Regioselectivity in Lateral Deprotonation of an Isoxazolecarboxamide of (*S*)-Prolinol. Conformational Correlation by Crystal Structure, Solid State and Solution ^{13}C NMR

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The conformation at the amide functional group in 3,5-dimethylisoxazole-4-(*S*-2′-hydroxymethyl-*N*-pyrrolidino)carboxamide (**1**) has been determined by a single crystal X-ray determination. The ^{13}C nmr in both deuteriochloroform solution and solid state show close agreement. The metalation behaviour of the amide is dependent upon the substitution on the 2′-hydroxymethyl moiety. Dianion studies indicate C-5 lateral metalation under both thermodynamic and kinetic conditions. Protection of this substituent as the methyl ether, **2**, gives rise to predominant C-3 lateral metalation under kinetic conditions and C-5 lateral metalation on equilibration. These observations can be explained using the Ireland-Evans model for chelation directed deprotonation.

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The lateral metalation of alkyl groups is a widely used synthetic tactic [2], and the lateral metalation of isoxazoles in particular has been utilized for the synthesis of numerous functionally complex isoxazoles [3,4]. In connection with our interest in the intrinsic biological activity of isoxazole congeners [5], we desired an efficient entry into functionalized isoxazoles with a carboxyl or functional equivalent in the C-4 position and have recently studied the scope of several strategies [6-8]. The metalation of simple alkyl isoxazoles usually gives rise to C-5 lateral metalation; however, kinetic metalation has been reported to lead to C-3 lateral metalation if the proper steric conditions exist [9]. We herein detail a novel case where an isoxazole substrate upon metalation, using the same base, gives rise to different regiochemical outcomes dependent upon kinetic versus thermodynamic control.

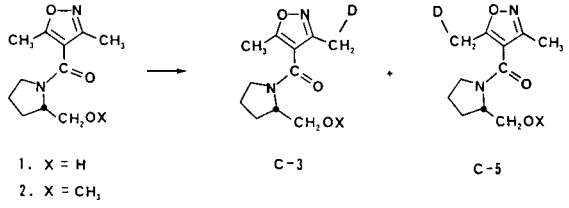


Table 1

Lateral Metalation and Deuterium Quenching of **1** and **2**

Entry	X	Time (Hours)	Deuterium C-3	Incorporation C-5	Conditions [a]
1	H	2	<5	>95	Thermodynamic
2	H	2	<5	>95	Kinetic
3	CH_3	2	<5	>95	Thermodynamic
4	CH_3	1	45	55	Thermodynamic
5	CH_3	1	93	7	Kinetic

[a] All reactions were performed in THF at −78°. For thermodynamic reactions *n*-BuLi in hexanes was added dropwise *via* syringe to a cold THF solution of the organic acid. For kinetic conditions, *n*-BuLi-TMEDA, 1:1, in THF was cooled and a cold THF solution of the organic acid was transfered *via* a cannula [10].

The metalation results are summarized in Table 1. Only C-5 metalation was observed for the dianion of **1** under both kinetic and thermodynamic conditions (entries 1 and 2). In sharp contrast, the metalation of 2′-methoxymethyl

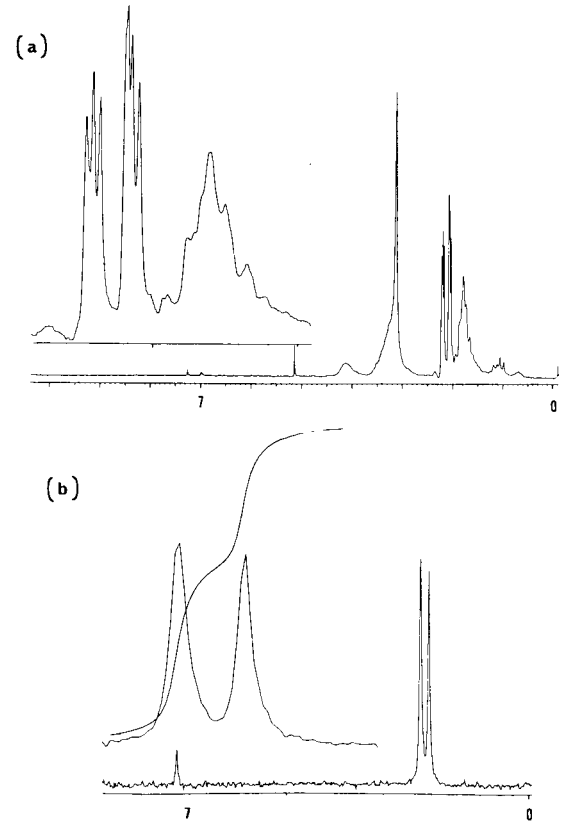


Figure 1. ^1H nmr (a) and ^2H nmr (b) of the product from Table 1, entry 4.

ether **2** for one hour at −78° indicated significant C-3 deuterium incorporation. Figure 1 clearly shows that the 45:55 mixture in entry 4 is readily observed in both the ^1H (a) and decoupled ^2H nmr (b). Kinetic conditions [10] gave rise to predominant C-3 deuterium incorporation (entry 5).

The X-ray data of **1** is summarized in Table 2, and the thermal ellipsoids of the crystal structure along with the atom numbering scheme are shown in Figure 2. The carbonyl group is not coplanar with the heteroaromatic ring, but adopts an *S-trans* conformation with respect to the isoxazole C-4 to C-5 double bond oxygen, as shown by the C(1)-C(2)-C(6)-O(2) dihedral angle of 119.6°. This is also reflected in the non-bonded distances between the carbonyl oxygen and the methyl groups. The closest distances to protons on these methyl groups are 2.79 Å (to the C-3) and 3.9 Å (to the C-5); thus, the carbonyl is much closer to the C-3 methyl group. The atomic coordinates and isotropic thermal parameters are given in Table 3 and the bond lengths and bond angles in Table 4.

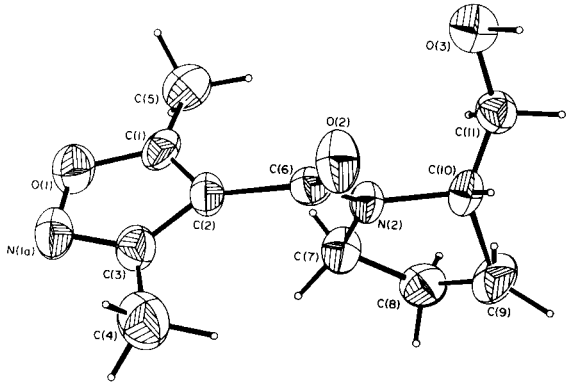


Figure 2. Thermal ellipsoids for compound **1**.

Table 2

Crystallographic Data for Chiral Amide

Formula	$C_{11}H_{16}N_2O_3$
Molecular Weight	224.3
Crystal Class	orthorhombic
a, Å	6.090 (1)
b, Å	10.261 (1)
c, Å	17.971 (5)
V, Å^3	1116.34
Z	4
D, g cm^{-1}	1.33
Space Group	$P2_12_12_1$
μ, cm^{-1}	0.92
F(000)	480
T, °K	298
2θ range, deg.	3-45
no. of measured reflections	1164
no. of unique reflections with F > 3 σ (F)	886
Largest peaks on final Fourier map, e$^-$/A^3	0.22-0.28
R =	0.049
R_w =	0.052

Table 3

Atomic Coordinates × 10^4 and Isotropic Thermal Parameters × 10^3 for Chiral Amide

	x	y	z	U (Å^2)
C(1)	1026(8)	1505(4)	7337(2)	41(1)
C(2)	1948(7)	1958(4)	7986(2)	35(1)
C(3)	3774(7)	2684(4)	7747(2)	43(1)
C(4)	5434(10)	3452(5)	8208(3)	65(2)
C(5)	−943(8)	756(5)	7171(3)	56(2)
C(6)	1107(7)	1865(3)	8761(2)	34(1)
C(7)	1838(9)	−1456(4)	9370(2)	50(2)
C(8)	1343(8)	−651(4)	10059(2)	49(1)
C(9)	−135(8)	414(4)	9773(2)	36(1)
C(10)	1739(9)	−538(4)	8731(2)	45(1)
C(11)	−2542(10)	5(4)	9741(3)	46(1)
N(1)	3975(7)	2641(4)	7010(2)	51(1)
N(2)	723(6)	651(3)	9022(2)	35(1)
O(1)	2212(7)	1904(3)	6754(2)	54(1)
O(2)	727(6)	2858(3)	9106(2)	51(1)
O(3)	−3950(6)	1001(3)	9491(2)	57(1)

Table 4

Bond Lengths (Å) and Bond Angles (°)

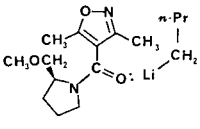
C(1)-C(2)	1.373(6)	C(1)-C(5)	1.453(7)
C(1)-O(1)	1.334(5)	O(3)-C(11)	1.405(6)
C(2)-C(3)	1.403(6)	C(2)-C(6)	1.485(5)
C(3)-C(4)	1.524(7)	C(3)-N(1)	1.327(5)
C(6)-N(2)	1.349(5)	C(6)-O(2)	1.212(4)
C(7)-C(8)	1.515(6)	C(7)-C(10)	1.482(6)
C(8)-C(9)	1.504(6)	C(9)-C(11)	1.523(8)
C(9)-N(2)	1.464(5)	C(10)-N(2)	1.461(5)
N(1)-O(1)	1.389(6)		
C(2)-C(1)-C(5)	133.5(4)	C(2)-C(1)-O(1)	109.9(4)
C(5)-C(1)-O(1)	116.5(4)	C(1)-C(2)-C(3)	104.0(3)
C(1)-C(2)-C(6)	129.2(4)	C(3)-C(2)-C(6)	126.4(4)
C(2)-C(3)-C(4)	129.1(4)	C(2)-C(3)-N(1)	111.1(4)
C(4)-C(3)-N(1)	119.8(4)	C(2)-C(6)-N(2)	116.3(3)
C(2)-C(6)-O(2)	119.3(3)	N(2)-C(6)-O(2)	124.3(3)
C(8)-C(7)-C(10)	106.1(3)	C(7)-C(8)-C(9)	103.6(3)
C(8)-C(9)-C(11)	112.8(4)	C(8)-C(9)-N(2)	102.8(3)
C(11)-C(9)-N(2)	110.7(3)	C(7)-C(10)-N(2)	105.6(3)
O(3)-C(11)-C(9)	113.4(4)	C(3)-N(1)-O(1)	106.0(4)
C(6)-N(2)-C(9)	122.2(3)	C(6)-N(2)-C(10)	124.9(3)
C(9)-N(2)-C(10)	109.9(3)	C(1)-O(1)-N(1)	108.9(3)

Table 5

^{13}C Chemical Shifts of **1**

Conditions	C=O	Isoxazole Ring			Alkyl groups		Prolinol
		C-3	C-4	C-5	C-3	C-5	
CP-MAS	160.22	164.35	114.8	167.45	10.43	12.02	64.66 60.54, 48.3 26.47, 24.11
Solution (Deuteriochloroform)	157.85	164.06	113.5	167.17	10.10	12.14	65.7 60.47, 49.46 28.03, 24.6

It has previously been noted that the most stable conformation in the crystal is not necessarily the low energy conformer in solution [11]. To determine whether divergent and/or multiple conformations of **1** were present in solution, both the solution ^{13}C nmr and CP-MAS spectrum were examined and are summarized in Table 5. The carboxamide carbon shows only a minimal difference in chemical shift, and this difference is consistent with a slight conformational shift towards coplanarity of the C=O and isoxazole C-4/C-5 double bond in solution.



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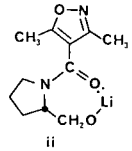

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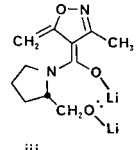

iii

We suggest that the observed regiochemistry can be explained by extending the Ireland-Evans model for stereoselective deprotonation of enolates [12] to this vinylogous imidate system. In the dianion produced from **1**, the initial equivalent of base removes the alcohol proton, and the alkoxide **ii** so produced may chelate to the carboxyl moiety. Thus, chelation controlled proximity directed metalation is precluded, and the determining factor in the regiochemical outcome is the greater thermodynamic stability of the resonance stabilized vinylogous imidate **iii** produced on C-5 lateral metalation. The methoxymethyl ether moiety of **2** should attain a non-chelating conformation **i**, which permits the carboxyl functional group to usher in the alkyl lithium and facilitate C-3 lateral metalation as shown.

EXPERIMENTAL

Mass Spectra were obtained on a VG Micromass 70/70 HS mass spectrometer with an 11/250 data system. The ^{1}H nmr were obtained on a Varian EM-360 instrument, ^{2}H nmr were obtained on a JEOL FX-90Q. Solution ^{13}C nmr were obtained on a Magnachem A-200 instrument, CP-MAS ^{13}C nmr were obtained on a Magnachem M-100S instrument. The Ft-ir were obtained on a Digilab FTS-80 instrument using a photoacoustic detector for solids and thin films on sodium chloride plates for liquids. Combustion analysis was performed by Desert Analytics, Tucson, Arizona. Specific rotation was measured on a Rudolph Research Autopol polarimeter. The X-ray structure determination was performed on a Syntex $P2_1$ diffractometer upgraded to Nicolet P3F specifications. Cell constants were determined by a least-squares fitting of setting angles of the diffractometer between 29° and 31°. Data were collected by the ω scan technique [13], using graphite monochromatized Mo-Kα radiation (λ = 0.71069 Å). The measured intensities were corrected for Lorentz and polarization effects but not for absorption. The structure was solved with the SHELXTL program [14] using direct methods. All non-hydrogen atoms were refined anitotropically; the atomic coordinates of all hydrogen atoms were calculated by constraining N-H, O-H and C-H distances to 0.96 Å and their thermal parameters set at 0.1. The final R values were 0.049 and R_w = 0.052 with w = $1/[\sigma^2(F)+g(F)^2]$ and g refined to a value of 0.00068. Tetrahydrofuran (THF) was distilled from sodium and benzophenone; organolithium reagents were titrated using the method of Ronald [15].

The amides **1** and **2** were prepared in analogy to the previously described procedure [7], using commercially available (*S*)-(+)-pyrrolidinemethanol and (*S*)-methoxymethylpyrrolidine [16], respectively.

3,5-Dimethylisoxazole-4-(2'-hydroxymethyl-*N*-pyrrolidino)carboxamide (**1**).

A solution of 43.5 g of freshly distilled 3,5-dimethylisoxazole-4-carboxylic acid chloride (0.27 mole) in 75 ml of chloroform was added dropwise to a 0° solution of 24.3 g of (*S*)-(+)-pyrrolidinemethanol (0.24 mole), 45 ml of triethyl amine and 500 ml of chloroform. The reaction was allowed to come slowly to room temperature with stirring over twelve hours. The reaction mixture was then washed with 2 × 250 ml of aqueous 2*N* hydrochloric acid, 2 × 250 ml of 10% aqueous sodium hydroxide, and 200 ml of water. The organic layer was dried over anhydrous sodium sulfate. The solution was filtered and concentrated *in vacuo* to give a solid which was recrystallized from ether/hexane to give 37 g of **1** as a white solid. The mother liquor was concentrated and chromatographed on silica gel with ethyl acetate/hexane (1:3) to give an additional 1.7 g of **1**, (total yield 72%) mp 93.5-95.5°; ^{1}H nmr (deuteriochloroform): δ 4.45 (br s, 1H), 3.4-3.9 (m, 5H), 2.5 (s, 3H), 2.3 (s, 3H), 1.8-2.2 (m, 4H); ir: 3405.8, 2987.9, 1640.6, 1467, 1446.9, 1156.2, 1076.2, 1007.8, 854.2, 783.3, 622.4; ms: m/z 225 (29.7, M+1), 193 (52), 124 (100), 82 (29); $[\alpha]_D$-120 (c 1.9, ethyl acetate).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.93; H, 7.35; N, 12.45.

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