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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 mediumsized 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 sizes⁶ 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 benzvloxycarbonyl 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 parameters⁹ 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



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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 ninemembered lactam 3, which is *trans* in the crystalline state due to intermolecular hydrogen bonding¹¹ and is a 4:1 equilibrium mixture of *cis* and *trans* isomers in CHCl₃,¹² **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 sp² 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 $1a\mathchar{-}d$ and 3

$ au_1$	a/°	$ au_2^{a/\circ}$	$\chi_{\rm N}^{/\circ}$	NC1/Å	N–C2/Å
1a 10 1b 13 1c 24 1d 15 3 —	0.2 (7.0) 3.5 (15.5) 4.2 (23.9) 5.3 (9.0)	28.5 (20.8) 27.4 (26.4) 32.3 (30.5) 35.4 (38.9) 17.1	1.7 11.9 15.8 9.2 23.1	1.403(2) 1.408(2) 1.407(2) 1.384(2)	1.410(2) 1.410(2) 1.400(2) 1.418(2) 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	ł
their $\Delta\delta$ values ^{<i>a</i>}							

	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 MH	Iz in CDCl ₃ . ^b δv	alues for 2a–d ar	e as follows: $\delta(2a)$	b); 170.6, δ(2b);

177.0, $\delta(2\mathbf{c})$; 177.5, $\delta(2\mathbf{d})$; 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 ¹H and ¹³C NMR spectroscopies. The NMR spectra showed that they are single isomers about the amide linkage. Table 2 lists the ¹³C 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 NCH₂ protons,¹⁵ whereas no such NOE was observed in **1d**. This means that the X-ray geometries of **1a–c** are retained in CDCl₃ 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 Nbenzyloxycarbonyl 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 nonsubstituted lactam **3**. Since no steric effect of the N-acyl groups on the *cis–trans* geometries was observed for a series of Nacyllactams **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 CDCl₃ 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.



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

In summary, we have shown for the first time that the *cistrans* 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. This work was partly supported by a Grant-in-Aid for Scientific Research (10640574) from Japan Society for the Promotion of Science and Research (13650901) from Ministry of Education, Science, and Culture, Japan.

Notes and references

† *Crystal data*: compound **1a**: C₁₀H₁₇NO₂, *M* = 183.25, monoclinic, *P*₂₁/*n*, $\mu = 0.692 \text{ mm}^{-1}$, *a* = 11.988(2), *b* = 7.2178(14), *c* = 11.446(2) Å, β = 99.370(12)°, *V* = 977.1(3) Å³, *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). *R*1 and *wR*2 are 0.0409 [*I* > 2 σ (*I*)] and 0.1681 (all data), respectively.

Compound **1b**: $C_{12}H_{21}NO_2$, M = 211.30, monoclinic, $P2_1/n$, $\mu = 0.621$ mm⁻¹, a = 10.068(4), b = 23.305(2), c = 5.1428(13) Å, $\beta = 91.86(3)^\circ$, V = 1206.0(6) Å³, 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, $P2_1/n$, $\mu = 0.598$ mm⁻¹, a = 10.462(2), b = 22.892(5), c = 5.5006(9) Å, $\beta = 94.201(14)^\circ$, V = 1313.8(4)Å³, 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**: C₁₆H₂₁NO₃, M = 275.34, triclinic, $P\bar{1}, \mu = 0.701$ mm⁻¹, a = 8.2108(13), b = 12.229(2), c = 7.602(2) Å, $\alpha = 96.600(14), \beta = 99.01(2), \gamma = 103.634(11)^{\circ}, V = 723.4(2)$ Å³, 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-K α radiation ($\lambda = 1.54178$ 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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