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N-Substituent effect on the *cis–trans* geometry of nine-membered lactams

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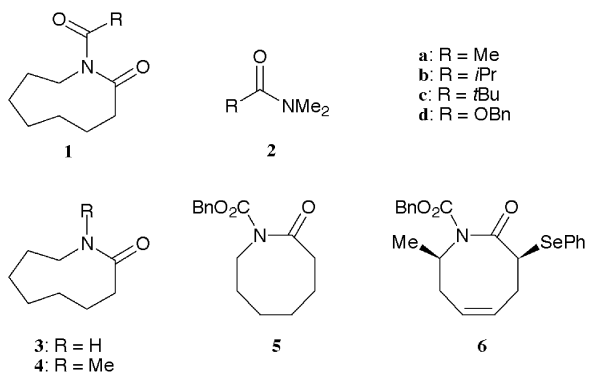
The *cis–trans* geometry of a nine-membered lactam significantly depends on the *N*-substituents; *N*-acyl-1-aza-2-cyclononanones (1a–c) exist as *cis* form; in contrast, *N*-Z-1-aza-2-cyclononanone (1d) exists as *trans* form both in the crystal and in solution.

The relationship between the *cis–trans* geometry of a medium-sized lactam and its bioactivity has received considerable attention. For instance, the *cis* form of indolactam V, an active fragment of teleocidine possessing a nine-membered lactam ring, is considered to have a much higher tumor-promoting activity than the *trans* form.[1] The twelve-membered cyclic depsipeptide hapalosin,[2] which exhibits a multidrug resistance reversing activity, exists as a 2.3:1 mixture of *cis* and *trans* isomers in solution, and the *cis* form is considered to be an active conformer.[3] Therefore, elucidation of the relationship between the structure and the conformation of lactams will attract significant interest among researchers.

Continuing our research program on the conformational studies of various *N*-acylamides,[4,5] we focused on the geometries of *N*-substituted nine-membered lactams, because the rotational barrier of nine-membered lactams is lower than that of lactams of other sizes[6] due to their significant steric strain,[7] and, therefore, the *N*-substituent seemed to affect the geometry of the lactam ring. Here we report that the *cis–trans* geometry significantly depends on the *N*-substituent of the amide moiety.

We prepared *N*-acetyl- (**1a**),[8] *N*-isobutylyl- (**1b**), *N*-pivaloyl- (**1c**) and *N*-benzyloxycarbonyl- (**1d**) 1-aza-2-cyclononanones by acylation of caplyrolactam with acyl chlorides or benzyloxycarbonyl chloride. To elucidate the *N*-substituent effect on their geometries, X-ray analyses of **1a–d**† were carried out. The most remarkable geometrical feature is that the amide linkage of *N*-Z lactam **1d** is *trans*, while all *N*-acyl derivatives **1a–c** have a *cis* amide linkage in the lactam ring with a similar conformation (Fig. 1). Table 1 lists the Winkler–Dunitz parameters[9] τ_1, τ_2 and χ_N, representing twist angles of the exocyclic and endocyclic amide linkages, and the pyramidalization of the nitrogen atom, respectively, and the N–C1 and N–C2 bond lengths. As the steric bulkiness of the acyl group increases, the τ_1 value increases from 10.2 to 24.2°. This can be attributable to the steric repulsion of the acyl group against the lactam ring. A similar substituent effect was observed in several



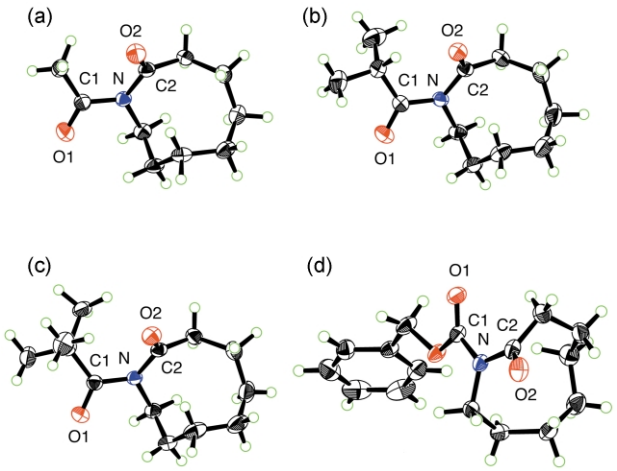


Fig. 1 ORTEP drawings for **1a** (a), **1b** (b), **1c** (c) and **1d** (d) at the 50% probability level.

series of *N*-acylamides.[10] On the other hand, the τ_2 values are much larger than τ_1 and lie in the narrower range of 27.4 to 35.4° regardless of the steric bulkiness of the *N*-substituent.

Compared with the geometry of non-substituted nine-membered lactam **3**, which is *trans* in the crystalline state due to intermolecular hydrogen bonding[11] and is a 4:1 equilibrium mixture of *cis* and *trans* isomers in $CHCl_3$,[12] **1a–d** have much larger twist angles τ_2, longer N–C2 bonds and smaller χ_N values (Table 1). These results clearly show that the *N*-acyl and *N*-Z substituents are responsible for the ring conformation; they reduce the double bond character of the endocyclic amide linkage, which results in lengthening of the N–C2 bond and twisting of the amide bond so as to diminish the ring strain originated from the planarity of the amide linkage. The much larger τ_1 than τ_2 described above would be the result of the relaxation of the ring strain triggered by the the *N*-substitution. The relatively smaller χ_N values would be due to the delocalization of the nitrogen lone pair electrons with the two carbonyl groups, which allows the N atom to retain sp^2 character similar to the observations in several *N*-acylamides.[13] The largest τ_2 and the longest N–C2 bond of **1d** among these lactams are ascribed to the much strained *trans* amide linkage in the nine-membered ring. The individual structural optimization by AM1 calculations predicted *cis* for **1a–c** and *trans* for **1d**

Table 1 Winkler–Dunitz parameters and the amide bond lengths for **1a–d** and **3**

	τ_1[a]/°	τ_2[a]/°	χ_N/°	N–C1/Å	N–C2/Å
1a	10.2 (7.0)	28.5 (20.8)	1.7	1.403(2)	1.410(2)
1b	13.5 (15.5)	27.4 (26.4)	11.9	1.408(2)	1.410(2)
1c	24.2 (23.9)	32.3 (30.5)	15.8	1.407(2)	1.400(2)
1d	15.3 (9.0)	35.4 (38.9)	9.2	1.384(2)	1.418(2)
3	—	17.1	23.1	—	1.334(3)

[a] Twist angles obtained by AM1 calculations are indicated in parentheses.

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Table 2 ^{13}C NMR chemical shifts for carbonyl groups of **1a–d** (ppm) and their $\Delta\delta$ values[a]

	δ_1	δ_2	$\Delta\delta_1$[b]	$\Delta\delta_2$[c]
1a	173.5	180.0	2.9	4.3
1b	181.3	180.1	4.3	4.4
1c	188.4	180.4	10.9	4.7
1d	154.4	182.2	−1.8	6.5

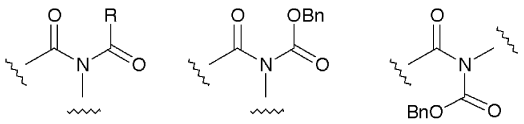
[a] 100 MHz in $CDCl_3$. [b] δ values for **2a–d** are as follows: δ(**2a**); 170.6, δ(**2b**); 177.0, δ(**2c**); 177.5, δ(**2d**); 156.2. [c] δ value for **4** is 175.7.

with very close geometries to those of the X-ray structures (Table 1).[14]

The geometries of **1a–d** in solution were studied by ^{1}H and ^{13}C NMR spectroscopies. The NMR spectra showed that they are single isomers about the amide linkage. Table 2 lists the ^{13}C NMR chemical shifts of the carbonyl carbons for **1a–d** and their $\Delta\delta$ values calculated using **2** and **4** as standards. As the steric bulkiness of the acyl group increases, both $\Delta\delta_1$ and $\Delta\delta_2$ values increase. Rough correlation was also observed between $\Delta\delta_1$ and τ_1, and $\Delta\delta_2$ and τ_2, indicating similarity in the geometry in solution and in the solid state. NOE experiments clarified the preference of the *cis–trans* geometry in solution. For **1a–c**, NOEs were observed between the methylene protons next to the ring carbonyl and the NCH_2 protons,[15] whereas no such NOE was observed in **1d**. This means that the X-ray geometries of **1a–c** are retained in $CDCl_3$ solution.

These remarkable conformational differences arising whether they have an *N*-acyl group or an *N*-Z group may be mainly attributable to the differences in the electronic properties of the *N*-substituents. The electronic repulsion between the *N*-benzyloxycarbonyl group and the lactam carbonyl in the *cis*-**1d(II)** would be much larger than those in the *trans* form **III** due to the close contact of the oxygen lone pairs, whereas such repulsion in the *cis*-**Ia–c(I)** of *N*-acyl compounds **1a–c** is less important (Fig. 2). As a result, **1d** would prefer *trans* to avoid the electronic repulsion and **1a–c** prefer *cis* similar to non-substituted lactam **3**. Since no steric effect of the *N*-acyl groups on the *cis–trans* geometries was observed for a series of *N*-acyllactams **1a–c**, the steric bulkiness of the *N*-Z group would not be a major factor in the *trans* preference of **6**.

Holmes and coworkers have reported that eight-membered *N*-Z lactam **6** has a significantly twisted *trans* amide linkage.[16] The *trans* preference of **6** may not be due to the *N*-Z substituent effect, since NOE experiments for *N*-Z-1-aza-2-cyclooctanone (**5**) in $CDCl_3$ solution predicted it to have a *cis* amide linkage; the two substituents around the amide functionality, the double bond in the ring or a crystal packing effect may play an important role in the *trans* preference.



I **II** **III**

Fig. 2 Schematic geometries around the amide moieties for *cis*-**la–c** (**I**), for *cis*-**1d** (**II**) and for *trans*-**1d** (**III**).

In summary, we have shown for the first time that the *cis–trans* geometry of a nine-membered lactam significantly depends on the *N*-substituents. *N*-acyl-1-aza-2-cyclononanones (**1a–c**) exist as *cis* form; in contrast, *N*-Z-1-aza-2-cyclononanone (**1d**) exists as *trans* form both in the crystal and in solution. The significant geometrical differences may perhaps be due to the electronic effects of the *N*-substituents. These results would provide insights into the relationship between the structure and the geometry of medium-sized lactams.

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Notes and references

† *Crystal data*: compound **1a**: $C_{10}H_{17}NO_2$, M = 183.25, monoclinic, $P2_1/n$, μ = 0.692 mm^{-1}, a = 11.988(2), b = 7.2178(14), c = 11.446(2) Å, β = 99.370(12)°, V = 977.1(3) Å^3, T = 230 K, Z = 4, D_c = 1.246 g cm^{-3}, A total of 1870 reflections were collected and 1781 are unique (R_{int} = 0.0344). $R1$ and $wR2$ are 0.0409 [$I > 2\sigma(I)$] and 0.1681 (all data), respectively.

Compound **1b**: $C_{12}H_{21}NO_2$, M = 211.30, monoclinic, $P2_1/n$, μ = 0.621 mm^{-1}, a = 10.068(4), b = 23.305(2), c = 5.1428(13) Å, β = 91.86(3)°, V = 1206.0(6) Å^3, T = 230 K, Z = 4, D_c = 1.164 g cm^{-3}, A total of 6101 reflections were collected and 2190 are unique (R_{int} = 0.0741). $R1$ and $wR2$ are 0.0460 [$I > 2\sigma(I)$] and 0.1776 (all data), respectively.

Compound **1c**: $C_{13}H_{23}NO_2$, M = 225.32, monoclinic, $P2_1/n$, μ = 0.598 mm^{-1}, a = 10.462(2), b = 22.892(5), c = 5.5006(9) Å, β = 94.201(14)°, V = 1313.8(4)Å^3, T = 293 K, Z = 4, D_c = 1.139 g cm^{-3}, A total of 3322 reflections were collected and 2395 are unique (R_{int} = 0.0178). $R1$ and $wR2$ are 0.0435 [$I > 2\sigma(I)$] and 0.1849 (all data), respectively.

Compound **1d**: $C_{16}H_{21}NO_3$, M = 275.34, triclinic, $P1$, μ = 0.701 mm^{-1}, a = 8.2108(13), b = 12.229(2), c = 7.602(2) Å, α = 96.600(14), β = 99.01(2), γ = 103.634(11)°, V = 723.4(2) Å^3, T = 230 K, Z = 2, D_c = 1.264 g cm^{-3}, A total of 4655 reflections were collected and 2627 are unique (R_{int} = 0.0601). $R1$ and $wR2$ are 0.0432 [$I > 2\sigma(I)$] and 0.2064 (all data), respectively.

The data were collected on a Rigaku AFC7R diffractometer with Cu-Kα radiation (λ = 1.54178 Å). The structures were solved by direct methods with SHELXS-86 and refined by full-matrix least-squares on F^2 using SHELXL-93. CCDC reference numbers 190921 (**1a**), 190922 (**1b**), 190923 (**1c**) and 190924 (**1d**). See http://www.rsc.org/suppdata/cc/b2/b207925a/ for crystallographic data in CIF or other electronic format.

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