(500.0070 calcd for $C_{20}H_{30}{}^{35}Cl_2{}^{79}Br^{81}Br$), m/z 502.0057 (502.0050 calcd for $C_{20}H_{30}{}^{35}Cl_2{}^{81}Br_2$). Anal. Calcd for $C_{20}H_{30}Cl_2Br_2$: C, 47.93; H, 6.03. Found: C, 47.80; H, 6.03.

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Registry No. (R^*,R^*)-(±)-**1**, 112506-35-1; (R^*,S^*)-**1**, 112506-36-2; **2**, 112506-31-7; **3**, 112506-34-0; diisopropylacetylene, 927-99-1; 1,4-diacetoxy-2-butyne, 1573-17-7; hexaisopropylbenzene, 800-12-4; tetraisopropylcyclopentadienone, 99458-90-9; hexakis(acetoxymethyl)benzene, 41267-57-6; 1,2-diisopropyl-3,4,5,6-tetrakis(acetoxymethyl)benzene, 112506-32-8; 1,2-bis(hydroxymethyl)-3,4,5,6-tetraisopropylbenzene, 112506-33-9.

Studies on the Keto–Enol Equilibria of the Methyl 2-Oxocycloalkanoates $MeOOCCH(CH_2)_nCO$ (n = 3–6) by IR, ^{13}C NMR, and Mass Spectrometry

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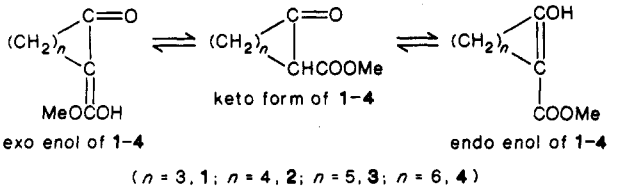
The alkyl esters of 2-oxocycloalkanecarboxylic acids are receiving considerable attention, not only from the viewpoints of synthesis[1–4] and reactivity[5–7] but also because of their spectroscopic behavior.[8] Several groups have examined the keto–enol equilibria of this class of β-keto esters. The extent of enolization has been found to depend upon solvent and temperature.

On the basis of bromine titrations and UV and ^1H NMR studies, Rhoads[9] concluded that amongst the ethyl esters of the C_5–C_{10} 2-oxocycloalkanecarboxylic acids, the even-membered systems exhibit 60–80% enol content while the odd-membered series exist as enols to a much lower extent, the lowest value of ~11% being observed for the cyclopentane derivative. On the other hand, Sterk[10] found that the C_5 keto ester (the terminology C_5, C_6, C_7, and C_8 in the current discussion and tables refer to the ring size of the cycloalkane derivatives) mentioned above exists exclusively in the keto form in DMSO or nitrobenzene in the temperature range of 20–120 °C, while the corresponding C_6 analogue showed an enol content of 80–50% in the same temperature range. However, Strohmeier and Hohne[11] concluded that the enol content of ethyl 2-oxocyclopentanecarboxylate varies from 27.6% to 13.5% over the 0–200 °C range. In addition to the apparent confusion concerning the C_5 cyclic β-keto ester, no gas-phase studies have been performed on the C_6–C_8 analogues and the methyl esters have not been examined at all. Furthermore, no ^{13}C NMR or mass spectral studies have been performed on either the methyl or the ethyl esters. Accordingly, we undertook an examination of the tautomeric equilibria of the methyl esters **1–4** by FTIR, ^{13}C NMR, and mass spectrometry to ascertain whether any differences exist in the keto:enol ratio for the pure liquid, solution, and gas phases (see Scheme I for the structures of the keto and enol forms).

Scheme I. Keto and Enol Forms of the Compounds Investigated



(n = 3, **1**; n = 4, **2**; n = 5, **3**; n = 6, **4**)

Results and Discussion

The ^{13}C NMR spectra of **1–4** in chloroform solution are given in Table I. In the solution phase, the keto:enol ratios were computed from peak integration corresponding to the alkoxy and carbonyl carbons of the carbomethoxy function representing enol and keto modifications. For the pure liquid form, the ester carbonyl peak absorbances in the IR at ~1750 (keto form) and ~1650 cm^{-1} (enol form) were used to calculate the keto:enol ratios. The low-resolution mass spectra of **1–4** did not yield any conclusive evidence concerning the extent of enolization, the major fragments observed being the $[M - CO]^+$, $[M - MeO^\bullet]^+$, and $[M - MeOH]^+$ ions. However, injection of the keto esters **1–4** into the inlet system saturated with D_2O would only exchange the enolic hydrogen with deuterium. Since the enolic form is expected to lose methanol through the participation of COOMe and the enolic hydrogen exclusively (in analogy with methyl salicylate[12]), the extent of MeOD loss must be proportional to this tautomeric form in the vapor phase. On the other hand, the extent of MeOH elimination from M^+ must be proportional to the keto form of the parent ions, since it is known[13] that methyl cyclohexane carboxylate loses MeOH by the involvement of the C_3 axial hydrogen. Thus, the $[M - MeOH]^+$:$[M - MeOD]^+$ ratio must represent the keto:enol ratio at equilibrium in the vapor phase. In addition to this approach, the metastable ion spectra of the molecular ions from **1–4** were examined to check whether any information could be obtained on the two tautomeric forms. In the MIKES spectra, if the loss of CO is attributed to the keto form exclusively, and elimination of H_2O from M^+ solely to the enol form, then the ratio of the intensities of these two ions must at least semiquantitatively represent the keto:enol ratio in the gas phase for the esters **1–4**. This argument seems to be valid, since the ratios obtained by this method were found to be close to those resulting from the deuterium-exchange experiments. The keto:enol ratios obtained by the three spectroscopic techniques described above are given in Table II.

The data in Table II indicates that methyl 2-oxocyclopentanecarboxylate exists solely in the keto form in all

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Table I. ^{13}C NMR Spectra of the Cyclic β-Keto Esters 1–4 (in $CDCl_3$, in ppm)

cyclic ester	keto form					enol form				
	CO	COOMe	CH_3O	CH	CH_2	COOMe	CH_3O	C=C—C=O	C=C—C=O	ring C
1 (C_5)	211.8	169.3	54.1	51.8	20.4, 26.9, 37.5					
2 (C_6)	205.4	169.8	56.7	51.5	23.0, 26.7, 29.6, 41.1	172.4	50.8	171.6	97.0	21.5, 22.0 (2), 28.6
3 (C_7)	208.5	170.6	58.4	51.7	24.0, 27.2, 27.7, 29.3, 42.7	173.0	51.1	179.3	101.1	24.3, 27.1, 27.5, 31.7, 35.0
4 (C_8)	211.3	169.9	56.2	51.7	24.2, 24.8, 24.9, 26.8, 28.8, 41.5	172.7	50.9	175.6	98.5	23.5, 25.7, 26.1, 28.3, 29.6, 31.8

Table II. Keto/Enol Ratios of the Cyclic β-Keto Esters 1–4

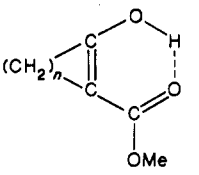
cyclic β-keto ester	keto/enol				
		solution phase[b]		gas phase[c]	
	ν_{COOMe}	C_{CH_3O}	C_{COOMe}	$\frac{[M - MeOH]^+}{[M - MeOD]^+}$ (d-exchange)	$\frac{[M - CO]^+}{[M - H_2O]^+}$ (MIKES)
1 (C_5)	100% keto	100% keto		100% keto	
2 (C_6)	5:6	1:2 3:4[d]	1:2 3:4[d]	2:1	2:1
3 (C_7)	6:1	6:1 10:1[d]	6:1 10:1[d]	3:2	3:2
4 (C_8)	5:6	3:4 2:1[d]	3:4 2:1[d]	5.5:1	6:1

[a] By FTIR. [b] By ^{13}C NMR. [c] By MS. [d] At 45 °C (upper row values are at 20 °C).

phases. On the other hand, the enol forms are more prevalent for **2** and **4** in the pure liquid and solution phase at 20 °C, but the keto forms predominate at 45 °C in solution and also at 100 °C in the gas phase in the mass spectrometer. The keto form amounts to ~85% in solution with the C_7 ester **3**, but surprisingly the enol form is considerably enhanced in the gas phase. The presence of two ester carbonyl carbons in the ^{13}C NMR corresponding to the keto and endo enol structures coupled with the absence of any signal corresponding to the conjugated ketonic carbonyl carbon rules out the exo–enol structure for the keto esters **2–4**.

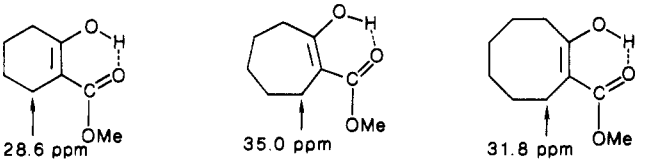
From the IR and ^{13}C NMR data, it can be presumed that the nature and strength of the intramolecular H bond in the enols from **2–4** is about the same. The assignments for the ester functon in the enol forms both in IR and ^{13}C NMR are close to the COOMe absorptions in methyl salicylate.[14] It is surprising that in the case of **1**, the keto form with the saturated cyclopentane is favored over the enol containing a cyclopentene ring. Cyclopentene is known to be less exothermic to hydrogenation than cyclohexene in view of the fact that the bond-eclipsing strain of cyclopentane is less favorable than the angular strain of cyclopentene.[15] Furthermore, the so-called "olefinic strain" as documented by McEwen and Schleyer[16] is negative for cyclopentene and cycloheptene while it is positive for cyclohexene, which should facilitate greater enolization with **1** and **3** compared to **2**. It therefore appears that the six-membered quasi-aromatic H-bonded system (a, Scheme II) introduces additional angular strain with the enol structure of **1** and **3**, which outweighs the enthalpy gain from H bonding. On the other hand, the entropic factor favors the keto form from **1** and **3** due to the ease of pseudorotation of these saturated systems. The energy barrier to pseudorotation is only 2.16 kcal/mol for cycloheptane and 4.0 kcal/mol for cyclopentane.[15] With

Scheme II. Quasi-Aromatic Structure of the Endo Enols



a
n = 4, 5, or 6 (2, 3, and 4)

Scheme III. ^{13}C NMR of the α-Carbons in the Enols 2–4



2, however, the half-chair conformation of cyclohexene with the syn disposition of the substituents at the double bond appears to be favorable thermodynamically in analogy with tetralin. The fusion strain for tetralin is reported to be minimal compared to other benzene ring-fused carbocycles.[17,18] On the other hand, with benzocycloheptane, the ring inversion energy is 14.6 kcal/mol and the enthalpy for pseudorotation is 11.1 kcal/mol.[19] Furthermore, Gunther and co-workers[20] observed that the benzylic carbons in benzocycloheptene absorb at 36.6 ppm, while the corresponding carbons in benzocyclohexene and benzocyclooctene absorb at 29.3 and 32.1 ppm, respectively. The α-carbons in the enols **2**, **3**, and **4** behave analogously (see Scheme III for values). These results are consistent with the fact that the enol of *3* is a highly strained system.

The energy barriers to pseudorotation in cyclooctane and cyclooctene are very close,[21] and *cis*-cyclooctene[15] and benzocyclooctene[22] have very low heat of hydrogenations. Thus, it is reasonable to assume that the keto and enol forms of **4** have very similar strain energies, which is reflected in their ratios in the pure liquid and solution phase (see Table V, supplementary material).

The extent of enolization is expected to diminish in the gas phase, as in the case of β-diketones and acyclic β-keto esters.[8] This is found to be true for **2** and **4**. However, **3** exhibits an enol content which is double that recorded in the solution phase. Since the solution spectra indicate that the enol of **3** exists only in the endo structure and its concentration decreases with increasing temperature, the

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proportion of this endo enol in the gas phase must by very low for **3**. Thus, it appears that the C_7 keto ester **3** exists in the exo enol form in the gas phase to a considerable extent. Previous solution chemistry results on the tautomeric equilibria of the enamines of cyclic β-keto esters and related systems indicate that the C_7 system with an exo double bond is more stable than a C_6 system which prefers an endo double bond.[23,24]

Although the saturated carbocyclic structures of the keto forms of **2**–**4** are favored in the gas phase (see Table V) the extent of methanol elimination from the molecular ions in this tautomeric form is much less for **4** compared to **2** and **3**. This is due to the fact that the energy barrier for the inversion of the equatorially oriented COOMe function to the axial orientation (which is necessary for MeOH loss) is about 7.7 kcal/mol in the case of the cyclooctane system.[15] The conformational free energies for the cyclohexane and cycloheptane systems are 1.2 and 0.9 kcal/mol, respectively.[15]

In conclusion, our study indicates that the tautomeric equilibria of the cyclic β-keto esters **1**–**4** are governed by enthalpy factors both in the solution and gas phases.

Experimental Section

The cyclic β-keto esters **1**–**4** were synthesized by treating the appropriate cyclic ketones with dimethyl carbonate in the presence of sodium hydride, according to the conditions previously described.[25]

The ^{13}C NMR spectra were recorded on a Varian XL-200 NMR spectrometer in deuterated chloroform solution at a concentration of 0.1 M. The solutions were equilibrated for 48 h at room temperature before recording the spectra.

The infrared spectra were recorded on a Nicolet 5-DX FTIR instrument as thin liquid films.

Metastable ion spectra of the molecular ions were examined by the MIKES technique[26] using a reverse-geometry VG Analytical ZAB-2FQ mass spectrometer at a 8-keV ion accelerating potential and a source temperature of 200 °C. Samples were introduced through a heated inlet system at 100 °C. The low-resolution spectra and the deuterium exchange experiments were also performed on the same instrument.

Supplementary Material Available: Tables containing the FTIR, normal mass spectra, and metastable ion spectra of compounds **1**–**4** and references on the keto–enol equilibria and the effect of solvent and temperature (4 pages). Ordering information is given on any current masthead page.

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An Efficient Synthesis of [8-^{13}C]Adenine

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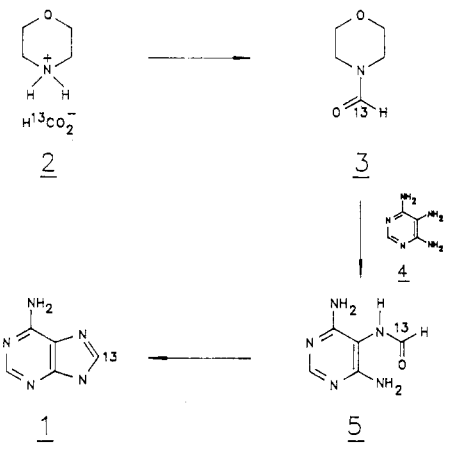
The increasing availability of sensitive, high field nuclear magnetic resonance spectrometers and the development of selective two-dimensional proton-heteronuclear pulse sequences make site-specific incorporation of magnetically active nuclei, especially ^{13}C and ^{15}N, an important technique for studying structure and dynamics of nucleic acids and proteins.[1,2] One can simultaneously take advantage of the high sensitivity inherent in ^1H signals, the chemical shift dispersion of directly attached ^{13}C or ^{15}N, and the suppression of signals for protons not bonded to labeled nuclei to provide important simplifications of complex spectra.[3-6]

Although uniformly labeled biopolymers can be obtained by growing microorganisms on minimal media supplemented with sources of labeled carbon or nitrogen, the use of recombinant plasmids[6] and auxotrophic strains[3-6] makes it possible to construct proteins or nucleic acids with labels positioned at specific locations within selected amino acids or nucleotides. Since incorporation experiments often consume substantial amounts of expensive labeled precursors, it is essential to have efficient syntheses of these materials from readily available sources. We now describe a synthesis of [8-^{13}C]adenine from sodium [^{13}C]formate based on formyl transfer from morpholine that uses equimolar quantities of formate and 4,5,6-triaminopyrimidine. The method is amenable to production of multigram quantities of material in good yield by a simple one-pot procedure.

The synthesis of [8-^{13}C]adenine (**1**) is outlined in Scheme I. Morpholinium [^{13}C]formate (**2**) was prepared from sodium [^{13}C]formate (99%) according to the procedures of Sharma and co-workers[7] and was then converted to the corresponding formamide **3** derivative. Upon heating a mixture of 4,5,6-triaminopyrimidine (**4**) and **3** in 1 N hydrochloric acid at 95 °C, **4** was slowly converted to **1**. When the progress of the reaction was monitored by HPLC, an intermediate, **5**, was observed. Compound **5** was isolated and determined to be the symmetric 5-formyl derivative of triaminopyrimidine (**4**) on the basis of mass spectral and NMR data. Under normal conditions **4** was converted to **1** without isolation of **5** in 61% overall yield based on sodium [^{13}C]formate.

Scheme I



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