Physical Image vs. Structure Relation, 4 [1].
Configuration and Conformation Determination of Some Bicyclic Lactams by \(^1\)H NMR and Theoretical Methods

by

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Summary. Resolution-enhanced \(^1\)H NMR spectra of six single diastereomers of fused-ring sulfur-containing lactams have been recorded and interpreted. In joint analysis of derived couplings \(^3\)J\(_{HH}\) performed with use of the Karplus-Conroy type relationship and results of static MM calculations, it was possible to determine the configuration of title compounds and the conformation elucidation of their six-membered rings. Simultaneously, the stereochemistry of the observed ring-closure reaction was determined. The application of TND0/2 method for the prediction of \(^n\)J\(_{HH}\) values is also briefly discussed.

High-resolution multinuclear NMR spectroscopy is an extremely powerful tool for investigating the structure of any organic molecules including carbo- and heterocyclic systems. This regards the configuration elucidation and, especially, analysis of the solution conformation of such kind of molecular objects [2, 3].

The results of this work show that the \(^1\)H NMR spectroscopy can be easily applied for structural studies of various diastereoisomeric fused bicyclic molecules, to some extent conformationally fixed. Thus partial interpretation of \(^1\)H NMR spectra measured for major products of novel radical cyclisation of conjugated systems 1 leading to fused-ring thiazole lactams 2 [4], was done. In this way, it was possible to determine the relative configuration of synthesised compounds 2A and 2B (for Ar, see Table 1) and the conformation elucidation of their six-membered lactam rings. Some com-

Key words: \(^1\)H NMR, resolution enhancement, interproton couplings, Karplus-Conroy relation, diastereomers, structure, radical cyclisations, ring-closure reactions, lactams, conformation, TND0/2 method, semi-empirical calculations, molecular mechanics.

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parative considerations of selected, experimentally found and theoretically calculated values of scalar (spin-spin) coupling constants, \(^{1}J_{HH}\), were performed as well.

\[
\begin{align*}
&\text{S} &\text{Ar} \\
&\text{(CH}_2\text{)}_m &\text{N} &\text{O} \\
\Downarrow &\text{H} &\text{SnBu}_3/\text{AIBN} \\
&\text{C}_6\text{H}_6, 1.5 \text{ h reflux} \\
&1A \ (m = 2) &1B \ (m = 3)
\end{align*}
\]

**Experimental**

*Materials.* All studied objects 2, i.e. the corresponding (hetero)aromatic derivatives of systems 2A (hexahydrop-thiazolo[3,2-a]pyridin-5-one) and 2B (hexahydropyrido[2,1-b]-1,3-thiazin-6-one), have been reported very recently [4]. Details of the used synthetic procedure, the separation of products (column chromatography on silica gel) and full characterisation of their major racemic diastereomers, will be published soon [5].

*NMR spectroscopy.* \(^{1}\text{H}\) and \(^{13}\text{C}\) NMR spectra were recorded in 5 mm diameter tubes on a Varian Gemini-200 BB spectrometer operating at frequencies 199.98 and 50.29 MHz for \(^{1}\text{H}\) and \(^{13}\text{C}\) nuclei, respectively, with magnetic field \(B_0\) of 4.7 T. Measurements were taken at a probe temperature (\(\approx 21^\circ\text{C}\)) in diluted CDCl\(_3\) solutions with TMS as an internal chemical shift reference.

In the case of one-dimensional (1D) \(^{1}\text{H}\) NMR spectra, 128–192 scans were accumulated. Thus obtained 32 K time-domain spectra were zero-filled to 64 K data point sets and resolution-enhanced with the Lorentzian-to-Gaussian function [6, 7] prior to the Fourier transformation. The optimal parameters for this method, AF and RE, were selected by the trial-and-error procedure available routinely as an option of the spectral post-processing. The 2D \(^{1}\text{H},^{1}\text{H}\) COSY-45 experiments, with the 45° mixing pulse applied for better cross-peaks visualisation [8], were performed by using the standard Varian software.

*Computational methodology.* Energetically preferred conformations of objects 2 were initially found by the Monte Carlo-like technique [9] in molecular mechanics (MM) [10] search with the use of the PCMODEL program (version 3.2, MMX force field) [11]. In the next stage, additional geometry refinement (see text) was carried out using the HyperChem package [12]; MM+ force field calculations. All calculations were carried out on isolated molecules in the gas phase; a bulk value of dielectric constant was used, \(\varepsilon = 1.50\) [13].

**Results and Discussion**

The aliphatic part of recorded \(^{1}\text{H}\) NMR spectra appears to be very similar inside each series of studied diastereomers 2 (strictly, racemic mixtures of their d and l isomers); representative spectrum of lactam 2A, Ar = Ph, is shown as an example in Fig. 1. Unequivocal assignments of some observed signals are mainly based on a selective proton 1D decoupling and/or 2D
Fig. 1. The alkyl shift range of the resolution-enhanced 200 MHz $^1$H NMR spectrum (in CDCl$_3$) of racemic diastereomer 2A (Ar = Ph)

$^1$H,$^1$H COSY-45 experiments as well as on a remarkably large magnitude of geminal (two-bond) interproton couplings, $^2J_{dd'}$, which is typical of the —CH$_2$(C==O) — spin systems [14]. On the other hand, the determination of relative configuration of the newly formed stereogenic centre, next to the sulfur atom, was resolved by careful examination of the acquired lowest-field multiplets of the angular methine protons (denoted hereafter as nuclei a, Table 1) and the other related resonance signals.

Selected values of the experimental coupling constants, $^nJ_{HH}$ where $n = 2-4$, derived directly (first-order approximation) from $^1$H NMR resolution-enhanced spectra of compounds 2, were compared with $^3J_{HH}$ values calculated using the empirically generalised Karplus-Conroy equation [15]; for couplings operating in six-membered ring fragments of studied molecules, see Table 1. The MM+ geometries, corresponding to global minima of the steric energy hypersurface, were applied in all of these calculations. Such energetically predominating conformations of both spectroscopically (especially in $^{13}$C NMR spectra of crude reaction mixtures) observed $dl$ pairs of isomeric lactams 2, i.e. diastereomers $R,R$ or $R,S$ (and their $S,S$ or $S,R$ enantiomers), were found in the computer-assisted molecular modelling; see Experimental.

For both series of single compounds 2, $m = 2$ or 3, very good agreement between the experimental and estimated theoretically (see above) values
of vicinal (three-bond) couplings $^3J_{HH}$ was established only for one of two possible configurations of fused systems in question. (A point to note is that the use of the corresponding MMX geometries, instead of the MM+ ones, leads to slightly weaker similarity of the values mentioned above.) This allowed us to make an easy choice between their stereoisomeric structures of type I and II, with an equatorial and axial orientation of the sulfur atom, respectively, see Figs. 2 and 3. At the same time the suitability and usefulness of the approach used here was proven. Thus, the calculated MM+ geometries are adequate molecular models of all bicyclic lactams under consideration.

In addition, TNDO/2 single point NMR simulations for preferred MM+ conformations of heterocycles 2, i.e. their structures of type I or II, were carried out using the HyperNMR program [16]. The results of such calculations are listed in Table 1, for comparison reasons. In accordance with some earlier reports concerning the use of the TNDO/2 method [17–20], the $^3J_{HH}$ values obtained in this way are only in qualitative agreement with those really observed for objects 2, especially for large couplings. However, the correct sign of proton-proton coupling constants calculated by this semi-empirical approach is remarkable.
<table>
<thead>
<tr>
<th>Compound / Ar</th>
<th>i,j (k = 2-4)</th>
<th>b,b'</th>
<th>d,d'</th>
<th>a,b</th>
<th>a,b'</th>
<th>b,c</th>
<th>b',c</th>
<th>c,d</th>
<th>c,d'</th>
<th>b,d'</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A C$_6$H$_5$</td>
<td>Exp. (-)12.8</td>
<td>(-)17.8</td>
<td>4.1</td>
<td>10.9</td>
<td>2.6s</td>
<td>12.8</td>
<td>5.5</td>
<td>12.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Karplus$^{(b)}$</td>
<td>—</td>
<td>—</td>
<td>3.9</td>
<td>11.8</td>
<td>2.8</td>
<td>12.3</td>
<td>5.4</td>
<td>11.7</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>TND0/2$^{(b)}$</td>
<td>-4.2</td>
<td>-10.1</td>
<td>3.1</td>
<td>16.2</td>
<td>2.5</td>
<td>18.9</td>
<td>6.1</td>
<td>17.8</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>2A 2-OMe-C$_6$H$_5$</td>
<td>Exp. (-)12.6</td>
<td>(-)17.7</td>
<td>4.1$_s$</td>
<td>10.9</td>
<td>2.6</td>
<td>12.8</td>
<td>5.3</td>
<td>12.0</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>2A 2-Furyl</td>
<td>Exp. 1</td>
<td>(-)12.9</td>
<td>(-)17.7</td>
<td>4.1</td>
<td>11.0</td>
<td>2.8</td>
<td>12.6</td>
<td>5.5</td>
<td>12.1</td>
<td>2.0</td>
</tr>
<tr>
<td>2B C$_6$H$_5$</td>
<td>Exp. (-)14.1</td>
<td>(-)17.1</td>
<td>2.0</td>
<td>5.7</td>
<td>3.1</td>
<td>12.5s</td>
<td>5.0</td>
<td>12.3</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Karplus$^{(b)}$</td>
<td>—</td>
<td>—</td>
<td>1.5</td>
<td>5.4</td>
<td>2.6</td>
<td>12.3</td>
<td>4.5</td>
<td>12.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>TND0/2$^{(b)}$</td>
<td>-5.6</td>
<td>-9.1</td>
<td>0.8</td>
<td>4.1</td>
<td>2.4</td>
<td>19.1</td>
<td>4.8</td>
<td>18.7</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>2B 2-OMe-C$_6$H$_5$</td>
<td>Exp. (-)13.9</td>
<td>(-)17.0</td>
<td>2.0</td>
<td>5.6</td>
<td>2.9s</td>
<td>12.3s</td>
<td>4.8</td>
<td>12.3</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>2B 4-Me-C$_6$H$_4$</td>
<td>Exp. (-)14.0</td>
<td>(-)17.1</td>
<td>1.9</td>
<td>5.7</td>
<td>3.1</td>
<td>12.4s</td>
<td>4.9</td>
<td>12.3s</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

(a) - W-type 1,3-di-equatorial arrangement of protons.
(b) - Calculations performed for the MM+ geometry (see text).

The performed study revealed, unexpectedly, that the spatial relationship between protons a and c in predominant diastereomeric products of the ring-closure reaction, 1 → 2, is dependent on the size of S$_N$-acetil moiety in the substrate. Thus, for m = 2 both considered protons of the major objects 2A are mutually cisoid (structure of type I) whereas in the case when m = 3 they are in the transoid relation (objects 2B, structure II); protons c display always the thermodynamically more stable axial orientation, see Table 1.

In order to understand the origin of the differences in ground state energy of both diastereomers of compounds 2, quantum-mechanical optimisations of their MM+ structures were also performed by standard methods (AM1 and PM3 hamiltonians, HyperChem). For any considered (hetero)aromatic substituent Ar the same thermodynamic preference of the stereoisomer I or II was found either by $\Delta H_{\text{formation}}$ values considering or from $\Delta E_{\text{thermical}}$ data obtained in performed MM calculations. All details of these results as well as deeper discussion of some mechanistic aspects of the cyclisation process 1 → 2 will be published in future.
With application of the "$^1$H NMR data / MM search / $^3J_{HH}$ prediction" combined approach presented above, it was also possible to elucidate conformations of six-membered ring moieties of predominant diastereomers 2. Close values of coupling constants, inside both series of studied heterocycles (i.e. of type A and B, Table 1), indicate great similarity of the geometry of their lactam rings. Indeed, according to $^3J_{HH}$ / MM data these structural fragments adopt always the half-chair conformation with carbonyl oxygen situated approximately in an average plane, see Figs. 2 and 3. The torsion (dihedral) angles, $\varphi_{ijkl}$, estimated for the above-mentioned moieties from MM+ geometries of representative objects 2, Ar = Ph, are collected in Table 2. Inspection of data obtained for these two diastereomers shows that

\[
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{Compound / Ar} & \varphi_{1234} & \varphi_{2345} & \varphi_{3456} & \varphi_{4561} & \varphi_{5612} & \varphi_{6123} \\
\hline
(1S,3S)-2A & \text{Ph} & -60.4 & 41.4 & -15.4 & 9.1 & -29.1 & 53.8 \\
(1S,3R)-2B & \text{Ph} & 59.7 & -47.45 & 23.6 & -10.1 & 21.55 & -46.5 \\
\hline
\end{array}
\]

the discussed ring for the A series is slightly less puckered around the amide system (three adjacent torsion angles considered), $\Delta \varphi = 0.5^\circ$.

Finally, it is worth noting that $^1$H NMR spectral parameters found experimentally for bicyclic lactams 2A are in good agreement with those of the corresponding five-membered thiaza rings of large, tricyclic monoterpenic alkaloid systems [22]. Further structural investigations on bicyclic compounds of type 2 are in progress.

REFERENCES


