set of resonances in the NMR spectrum irrespective of the substitution pattern at C-4 or C-5 (entries 7,8). The CF_3 group has been reported to diminish the barrier[13] in amides, however, the effect appears to be energetically minimal and rotation, in similar circumstances, should therefore remain slow on the NMR time scale. One rationale which we offer may be found in the presence of subtle fluorine-ring oxygen lone pair–lone pair interactions thereby destabilizing the *Z* isomer in the ground state. Of course, the remote possibility that degeneracies exist in this series cannot be formally ruled out.

Some additional experimental observations are also worthy of mention. Generation of a C-5 secondary pivalamide (e.g., **4**) gives rise to a single conformer (entry 9). Presumably the bulky *tert*-butyl moiety occupies the s-trans configuration.

Aroyl halides likewise participate in the formation, in this case, of C-5 secondary benzamides (e.g., **5**), which also



4



5

display rotamers in solution. Interestingly, the observed ratio (1:1), when compared with that seen with the corresponding acetamides (2:1), reflects an increased percentage of one conformer (presumably *Z*) at the expense of the other. The explanation for such a contrathermodynamic shift in isomer population density remains clouded at this time. Both steric and electronic arguments would predict increased predominance of the *E* form.

Summary

Construction of 5-(acylamino)oxazoles, originally for synthetic purposes, has led to the realization that appropriately substituted cases afford rare examples of observable rotameric mixtures at ambient temperatures. Variable temperature NMR studies have permitted a semiquantitative evaluation of the rotational barriers involved. NOE difference spectroscopy experiments in the acetamide series provided data which have allowed the rigorous assignment of resonances to either a *E* or *Z* isomer, the former form predominating in solution. Similar studies in the benzamide system lead to a considerably different ratio of rotamers, while the related trifluoroacetamide analogues do not follow suit, invariably displaying a single, presumably *E* isomer, regardless of the level of substitution on the oxazole ring.

(6) Jackman, L. M. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; pp 203–253.

(7) Sternall, S. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; p 195.

(8) Abraham, R. J.; Loftus, P. In "Proton and Carbon-13 NMR Spectroscopy" Heyden: London, 1980; p 167.

(9) Total line shape analysis was not performed. The experiment is meant to show that the rotational barrier is within the range of a "normal" amide.[6]

(10) DeShong, P.; Dicken, M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397. Eggert, H.; Nielsen, P. H. *Tetrahedron Lett.* 1981, *22*, 4853.

(11) In a separate experiment, we found that presaturation of the N–H signals at −20 °C did not lead to any enhancement of the methyl resonances, perhaps not surprising as an NOE for this functional group is oftentimes not observed.[12]

(12) Noggle, J. H.; Schirmer, R. E. In "The Nuclear Overhauser Effect, Chemcial Applications"; Academic Press: New York, 1971. See also: Lewin, A. H.; Frucht, M. *Org. Magn. Res.* **1975**, *7*, 206.

(13) See ref 6, p 209.

Experimental Section

NMR spectra were recorded on a Nicolet NT 300 spectrometer in $CDCl_3$ with tetramethylsilane (Me_4Si) as internal standard by using 16K data points and a sweep width of 3412 Hz. Variable temperature spectra were recorded in toluene-d_8 with Me_4Si as internal standard. The NOE experiment was conducted by using a freeze-degassed sample. To minimize the effect of magnetic perturbations, 8 FID's were acquired with the decoupler set at a given frequency. Likewise, 8 FID's were also recorded with the decoupler off resonance. The process was repeated until 1440 pulses had been accumulated for each individual experiment. Subsequent subtraction of the two spectra afforded the net enhancement. A recovery time of 5 s was used. IR spectra were recorded in $CHCl_3$ by using a Perkin-Elmer Model 283 spectrophotometer.

All compounds used in this study were prepared as previously described.[1]

Acknowledgment. Financial support provided by the National Institutes of Health (GM 28128) is gratefully acknowledged. Technical assistance and discussions with Prof. J. T. Gerig, Dr. Steve Hammond, and Curt Brenneman are greatly appreciated.

Registry No. 1 ($R = R_3 = CH_3$; $R_1 = CH_2CH(CH_3)_2$; $R_2 = H$), 87783-73-1; 1 ($R = R_3 = CH_3$; $R_1 = CH_2Ph$; $R_2 = H$), 87783-75-3; 1 (R = CH=CHPh; $R_1 = CH_2Ph$; $R_2 = H$; $R_3 = CH_3$), 87783-76-4; 1 (R = Ph; $R_1 = CH_2Ph$; $R_2 = H$; $R_3 = CH_3$), 87783-79-7; 1 ($R = CH_3$; $R_1 = CH_2Ph$; $R_2 = CH_2CBr{=}CH_2$; $R_3 = CH_3$), 87783-94-6; 1 ($R = CH_3$; $R_1 = CH_2CH(CH_3)_2$; $R_2 = H$; $R_3 = Ph$), 87783-88-8; 1 ($R = CH_3$; $R_1 = CH_2CH(CH_3)_2$; $R_2 = CH_2Ph$; $R_3 = CF_3$), 87783-64-0; 1 ($R = CH_3$; $R_1 = CH_2CH(CH_3)_2$; $R_2 = H$; $R_3 = CF_3$), 87784-00-7; 1 ($R = H$; $R_1 = CH_2CH(CH_3)_2$; $R_2 = H$; $R_3 = t$-Bu), 87783-83-3; 1 (R = CH=CHPh; $R_1 = R_2 = H$; $R_3 = CH_3$), 87783-77-5; 1 ($R = R_3 = CH_3$; $R_1 = H$; $R_2 = CH_2Ph$), 87783-90-2.

Benzopentathiepins: Synthesis via Thermolysis of Benzothiadiazoles with Sulfur†

B. L. Chenard* and T. J. Miller

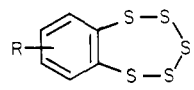
Central Research & Development Department, E. I. du Pont de Nemours & Company, Experimental Station, Wilmington, Delaware 19898

Received August 19, 1983

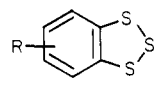
A general synthesis of benzopentathiepins has been developed by the thermolysis of benzothiadiazoles with sulfur. Dabco was found to enhance the yield of benzopentathiepin by approximately 2-fold. The scope and limitations of the method are also discussed.

Introduction

Polysulfides have been of great interest owing to their diversity in nature and their biological activity.[1] Some fundamental studies concerning sulfide exchange[2] and sulfur–sulfur bond cleavage processes in linear polysulfides[3] have recently appeared. Most of the synthetic work in this area has been limited to the construction of linear polysulfides[4] although some synthetic cyclic polysulfides have been described.[5] We became interested in cyclic polysulfides with five contiguous sulfur atoms, the benzopentathiepins **1**, and were intrigued by the fact that cyclic

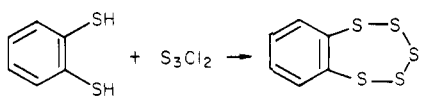


1



2

polysulfides fused to a benzene ring have been synthesized in both the pentathiepin[5a,6] and the trithiole[7] (**2**) forms. We want to address two fundamental questions: first, what are the factors which control the polysulfide ring size, and second, can we observe equilibration between these and other benzopolysulfide species? To probe these questions, a series of benzopentathiepins would be required. The methodology for benzopentathiepin preparation is severely limited. The only useful synthesis is due to Fehér[5a,6] (eq 1), although the sulfur monochloride route to an isothiazolopentathiepin might be applicable.[8] Both of these methods require a vicinal dithiol and since substituted benzene *o*-dithiols are not readily available, we desired a more general route to benzopentathiepins which avoided this intermediate.



(1)

The thermal decomposition of 1,2,3-benzothiadiazoles at 200–230 °C has been known for over 90 years.[9] Recently, it was reported that the pyrolysis temperature could be lowered to 80–120 °C by using di-*tert*-butyl peroxide as an initiator.[10] The intermediates from the thermolysis

† Contribution number 3327.

(1) See, for example: Still, I. W. J.; Kutney, G. W. *Tetrahedron Lett.* **1981**, *21*, 1939–1940. Morita, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1967**, *15*, 988; *Tetrahedron Lett.* **1966**, 573. Wratten, S. J.; Faulkner, D. J.; *J. Org. Chem.* **1976**, *41*, 2465. Rahman, R.; Safe, S.; Taylor, A. *J. Chem. Soc. C* **1969**, 1665. Brewer, D.; Rahman, R.; Safe, S.; Taylor, A. *J. Chem. Soc., Chem. Commun.* **1968**, 1571.

(2) Whitesides, G. M.; Houk, J.; Patterson, M. A. K. *J. Org. Chem.* **1983**, *48*, 112–115 and references cited therein.

(3) Harpp, D. N.; Smith, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 6045–6053.

(4) Tsurugi, J.; Nakabayashi, T. *J. Org. Chem.* **1959**, *24*, 807–810. Nakabayashi, T.; Tsurugi, J.; Yabuta, T. *Ibid.* **1964**, *29*, 1236–1238. Reid, E. E. "Organic Chemistry of Bivalent Sulfur"; Chemical Publishing Co.: New York, 1960; Vol. III, pp 387–389.

(5) (a) Fehér, F.; Langer, M. *Tetrahedron Lett.* **1971**, 2125–2126. (b) Fehér, F.; Glinka, K.; Malcharek, F. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 413–414. (c) Shields, T. C.; Kurtz, A. N. *J. Am. Chem. Soc.* **1969**, *91*, 5415–5416. (d) Harpp, D. N.; Granata, A. *J. Org. Chem.* **1979**, *44*, 4144. (e) Kato, A.; Hashimoto, Y.; Otsuka, I.; Nakatsu, K. *Chem. Lett.* **1978**, 1219–22.

(6) Fehér, F.; Engelen, B. *Z. Anorg. Allg. Chem.* **1979**, *452*, 37–42. Fehér, F.; Langer, M.; Volkert, R. *Z. Naturforsch. B* **1972**, *27*, 1006.

(7) Rasheed, K.; Warkentin, J. D. *J. Org. Chem.* **1980**, *45*, 4806–4807; *Ibid.* **1979**, *44*, 267–274.

(8) Vladuchick, S. A. U.S. Patent 4 094 985.

(9) Jacobsen, P.; Ney, E. *Chem. Ber.* **1889**, *22*, 904. Jacobsen, P.; Janssen, H. *Liebigs Ann. Chem.* **1893**, *277*, 218.

(10) Montevecchi, P. C.; Tundo, A. *J. Org. Chem.* **1981**, *46*, 4998–4999.

0022-3263/84/1949-1221$01.50/0