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Lactams. XXV.[1] Reassignments of the C=C and C=O Stretching Vibrations in Six-Membered α,β-Unsaturated Lactams

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A new method for differentiating the lactam CO infrared (IR) absorption from the C=C absorption in the six-membered, α,β-unsaturated lactam system (type **2**) has been developed by utilizing association of dichloroacetic acid or a similar carboxylic acid with the lactam CO, which decreases the frequency of the lactam CO absorption by 20—40 cm^{-1}. On the basis of such an association shift as well as the results obtained from solvent shift experiments with the lactams **5**, **6**, **15**, and **17**—**19**, the lactam CO and the conjugated C=C absorptions observed for each of the α,β-unsaturated lactams **14**—**19** in the 1590—1670 cm^{-1} region were differentiated from each other. As a result, it has now become clear that in six-membered lactams the carbonyl frequency is slightly (10—20 cm^{-1}) lowered by conjugation with a double bond, in line with the usual lowering. This is the opposite of what has been proposed in the literature. In addition, the deuterated α,β-unsaturated lactam **24** was prepared from the exocyclic methylene lactam **23** by treatment with NaOD in a mixture of D_2O and EtOD. This deuterium labeling was found to decrease the frequency of the 1666 cm^{-1} absorption, assigned to the C=C stretching vibration, by 17 cm^{-1}, supporting the correctness of the above differentiation.

Keywords——lactam carbonyl stretching vibration; lactam carbonyl IR frequency solvent shift; lactam carbonyl–carboxylic acid association; lactam carbonyl IR frequency association shift; α,β-unsaturated lactam IR conjugation effect; α,β-unsaturated lactam IR deuterium-labeling effect; lactam acid solution IR dilution effect

It appears to be widely accepted that in six-membered lactams (type **1**) the infrared (IR) carbonyl frequency is slightly raised by conjugation with a double bond (type **2**) as opposed to the more usual lowering.[2,3] Kruk and Spaargaren[4] have reported that an α,β-unsaturated *N*,*N*-dimethylamide in the s-*cis* form (type **3**) showed a similar carbonyl-frequency raise (relative to ν_{CO} of *N*,*N*-dimethylacetamide), exerting an apparent "negative conjugate effect,"[5] whereas the compound with the s-*trans* conformation (type **4**) exhibited the usual carbonyl-frequency fall. Their report is significant because the α,β-unsaturated amide system in *N*-substituted six-membered lactams (type **2**) corresponds to that of the above s-*trans* conformation (**4**) and, therefore, it may show the usual conjugation effect, contrary to general opinion. During the course of our synthetic studies on the benzo[*a*]quinolizidine-type *Alangium* alkaloids,[6] we prepared the α,β-unsaturated lactam intermediate **16** as well as its analogs **14**, **15**, and **17**—**19** and encountered the problem of characterizing two IR absorption bands with strong intensities in the 1600—1700 cm^{-1} region. One of the two bands must arise from the lactam CO stretching vibration, and the other from the C=C stretching vibration, whose strong intensity is expected to be due to conjugation with the lactam CO group.[7] However, immediate assignments of these two bands on the basis of the band position or intensity were difficult for the reasons described above. In this paper, we present two convenient methods for differentiating between two bands arising from the lactam CO and the

C=C group in such a system and propose a conjugation effect opposite to what has been suggested[2,3] for six-membered, α,β-unsaturated lactams.

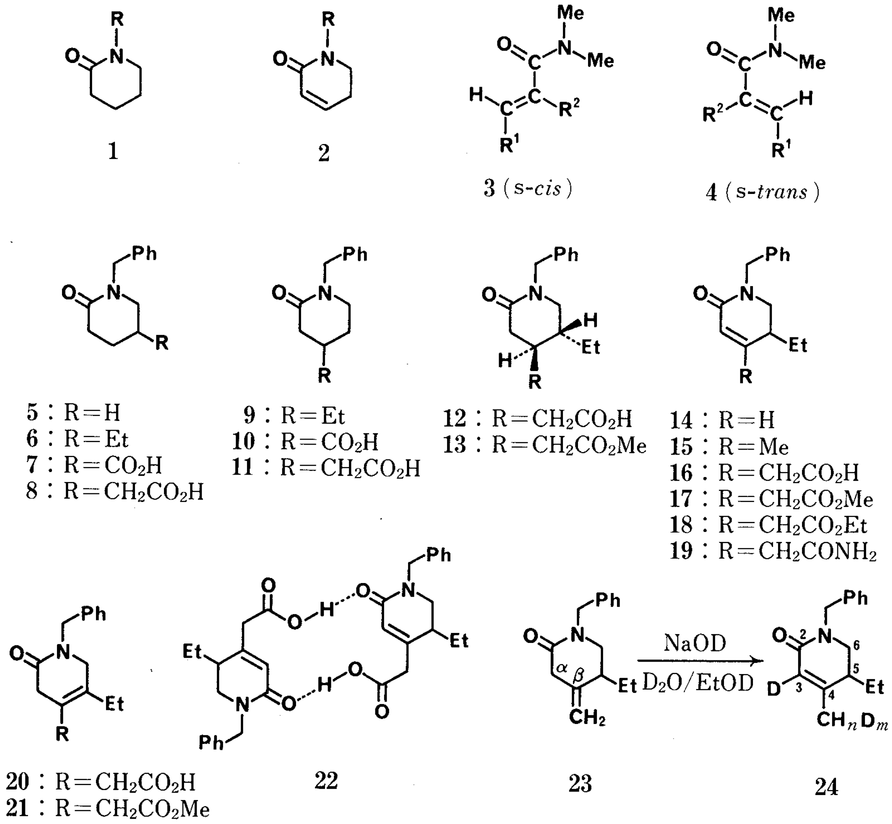
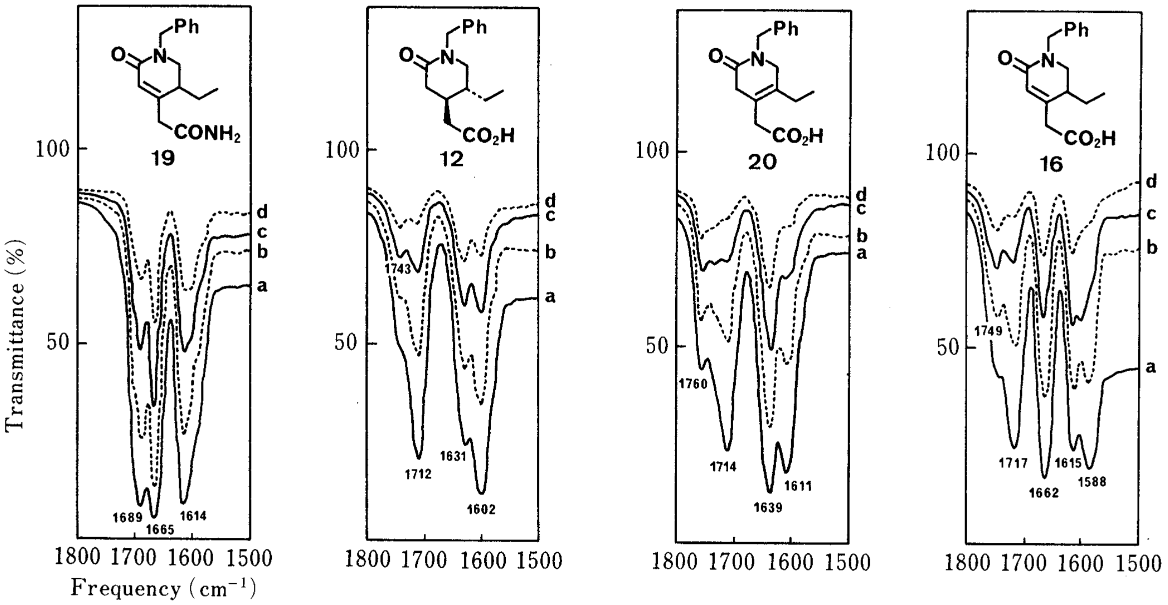


Chart 1

Our previous work has already shown that in dilute (0.005 M) $CHCl_3$ solutions the six-membered, saturated lactams **5**—**11** exhibit their ν_{CO} bands in the region of 1627—1633 cm^{-1}, regardless of the presence or absence of a carboxy group, whereas in the solid state, only the piperidones possessing a carboxy function (**7**, **8**, **10**, **11**) show a decrease in the frequency of their lactam ν_{CO} bands by 20—39 cm^{-1}.[8] Such a shift in frequency has been explained by intermolecular interaction of the lactam CO group with the carboxy group as a hydrogen donor.[8] A similar interaction has been detected for the lactam acids **12** and **16** by means of IR spectroscopy,[9,10] and an X-ray analysis of a single crystal of **16** disclosed that the carboxylic hydroxy and the lactam CO group in the molecule of **16** form hydrogen bonds with the lactam CO and the carboxy group, respectively, of another molecule, producing the cyclic dimer **22**.[11] In the present work, we first tried to detect the existence of an analogous carboxy–lactam CO interaction in the lactam acids **12**, **16**, and **20** in $CHCl_3$ solution. It may be seen from Fig. 1 that in $CHCl_3$ solution at 0.004 M concentration the α,β-unsaturated lactam amide **19** showed two bands at 1614 and 1665 cm^{-1} besides the one at 1689 cm^{-1} arising from the amide ν_{CO} [Fig. 1(A)]. The positions and relative intensities of these absorptions remained essentially unchanged on dilution with $CHCl_3$ to 0.002, 0.001, and 0.0005 M. The saturated lactam acid **12** showed the lactam ν_{CO} band at 1607 cm^{-1} in 0.2 M $CHCl_3$ solution.[9] Dilution to 0.004 M caused this band to split into two bands at 1602 and 1631 cm^{-1}, and further dilution to 0.0005 M caused the relative intensity of the 1631 cm^{-1} band to become greater than that of the 1602 cm^{-1} band [Fig. 1(B)]. The 1631 cm^{-1} band apparently corresponds to the lactam ν_{CO} band of the saturated lactam ester **13** at 1630 cm^{-1}.[9] The broad band at 1712 cm^{-1} arising from the dimeric and associated carboxy groups in 0.004 M $CHCl_3$ solution



(A) (B) (C) (D)

Fig. 1. Effect of Concentration on Carbonyl Frequencies of the Lactams **12**, **16**, **19**, and **20** in $CHCl_3$

Curve a, 0.004 M solution; curve b, 0.002 M solution; curve c, 0.001 M solution; curve d, 0.0005 M solution.

was also found to split concomitantly into two bands at 1712 and 1743 cm^{-1} on dilution. The 1743 cm^{-1} band is assignable to the monomeric carboxy ν_{CO}, and these findings indicate that the 1602 cm^{-1} band arises from the lactam CO associated with the carboxy group; the 1631 cm^{-1} band arises from the unassociated lactam CO. Dilution experiments with the β,γ-unsaturated lactam acid **20** gave similar results, as shown in Fig. 1(C), leading to the assignments of the 1611 cm^{-1} band to the associated lactam ν_{CO}, and the 1639 cm^{-1} band to the unassociated lactam ν_{CO}.[12] Similar dilution experiments with the α,β-unsaturated lactam acid **16** disclosed analogously changing bands in the 1588—1615 and 1717—1749 cm^{-1} regions together with an unchanging band at 1662 cm^{-1} [Fig. 1(D)]. This led us to assign the 1588 and 1615 cm^{-1} bands to the associated and unassociated lactam CO's, respectively, and the 1662 cm^{-1} band to the conjugated C=C group. It follows that the 1614 cm^{-1} and the 1665 cm^{-1} bands observed for **19** [Fig. 1(A)] probably arise from the lactam CO and the α,β-conjugated C=C, respectively.

The previous and present results described above thus suggested the use of a carboxylic acid as a tool for differentiating a lactam ν_{CO} band from a $\nu_{C=C}$ band. To examine this possibility, we then measured the IR spectrum of the simple lactam **5** in $CHCl_3$ in the presence of an equimolar amount of a carboxylic acid. The acids selected for this measurement were acetic, cyclohexaneacetic, chloroacetic, dichloroacetic, trichloroacetic, and trifluoroacetic acids, which are all soluble in $CHCl_3$, have various levels of acidity,[13] and are practically transparent in the 1600—1700 cm^{-1} region. It may be seen from Fig. 2 that in 0.2 M $CHCl_3$ solution the addition of an equimolar amount of acetic acid or cyclohexaneacetic acid did not cause the 1626 cm^{-1} band position itself to shift, but caused the band width to broaden remarkably to the lower frequency side [Figs. 2(A) and 2(B)]. However, replacement of the weak carboxylic acid by stronger acids such as mono-, di- and trichloroacetic acids, and trifluoroacetic acid was found to lower the unassociated lactam CO band by 31—46 cm^{-1}, as shown in Figs. 2(C)—2(F). Since all the spectra obtained in the presence of the carboxylic acids showed a strong absorption in the 1700 cm^{-1} region, the carboxylate ion species that

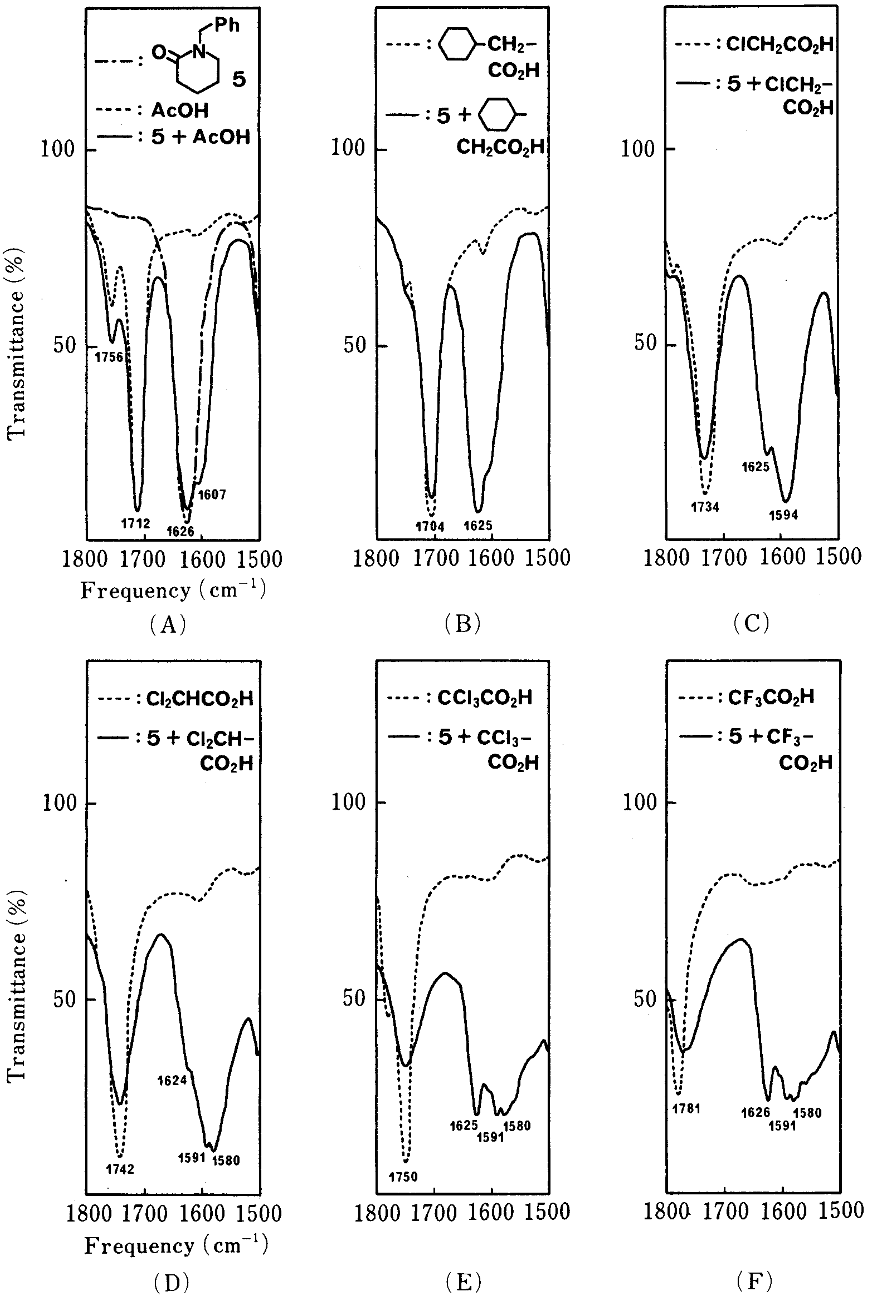
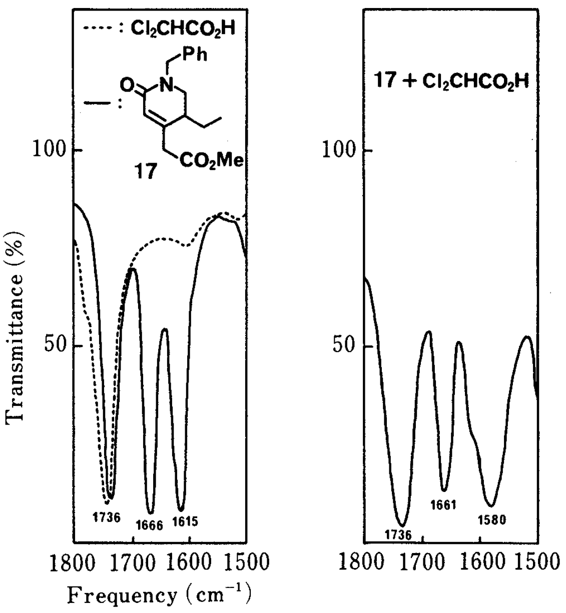


Fig. 2. The CO Frequency of the Lactam **5**: Effect of an Equimolar Amount of a Coexisting Carboxylic Acid in 0.2 M Solution in $CHCl_3$

should arise from protonation at the lactam CO and should exhibit the COO^- absorption in the 1605—1671 cm^{-1} region[14] must have been absent or negligible, permitting the above association shifts to be directly observed. The shoulders or weak bands near 1625 cm^{-1} found in Figs. 2(C)—2(F) are probably due to coexisting species free from association with the carboxylic acids, and splitting of the associated ν_{CO} bands into two with a separation of *ca.* 10 cm^{-1} [Figs. 2(D)—2(F)] is suggestive of the presence of two associated forms in which the conformations in the carboxylic acid moieties are different.

In view of the simplicity of the band shape in Fig. 2(D), we decided to use dichloroacetic acid from the test acids for identifying the lactam CO absorptions in other lactams. Figure 3 indicates that in $CHCl_3$ solution the α,β-unsaturated lactam ester **17** absorbs at 1615 and 1666 cm^{-1} and the two bands move down to 1580 and 1661 cm^{-1}, respectively, on addition of



(A) (B)

Fig. 3. The CO and C=C Frequencies of the α,β-Unsaturated Lactam **17** in $CHCl_3$ at 0.2 M Concentration

an equimolar amount of dichloroacetic acid. The shift of the $1615\,cm^{-1}$ band is of the order $-35\,cm^{-1}$, which is comparable to that (-35 to $-46\,cm^{-1}$) of the $1626\,cm^{-1}$ band in **5** [Figs. 2(A) and 2(D)], whereas the shift of the $1666\,cm^{-1}$ band is insignificant. This led us to assign the $1615\,cm^{-1}$ band to the lactam ν_{CO}, and the $1666\,cm^{-1}$ band to $\nu_{C=C}$. Table I lists such association shifts observed for the lactams **5**, **6**, and **14**—**21**. It may be seen that in the saturated lactams **5** and **6** and in the β,γ-unsaturated lactam ester **21** the association shift is about $-40\,cm^{-1}$. Although the β,γ-unsaturated lactam acid **20** displays a smaller association shift in the $1611\,cm^{-1}$ band, this is not unreasonable since the compound has a carboxy group within the molecule, already lowering the lactam CO absorption without recourse to the extra carboxylic acid. In the cases of the α,β-unsaturated lactams **14**—**19**, the association shift is much larger for the lower frequency band (at 1592—$1615\,cm^{-1}$) than for the higher frequency band (at 1661—$1666\,cm^{-1}$), and the magnitude of the shift of the former band is similar to that of the lactam ν_{CO} of the saturated lactams **5** and **6**, except for the $1592\,cm^{-1}$ band of the lactam acid **16**. This exception seems to arise for the same reason as discussed above for the β,γ-unsaturated lactam acid **20**. Thus, we conclude that in the α,β-unsaturated lactams **14**—**19** the 1608—$1615\,cm^{-1}$ absorptions (a fall of 10—$20\,cm^{-1}$ from ν_{CO} of the saturated lactam **5**) and the $1592\,cm^{-1}$ absorption arise from the lactam CO stretching vibration, and the 1661—$1666\,cm^{-1}$ absorptions from the C=C stretching vibration. It follows that in six-membered lactams the IR carbonyl frequency is slightly lowered by conjugation with a double bond (type **2**), being in line with the usual lowering but opposite to what has been suggested.[2,3)]

Finally, the correctness of the above assignment of the lactam CO bands was further checked through two additional approaches. It may be seen from Table II that in the saturated lactams **5** and **6** the $1648\,cm^{-1}$ band observed in tetrahydrofuran (THF) solution moved down toward that at 1626—$1628\,cm^{-1}$ in $CHCl_3$ as the solvent was changed to dioxane, MeCN, and Me_2SO in that order. The 1627—$1629\,cm^{-1}$ bands (in THF) in the α,β-unsaturated lactams **15** and **17**—**19** showed similar solvent shifts, whereas the shifts in the 1671—$1672\,cm^{-1}$ bands (in THF) were smaller, supporting the assignments made in Tables I and II.

The other approach was based on deuterium labeling. We have already reported that the exocyclic methylene lactam **23** isomerizes to the α,β-unsaturated lactam **15** on treatment with KOH in aqueous EtOH at room temperature.[9)] In the light of the proposed isomerization

TABLE I. Infrared Group Frequencies of Lactams: Association Shift

Lactam	IR frequency (cm^{-1}) in $CHCl_3$[a]					
	Lactam alone		With Cl_2CHCO_2H[b]		$\Delta\nu_{C=C}$[c]	$\Delta\nu_{CO}$[d]
	C=C	Lactam CO	C=C	Lactam CO		
5	—	1626	—	1591	—	−35
				1580		−46
6	—	1628	—	1591	—	−37
				1581		−47
14	1661	1608	1649	1574	−12	−34
15	1666	1612	1657	1573	−9	−39
16	1662	1615[e]	1660	1585	−2	−30
		1592[f]				−7
17	1666	1615	1661	1580	−5	−35
18	1666	1615	1661	1580	−5	−35
19	1665	1614	1662	1592	−3	−22
20	—[12]	1639[e]	—[12]	1602	—[12]	−37
		1611[f]				−9
21	—[12]	1639	—[12]	1600	—[12]	−39

a) Measured at 0.2 M concentration with respect to a lactam. *b*) At 0.2 M concentration with respect to the acid. *c*) $\Delta\nu_{C=C}=\nu_{C=C}$ (with Cl_2CHCO_2H) $-\nu_{C=C}$ (lactam alone). *d*) $\Delta\nu_{CO}=\nu_{\mathrm{lactam\,CO}}$ (with Cl_2CHCO_2H) $-\nu_{\mathrm{lactam\,CO}}$ (lactam alone). *e*) A weak absorption probably arising from the unassociated species. *f*) A strong absorption probably arising from the species associated with the carboxy group.

TABLE II. Infrared Group Frequencies of Lactams: Solvent Shift

Group	Solvent[a]	IR frequency (cm^{-1}) in 0.2 M solution					
		Lactam					
		5	**6**	**15**	**17**	**18**	**19**
C=C	A	—	—	1671	1672	1672	1671[b]
	B	—	—	1670	1672	1672	1670[b]
	C	—	—	1668	1669	1669	1669[b]
	D	—	—	1664	1666	1667	1665
	E	—	—	1666	1666	1666	1665
$\Delta\nu_{C=C}$[c]	B	—	—	−1	0	0	−1
	C	—	—	−3	−3	−3	−2
	D	—	—	−7	−6	−5	−6
	E	—	—	−5	−6	−6	−6
Lactam CO	A	1648	1648	1627	1629	1628	1627[b]
	B	1646	1646	1626	1627	1627	1626[b]
	C	1636	1636	1620	1621	1620	1620[b]
	D	1632	1632	1616	1618	1618	1616
	E	1626	1628	1612	1615	1615	1614
$\Delta\nu_{CO}$[d]	B	−2	−2	−1	−2	−1	−1
	C	−12	−12	−7	−8	−8	−7
	D	−16	−16	−11	−11	−10	−11
	E	−22	−20	−15	−14	−13	−13

a) The letter A designates the solvent THF; B, dioxane; C, MeCN; D, Me_2SO; E, $CHCl_3$. *b*) Measured at 0.05 M concentration because of the poor solubility of **19**. *c*) $\Delta\nu_{C=C}=\nu_{C=C}-\nu_{C=C}$ (in A). *d*) $\Delta\nu_{CO}=\nu_{\mathrm{lactam\,CO}}-\nu_{\mathrm{lactam\,CO}}$ (in A).

Table III. Effects of Deuterium Labeling on Infrared Group Frequencies of the α,β-Unsaturated Lactam **15**

Lactam			IR frequency[a] (cm^{-1})			
No.	% deuterium		$C=C$	$\Delta\nu_{C=C}$[b]	$C=O$	$\Delta\nu_{CO}$[b]
	$C_{(3)}$	4-Me				
6	—	—	—	—	1628	—
15	0	0	1666	—	1612	—
24	78	42	1649[c]	−17	1608	−4

a) Measured in $CHCl_3$ at 0.2 M concentration. *b*) $\Delta\nu=\nu(\mathbf{24})-\nu(\mathbf{15})$. *c*) With a weak shoulder at 1666 cm^{-1}, which is probably due to the presence of a small amount (22%) of the species unlabeled at the 3-position.

mechanism involving an anion at the α-position,[9] **23** was treated with NaOD in D_2O–EtOD at room temperature overnight to obtain the labeled lactam **24**. The desired lactam **24** thus produced was found to contain 0.78D at the 3-position and 1.26D at the 4-Me group. It may be seen from Table III that deuterium substitution, as in **24**, lowers the 1666 cm^{-1} band of **15** much more than the 1612 cm^{-1} band. Since deuterium substitution can lower the $C=C$ frequency by 10—20 cm^{-1},[15] it is reasonable to assign the 1666 cm^{-1} band to the $C=C$ absorption of the α,β-unsaturated system of **15**, and the 1612 cm^{-1} band to the lactam CO absorption, a fall of 16 cm^{-1} from ν_{CO} of the saturated lactam **6** at 1628 cm^{-1}. Thus, the result of the deuterium-labeling approach is in agreement with the findings described above.

In conclusion, the present results have thus led to the generalization that in six-membered lactams the carbonyl frequency is slightly (10—20 cm^{-1}) lowered by conjugation with a double bond (type **2**), in line with the usual lowering. This is the opposite to what has been proposed in the literature.[2,3] It should also be emphasized that the above new diagnostic method for the identification of a lactam CO absorption by utilizing association with dichloroacetic acid (or a similar carboxylic acid) may be applicable to the α,β-unsaturated tertiary amide system, where differentiation between the $C=C$ and the CO absorptions[16,17] is still required.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Mass spectra (MS) were measured with a JEOL JMS-01SG mass spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with a JEOL JNM-FX-100 spectrometer at 24 °C using Me_4Si as an internal standard.

Materials——The known lactams selected for the IR spectroscopic study were taken from stocks which had been prepared according to published procedures: **5**;[18] **6**;[19] **12**;[20] **14**;[20b] **15**;[9] **16**;[20b] **17**;[9] **18**;[9] **19**;[9] **20**;[9] **21**.[9] The deuterated lactam **24** was obtained as described below.

1-Benzyl-5,6-dihydro-5-ethyl-4-([^{2}H]methyl)[3-^{2}H]-2(1*H*)-pyridinone (24)——The following procedure was based on that reported[9] for the preparation of the unlabeled lactam **15** from **23**. A solution of **23**[9] (106 mg, 0.46 mmol) in EtOD (99.0% isotopic purity) (5 ml) containing a 10% solution (0.2 ml) of NaOD (99% isotopic purity) in D_2O (99.8% isotopic purity) was kept at room temperature overnight. The reaction mixture was then concentrated *in vacuo* to leave an oil, which was dissolved in H_2O (5 ml). The aqueous solution was made acid (pH 1) with concentrated hydrochloric acid and extracted with benzene. The benzene extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a solid (84 mg), mp 36.5—41 °C. Recrystallization of the solid from hexane furnished **24** as colorless pillars, mp 43—44 °C; MS *m/e*: 233 [d_4 (3%)], 232 [d_3 (28%)], 231 [d_2 (41%)], 230 [d_1 (25%)], 229 [d_0 (3%)];[21] IR (Tabel III). The NMR spectrum of this sample in $CDCl_3$ was virtually identical with that of **15**,[9] apart from the decreases in the area of the olefinic proton and the 4-Me proton peaks at δ 5.72 and 1.88. On the basis of these decreases and the above mass spectral analysis, 78% D labeling at the 3-position and 42% D labeling at the 4-Me group were estimated for this sample of **24**.

Infrared Absorption Measurements——The solution IR spectra were recorded on a JASCO IRA-2 or a JASCO A-202 spectrophotometer using a 0.1-mm or 5-mm solution cell fitted with KBr windows. Wavelength calibration was done by using the standard absorptions of polystyrene. The solvents used were of "Spectro" grade, but $CHCl_3$ was further purified by passing it through an alumina column and by subsequent distillation. The carboxylic acids employed for the association shift experiments were of "Guaranteed Reagent" grade apart from cyclohexaneacetic acid [mp 29.5 °C (lit.$^{22)}$ mp 30 °C)], which was prepared and purified according to the literature procedures$^{23)}$ with slight modifications.

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