Slow Ring-inversion of the Nine-membered Lactam in 4-Azabicyclo[5,2,2]-undeca-8,10-dien-3-one Systems

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The kinetic parameters for hindered inversion of the nine-membered lactam ring in 4-azabicyclo[5,2,2]undeca-8,10-dien-3-one systems have been determined by n.m.r. total line-shape analysis. These data may provide an example of hindered ring-inversion of a medium-sized ring caused by hindered rotation of the amide group.

SINCE the initial kinetic studies of hindered internal rotation in amides by high-resolution n.m.r. spectroscopy,[1] a number of reports for various amides have been published,[2] and recently the inversion in amines or in amides has received considerable attention.[2,3]

In the course of our extensive studies on the photochemistry of pharmacodynamic amines, a novel bicyclic

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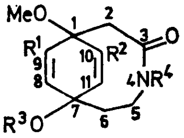
[1] G. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

[2] For reviews see W. E. Stewart and T. H. Siddall, tert., *Chem. Revs.*, 1970, **70**, 517; H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9**, 219.

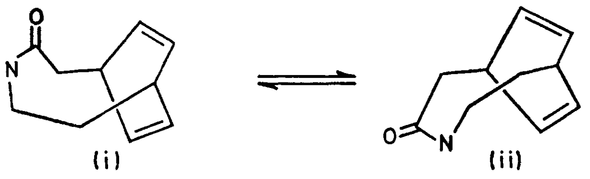
[3] W. B. Jenning and R. Spratt, *Chem. Comm.*, 1971, **54**; D. L. Griffith, B. L. Olson, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 1648.

compound, 7-hydroxy-1,9,10-trimethoxy-4-azabicyclo-[5,2,2]undeca-8,10-dien-3-one (I) was synthesized.[4] In its n.m.r. spectrum in D_2O, the two methoxy-groups at C-9 and -10 appear at δ 3·55 and 3·73 p.p.m. as distinct singlets with equal intensity. The methoxy-group at C-9 in the analogous compound, 7-hydroxy-1,9-dimethoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (II),[5] splits into two peaks at δ 3·56 and 3·74 p.p.m. with unequal intensity (0·46 : 0·54). The signals of the vinyl protons in compound (II) are complicated and are virtually the mean of those of compounds (I) and (III).[5]



(I) $R^1 = R^2 = \text{OMe}, R^3 = R^4 = \text{H}$
(II) $R^1 = \text{OMe}, R^2 = R^3 = R^4 = \text{H}$
(III) $R^1 = R^2 = R^3 = R^4 = \text{H}$
(IV) $R^1 = R^2 = \text{OMe}, R^3 = \text{H}, R^4 = \text{Ac}$
(V) $R^1 = R^2 = \text{OMe}, R^3 = \text{Me}, R^4 = \text{H}$
(VI) $R^1 = \text{OMe}, R^2 = R^4 = \text{H}, R^3 = \text{Me}$
(VII) $R^1 = \text{OMe}, R^2 = R^3 = \text{H}, R^4 = \text{Ac}$
(VIII) $R^1 = \text{OMe}, R^2 = \text{H}, R^3 = R^4 = \text{Ac}$
(IX) $R^1 = R^2 = R^3 = \text{H}, R^4 = \text{Ac}$
(X) $R^1 = R^2 = \text{H}, R^3 = R^4 = \text{Ac}$
(XI) $R^1 = R^2 = R^4 = \text{H}, R^3 = \text{COCF}_3$

Since 2-methyl-2-azacyclononanone exists purely in the *cis*-form though inspection of models indicates that both *cis*- and *trans*-arrangements are possible,[6] interconversion between the *cis*- and *trans*-isomers of the amide group in (I) and (II) should not occur. Therefore the splitting of the n.m.r. signals indicates that the methoxy-groups at C-9 and -10 are in a different magnetic environment caused by the hindered inversion of the nine-membered lactam ring (i $\rightleftharpoons$ ii). The high-field signal can be ascribed to the shielding effect of the close approach of the anisotropic amide group to the methoxy-group. In fact, the intra-ring distance between C-3 and -9 is only 2·78 Å from *X*-ray analysis.[4]



SCHEME

Since in 2-methyl-2-azacylononanone not only no *trans*-form exists but the methylene groups invert easily, it is very difficult to estimate kinetic parameters for twisting of the C–N bond in the amide group by the usual temperature dependent n.m.r. analysis. However in compounds (I) and (II), inspection of models indicates that twisting of the C–N bond may be essential for ring inversion, because C-1, -7, -10, and -11 are fixed in the bicyclic system.

On the other hand, in the *N*-acetyl compound (IV)[4] methoxy-groups at C-9 and -10 appear as a sharp singlet (6H), which is broadened at −60 °C. The signals of vinyl and methoxy-protons of other similar compounds are summarized in Table 1.

TABLE 1

Chemical shifts and coupling constants in compounds (V)—(XI)

Compound	Solvent	δ_{MeO}/(p.p.m.)[a]	δ_{H}/(p.p.m.)[b]
(V)	D_2O	3·63 (3H, s), 3·80 (3H, s)	5·05 (2H, s)
(VI)	D_2O	3·61 (s), 3·79 (s), (total 3H)	5·05—5·24 (1H), 5·66—6·27 (2H)
(VII)	$CDCl_3$	3·61 (3H, s)	4·88 (d, $J_{8.11}$ 2·5 Hz, 8-H) 5·77 (d, $J_{10.11}$ 10 Hz, 10-H) 5·97 (q, J 2·5, 10 Hz, 11-H)
(VIII)	$CDCl_3$	3·63 (3H, s)	5·01 (d, $J_{8.11}$ 2·5 Hz, 8-H) 5·82 (d, $J_{10.11}$ 10 Hz, 10-H) 6·05 (q, J 2·5, 10 Hz, 11-H)
(IX)	$CDCl_3$		5·98 (4H, s)
(X)	$CDCl_3$		6·00 (4H, s)
(XI)	$CDCl_3$		6·09 (s), 6·03 (d, $J_{8.9}$ 11 Hz), 6·28 (d, J 11 Hz) (total 4H)

[a] MeO at C-9 or -10. [b] Vinyl protons.

In order to explain these observations the n.m.r. total line-shape analysis method[1] was applied.

EXPERIMENTAL

Materials.— 7-Hydroxy-1,9,10-trimethoxy-4-azabicyclo-[5,2,2]undeca-8,10-dien-3-one (I) had m.p. 230—232°;[4] 7-hydroxy-1,9-dimethoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (II) had m.p. 210—213°;[5] and *N*-acetyl-7-hydroxy-1,9,10-trimethoxy-4-azabicyclo[5,2,2]undeca-8,10-dien-3-one (IV), had m.p. 188—189·5°.[4]

Variable Temperature Spectra.—Spectra were recorded with a Hitachi-R22 (90 MHz) n.m.r. spectrometer equipped with a variable temperature accessory. Temperatures are estimated to be accurate to ±1° or ±2%.

Calculation of Theoretical Spectra.—The total line-shape equation of Gutowsky and Holm[1] for an uncoupled two-site exchange was programmed in FORTRAN IV. Calculations were performed on a FACOM 230—60 computer (Fujitsu Ltd.) using the following input data obtained from the observed spectra; transverse relaxation time (T_2) [(I), 0·4 s; (II), 0·4 s; (IV), 0·2 s], nonexchanging chemical shift ($\delta\nu$) [(I), $\delta\nu_{\text{A}} = 8{\cdot}2$, $\delta\nu_{\text{B}} = -8{\cdot}2$; (II), $\delta\nu_{\text{A}} = 8{\cdot}15$, $\delta\nu_{\text{B}} = -8{\cdot}15$; (IV), $\delta\nu_{\text{A}} = 4{\cdot}5$, $\delta\nu_{\text{B}} = -4{\cdot}5$ Hz], relative population (P_{A} and P_{B}). The spectra best fitted to those observed were obtained by least-squares refinement. The values of P_{A} and P_{B}, mean lifetime (τ), and mean rate constant (k) are summarized in Table 2.

RESULTS AND DISCUSSION

Compounds (I), (II), and (IV) were chosen for the n.m.r. total line-shape analysis. On raising the temtemperature, the doublet of the methoxy-groups at

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[4] O. Yonemitsu, H. Nakai, Y. Kanaoka, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.*, 1969, **91**, 4591; 1970, **92**, 5691.

[5] O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi, and B. Witkop, *Photochem. Photobiol.*, 1972, **15**, 509; H. Nakai, K. Hemmi, and O. Yonemitsu, *Chem. Pharm. Bull. Japan*, 1972, **20**, 998.

[6] R. M. Moriarty, *J. Org. Chem.*, 1964, **29**, 2748; 1966, **31**, 3007.

TABLE 2

Kinetic data for compounds (I), (II), and (IV)

Compound	Solvent	Temp. (°C)	$P_A : P_B$	τ (sec)	k/s^{-1}
(I)	D_2O [a]	35	0·500 : 0·500	0·1883	2·655
		60		0·0633	7·899
		80		0·0270	18·519
		97		0·0110	45·545
		100		0·0086	58·14
		120		0·0031	161·29
(II)	D_2O [a]	0	0·540 : 0·460	0·4070	1·229
		60	0·525 : 0·475	0·0668	7·175
		80	0·515 : 0·485	0·0266	18·80
		93	0·510 : 0·490	0·0117	42·74
		95	0·508 : 0·492	0·0102	46·52
		100	0·506 : 0·494	0·0078	64·10
		110	0·505 : 0·495	0·0047	104·6
(IV)	$CDCl_3$	−60	0·500 : 0·500	0·0805	6·22
		−40		0·0258	19·38
		−38		0·0242	20·66
		−20		0·0125	40·00
		0		0·0062	80·65

[a] Both (I) and (II) are soluble only in water.

C-9 and -10 in compound (I) gradually collapses to a singlet with the coalescence temperature (T_c) being 97 °C. The usual Arrhenius plots [2] (Figure 1) of these data gave the activation parameters as shown in Table 3.

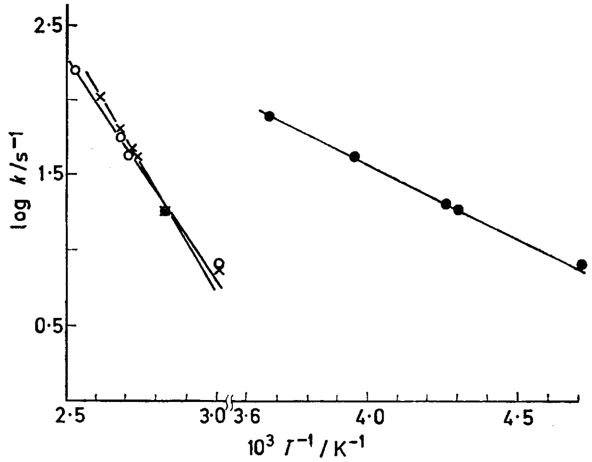

FIGURE 1 Arrhenius plots for: ○, (I), ×, (II); ●, (IV)

TABLE 3

Coalescence temperature and activation parameters

Compound	T_c (°C)	E_a/ kcal mol^{-1}	$\Delta G^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal K^{-1} mol^{-1}
(I)	97	13·7	19·0	−14·3
(II)	95	15·4	18·9	−9·5
(IV)	−38	4·5	12·2	−32·4

Compound (II) with methoxy-signals of different intensities was treated in the same way. The coalescence temperature and the activation parameters are also shown in Table 3. Typical observed and computer-generated spectra are compared in Figure 2.

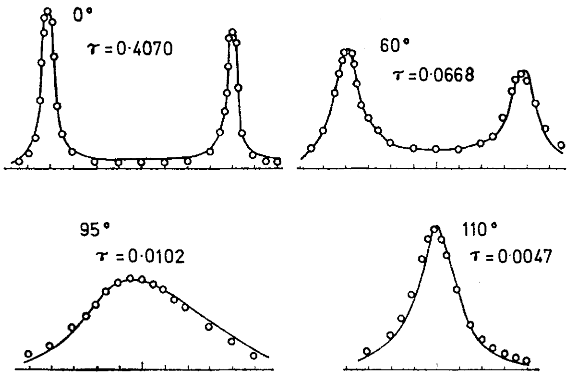

FIGURE 2 Observed (—) and calculated (○) spectra of compound (II) at various temperatures. 1 Scale division = 2 Hz

These values, especially $\Delta G^{\ddagger}$, are quite similar to those for the well known hindered rotation of amides, such as *NN*-dimethylacetamide.[2,7] Since the amide group of compound (I) is almost planar (*X*-ray analysis [4]), the energy barrier for the inversion at the nitrogen atom is negligible.[8] Therefore the slow ring-inversion is mainly caused by the hindered twisting of the C–N bond in the amide group because of its double-bond character. In fact the C–N bond length [4] is 1·318 Å, which indicates relatively high double-bond character.

Since *N*-acetylation of compound (I) to give compound (IV) reduces the bond order of the C–N bond and causes more rapid inversion of the nine-membered lactam ring, its n.m.r. spectrum for a $CDCl_3$ solution at room temperature shows the two methoxy-groups at C-9 and -10 and the vinyl protons at C-8 and -11 as sharp singlets at δ 3·65 and 4·95 p.p.m. respectively. Even at −60 °C, the methoxy-signal only broadens; however, the singlet of the vinyl protons splits into a doublet. The n.m.r. analysis was also applied in this case to give the activation parameters shown in Table 3. Even taking into account the solvent effect, the E_a value clearly indicates that the reduction of the bond order of the C–N bond gives rise to the rapid ring inversion. The relatively large value of $\Delta S^{\ddagger}$ in compound (IV) probably indicates that (IV) in its transition state exists in a more sterically hindered form.

These results provide the first example of hindered ring inversion of a medium-sized ring caused by hindered twisting of amide.

We thank Dr. Hanyu for n.m.r. measurements.

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[7] R. C. Neuman, jun., and V. Jonas, *J. Amer. Chem. Soc.*, 1968, **90**, 1970.

[8] *Cf.*, Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, 1967, **89**, 4910.