were added aqueous 5 N sodium hydroxide (50 mL), $Co_2(CO)_8$ (1 mmol), and benzyltriethylammonium bromide (20 mmol). The reaction mixture was then heated to 65 °C under a slow stream of carbon monoxide (heating was assured by the IR device of the sun lamp). Irradiation was achieved with the sun lamp placed about 30 cm from the flask. After stirring overnight under these conditions, classical workup afforded pure phenylacetic acid (85% yield).

Acknowledgment. This work was supported by the Société Nationale Elf Aquitaine (Production) and by the Centre National de la Recherche Scientifique (France), both of which are gratefully acknowledged.

Registry No. $PhCH_2NEt_3^+Br^-$, 5197-95-5; $PhCH_2NEt_3^+Cl^-$, 56-37-1; $2\text{-}CH_3C_6H_4CH_2NEt_3^+Br^-$, 85267-31-8; $2\text{-}CH_3C_6H_4CH_2NEt_3^+Cl^-$, 85267-32-9; $4\text{-}CH_3C_6H_4CH_2NEt_3^+Br^-$, 85267-33-0; $3\text{-}CH_3C_6H_4CH_2NEt_3^+Cl^-$, 85267-34-1; $4\text{-}ClC_6H_4CH_2NEt_3^+Cl^-$, 5197-90-0; $4\text{-}BrC_6H_4CH_2NEt_3^+Br^-$, 85267-35-2; $2\text{-}BrC_6H_4CH_2NEt_3^+Br^-$, 85267-36-3; $4\text{-}CNC_6H_4CH_2NEt_3^+Br^-$, 85267-37-4; $CH_2{=}CHCH_2NEt_3^+Br^-$, 29443-23-0; (*E*)-$PhCH{=}CHCH_2NEt_3^+Cl^-$, 85267-38-5; $PhCH_2COOH$, 103-82-2; $Co_2(CO)_8$, 10210-68-1; $2\text{-}CH_3C_6H_4CH_2COOH$, 644-36-0; CO, 630-08-0; $4\text{-}CH_3C_6H_4CH_2COOH$, 622-47-9; $3\text{-}CH_3C_6H_4CH_2COOH$, 621-36-3; $4\text{-}HOOCC_6H_4CH_2COOH$, 501-89-3; $2\text{-}HOOCC_6H_4CH_2COOH$, 89-51-0; (*E*)-$CH_3CH{=}CHCOOH$, 107-93-7; (*E*)-$PhCH{=}CHCH_2COOH$, 1914-58-5.

A Comparison of the Regioselectivity in the Enol Acetate Formation and the Vilsmeier–Haack Reaction of Some Methyl-Substituted Cycloalkanones

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Substituted cycloalkanones are of great importance as starting materials and building blocks in organic synthesis. Unsymmetrically substituted cycloalkanones introduce an element of selectivity between two nonequivalent α-positions (α and α'), and isomeric mixtures may result when such compounds participate in a chemical reaction.

The Vilsmeier–Haack reaction of cycloalkanones[2,3] (also known as chloroformylation) leads to β-chlorovinyl aldehydes **1**, which are interesting intermediates that lend themselves to further useful elaboratories.[4,5]

Although a number of cyclic β-chlorovinyl aldehydes has been prepared,[2b,4] the problem of regiochemistry in the reaction between unsymmetrically substituted alicyclic ketones and the Vilsmeier–Haack reagent has not been much discussed.[6]

In the Vilsmeier–Haack reaction the enol form of the ketone is thought to be attacked by the electrophile, the chloro(dimethylamino)methyl cation, formed from dimethylformamide and phosphoroxychloride.[2] Ketones forming two different enols should give rize to two products, and we became interested in how a small substituent such as the methyl group in the β-position of cyclic ketones would affect the product distribution by steric interaction. Work along these lines has only rarely been reported.[7]

We now report our results on the regiochemistry of the chloroformylation of some methyl cycloalkanones using the dimethylformamide–$POCl_3$ reagent in trichloroethene.[3]

For comparison we determined the product distribution of the enol acetate formation under acidic conditions[8] for the same methylcycloalkanones.

Results and Discussion

The methyl-substituted cycloalkanones **2**, **7**, **12**, **17**, and **22** were treated with a slight excess of the DMF–$POCl_3$ (1.3:1.1) reagent in trichloroethene at 55–60 °C for 3 h[3] to give the chloroformylated derivatives shown in Table I, reaction A.

The enol acetates of the same ketones (except for **22**) were prepared by isopropenyl acetate/*p*-toluenesulfonic acid treatment at 60–90 °C overnight.[8] The results are shown in Table I, reaction B. When acetic anhydride was used instead of isopropenyl acetate in the case of **2**, the GC yield was much lower (10% instead of 90%) but the relative ratio of enol acetates remained the same. When acetic anhydride was used in the case of **7**, the ratio of the enol acetates was 66:34 as determined by ^1H NMR spectroscopy and 60:40 as determined by GC.[9] Performing the reactions in trichloroethene as solvent did not alter the results.

The product distributions of reactions A and B were determined by GC analysis and ^1H NMR spectroscopy on the crude products.

Since the Vilsmeier–Haack reaction produced dark unknown side products, the crude products were not suitable for a direct NMR analysis and had to be distilled. This operation did not change the relative ratios of β-chlorovinyl aldehydes as could be seen by addition of $Eu(fod)_3$ to the NMR samples. The formyl proton resonances separated completely, and integration gave the same ratio of isomers as the GC analyses. The structures of the products were determined by ^1H NMR spectroscopy and deserve some comments.

Information about the structures was obtained by examining the resonances of the allylic protons, which appeared as overlapping multiplets in the original spectra but were completely separated upon addition of $Eu(fod)_3$. In each isomeric couple the isomer with the methyl group distant from the aldehyde group has four allylic protons, while the other one has only three, except for **23** and **24**, which both have four. However, since **23** and **24** were formed in equal amount, the problem of differentiating between them did not arise in this context. Thus, by comparing the integrals and coupling patterns, structures **3**, **4**, **8**, **9**, **13**, **14**, and **18** were established.

The europium atom is assumed to coordinate to the oxygen atom of the aldehydes, which would shift the signals of the proximate methyl and allyl protons more downfield as compared to the distant ones. This was quite clear from the NMR spectra and provided additional structural evidence.

The structures of the enol acetates **5**, **6**, **15**, **16**, **20**, and **21** were determined by ^1H NMR analysis on the crude

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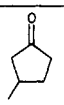
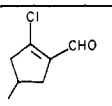
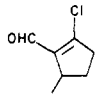
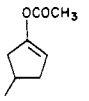
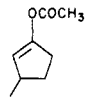
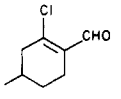
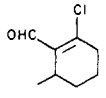
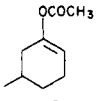
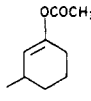
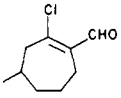
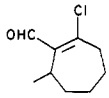
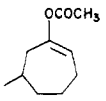
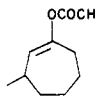
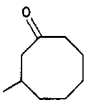
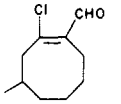
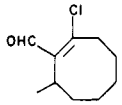
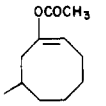
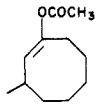
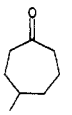
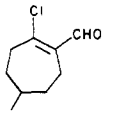
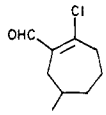
Table I. Yields and Ratios of Isomers of the β-Chlorovinyl Aldehydes and Enol Acetates

starting material	reactn[a]	products C	products D	ratio[b] C:D	total yield, %
 2	A	 3	 4	60:40	43[d]
	B	 5	 6	49:51	90[c]
 7	A	 8	 9	90:10	52[d]
	B	 10	 11	60:40	95[c]
 12	A	 13	 14	95:5	42[d]
	B	 15	 16	62:38	97[c]
 17	A	 18	 19	100:0	56[d]
	B	 20	 21	62:38	98[c]
 22	A	 23	 24	50:50	48[d]

[a] Reaction A: $POCl_3$–DMF in trichloroethene; reaction B: acetic anhydride or isopropenyl acetate and a catalytic amount of *p*-toluenesulfonic acid. [b] Determined by GC (See Experimental Section). [c] GC yields. [d] Isolated yields.

benzene-d_6 solutions at 200 MHz. The resonances of the vinylic protons were completely separated and could be appropriately analyzed in terms of integrals and coupling patterns (see Experimental Section).

A striking feature of Table I is that in the Vilsmeier–Haack reactions the regioselectivity increases with increasing ring size of the 3-methyl cycloalkanones. This was somewhat unexpected since the larger rings would be more flexible and one might have expected that the increased flexibility would more or less eliminate the influence of the 3-methyl groups.

Since the enols are involved as reactive species in both the Vilsmeier–Haack reaction[2] and the enol acetate formation,[8] we used the latter reaction as a means of estimating the enol ratio at equilibrium (vide infra). As can be seen in Table I the enol acetate ratios are relatively constant for all the ring sizes and do not change in equilibration experiments at higher temperatures (see Experimental Section). The slight preference for one of the enol acetates (**10**, **15**, and **20**) in three of the cases may be explained by the concept of allylic strain, which has been reviewed with special emphasis on six-membered alicyclic systems.[10] Since the enol acetates in the six-membered case can be expected to exist predominantly as half-chairs[11] with pseudoequatorial methyl groups,[12] their relative ratio could be explained as being due to the allylic strain between the vinylic hydrogen and the pseudoequatorial allylic methyl group in **11**. This would hold also for the seven- and eight-membered cases, as indicated by molecular models. In the five-membered case, however, the vinylic proton and the allylic methyl group in **6** ought

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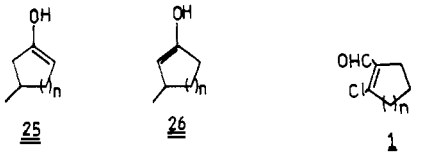
(11) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965, Chapter 2.
(12) It has been shown that the methyl group of 3-methylcyclohexene preferentially occupies a pseudoequatorial position, and it seems reasonable that the same should be true for enol **11** (Lessard, J.; Tan, P. V. M.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015).

to interfere less, since in this case the vinylic hydrogen and the allylic methyl group are essentially staggered. The enol acetate ratio (49:51) is in accordance with this.

We believe that the conditions used in the Vilsmeier–Haack reaction give rise to an equilibrated mixture of the enols **25** and **26**. The enols are then irreversibly attacked



25 **26** **1**

by the Vilsmeier–Haack reagent, which seems to be very sensitive toward the steric hindrance exerted by the methyl groups in the enols **26**. In the enol acetate formation, however, the isopropenyl acetate or acetic anhydride is attacking the remote oxygen atom under equilibrating conditions. This reaction could therefore be used as a probe for the enol distribution at equilibrium.

In conclusion we have shown that a relatively small group such as the methyl group in the 3-position of cycloalkanones has a strong steric influence on the attack of the Vilsmeier–Haack reagent on the enols in the six-, seven-, and eight-membered rings, while this is not so for the five-membered case. It is also obvious that these results may be used in synthetic schemes involving cycloalkanones as starting materials. Larger groups than methyl would probably increase the regioselectivity and also exert their steric (and electronic) effects even more distant from the carbonyl groups in cyclic ketones. These aspects are now being investigated in these laboratories.

Experimental Section

The ^1H NMR spectra were recorded with Jeol MH 100 and Varian XL 200 NMR spectrometers. Gas chromatograms were recorded with Perkin-Elmer 900 and Perkin-Elmer F 21 preparative gas chromatographs.

3-Methylcyclopentanone and 3-methylcyclohexanone were commercially available. 3-Methylcycloheptanone and 3-methylcyclooctanone were prepared from cyclohept-2-enone[13] and cyclooct-2-enone[13] and lithium dimethylcuprate, respectively.[14] 4-Methylcycloheptanone was prepared from 4-methylcyclohexanone by the method described in ref 15.

General Procedure for the Chloroformylation. The method described by Ziegenbein and Lang[3] was used throughout. Dimethylformamide (1.3 equiv) was dissolved in trichloroethene (1 mL/mol) and 1.1 equiv of $POCl_3$ was added dropwise at 5–10 °C under a nitrogen atmosphere. When the resulting mixture had reached ambient temperature, 1.0 equiv of the appropriate ketone dissolved in an equal amount of trichloroethylene as was used for the DMF above was added. The mixture was heated and kept at 55–60 °C for 3 h. After cooling, it was poured into 4 equiv of sodium acetate in ice water. The organic layer was collected, and the aqueous phase was extracted with three portions of methylene chloride. The combined organic phases were washed with water, dried ($MgSO_4$), and evaporated. Distillation afforded the following:

2-Chloro-1-formyl-4-methylcyclopentene (3) and 1-chloro-2-formyl-3-methylcyclopentene (4): 43% from 40 mmol of **2**, bp 66–8 °C (8 mm); IR (film) 1620 and 1680 cm^{-1} (α,β-unsat. aldehyde); NMR ($CDCl_3$) δ 1.00 (d, J = 7 Hz, CH_3 of **3**), 1.01 (d, CH_3 of **4**), 1.0–3.2 (m, aliphatic), 10.00 (br s, CHO). Anal. Calcd for C_7H_9ClO: C, 58.1; H, 6.27. Found: C, 58.3; H, 6.36.

2-Chloro-1-formyl-4-methylcyclohexene (8)[6a] **and 1-chloro-2-formyl-3-methylcyclohexene (9)**: 52% from 40 mmol of **7**, bp 90–1 °C (9 mm); IR (film) 1630 and 1685 cm^{-1} (α,β-unsat. aldehyde); NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, CH_3 of **8**), 1.03 (d, J = 7 Hz, CH_3 of **9**), 1.0–2.8 (m, aliphatic), 10.17 (s, CHO of **9**), 10.19 (s, CHO of **8**).

2-Chloro-1-formyl-4-methylcycloheptene (13) and 1-chloro-2-formyl-3-methylcycloheptene (14): 42% from 40 mmol of **12**, bp 97–101 °C (12 mm); IR (film) 1620 and 1685 cm^{-1} (α,β-unsat. aldehyde); NMR ($CDCl_3$) δ 0.99 (d, J = 7 Hz, CH_3 of **14**), 1.01 (d, J = 7 Hz, CH_3 of **13**), 1.0–3.0 (m, aliphatic), 10.11 (s, CHO of **13**), 10.12 (s, CHO of **14**). Anal. Calcd for $C_9H_{13}ClO$: C, 62.6; H, 7.59. Found: C, 62.5; H, 7.66.

2-Chloro-1-formyl-5-methylcycloheptene (23) and 1-chloro-2-formyl-4-methylcycloheptene (24): 48% from 40 mmol of **22**, bp 104–105 °C (9 mm); IR (film) 1620 and 1680 cm^{-1} (α,β-unsat. aldehyde); NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, CH_3), 1.0–3.2 (m, aliphatic), 10.11 (br s, CHO). Anal. Calcd for $C_9H_{13}ClO$: C, 62.6; H, 7.59. Found: C, 62.5; H, 7.49.

2-Chloro-1-formyl-4-methylcyclooctene (18) and 1-chloro-2-formyl-3-methylcyclooctene (19): 56% from 36 mmol of **17**, bp 112–115 °C (7 mm); IR (film) 1605 and 1665 cm^{-1} (α,β-unsat. aldehyde); NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, CH_3), 1.0–2.9 (m, aliphatic), 10.17 (dd, J = 0.3, 0.9 Hz, CHO). Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.3; H, 8.10. Found: C, 64.2; H, 8.07.

Preparation of the Enol Acetates. The enol acetates were prepared from 40 mmol of isopropenyl acetate, 30 mg of *p*-toluenesulfonic acid, and 20 mmol of the ketones **2**, **7**, **12**, and **17**, respectively, following the procedure described by House and Kramar[8] (reflux overnight, 60–90 °C). The yields and isomeric ratios are shown in Table I. The ratios were determined by measuring the integrals under the vinylic protons of each isomer in the ^1H NMR spectra (benzene-d_6) of the crude products. When acetic anhydride was used instead of isopropenyl acetate with **2**, the isomeric ratio remained the same, whereas the yield (GLC) was much lower, 10%. A pure sample of the acetoxycyclopentenes **5** and **6** was collected by preparative gas chromatography (NPG succinate on Chromosorb W(AW) 60/80 mesh). Pure samples of the acetoxycycloheptenes **15** and **16** and the acetoxycyclooctenes **20** and **21** were obtained by chromatography on a short column of neutral alumina with petroleum ether as eluent.

Equilibration Experiments. Samples of mixtures of **15** and **16** and **20** and **21** were heated with 10% *p*-toluenesulfonic acid in sealed tubes at 120 °C overnight.[8] Although considerable decomposition had occurred, the ratios of the undestroyed enol acetates remained the same.

2-Acetoxy-4-methylcyclopentene (5) and 1-acetoxy-3-methylcyclopentene (6): IR 1750 (C=O), 1660 cm^{-1} (C=C); NMR (benzene-d_6) δ 0.92, 0.93 (2 d, J = 7 Hz, $CHCH_3$), 1.0–2.9 (m, aliphatic), 1.70 (s, $COCH_3$), 5.45 (pent, J = 2 Hz, 1-H of **5**), 5.51 (q, J = 2 Hz, 2-H of **6**). Anal. Calcd for $C_8H_{12}O_2$: C, 68.5; H, 8.63. Found: C, 68.6; H, 8.64.

2-Acetoxy-4-methylcycloheptene (15) and 1-acetoxy-3-methylcycloheptene (16): IR 1750 (C=O), 1680 cm^{-1} (C=C); NMR (benzene-d_6) δ 0.81 (d, J = 7 Hz, $CHCH_3$ of **15**), 0.88 (d, J = 7 Hz, $CHCH_3$ of **16**), 1.0–2.5 (m, aliphatic), 1.71 (s, $COCH_3$), 5.23 (br d, J = 3.8 Hz, 2-H of **16**), 5.46 (br t, J = 6.6 Hz, 1-H of **15**). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.59. Found: C, 71.1; H, 9.50.

2-Acetoxy-4-methylcyclooctene (20) and 1-acetoxy-3-methylcyclooctene (21): IR 1750 (C=O), 1680 cm^{-1} (C=C); NMR (benzene-d_6) δ 0.80 (d, J = 7 Hz, $CHCH_3$ of **20**), 0.90 (d, J = 7 Hz, $CHCH_3$ of **21**), 1.0–2.5 (m, aliphatic), 1.72 (s, $COCH_3$), 4.96 (d, J = 8.7 Hz, 2-H of **21**), 5.27 (t, J = 8.6 Hz, 1-H of **20**). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 9.95. Found: C, 72.3; H, 9.90.

The acetoxycyclohexenes **10** and **11** are characterized in ref 9.

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Registry No. **2**, 591-24-2; **3**, 85355-88-0; **4**, 85355-89-1; **5**, 79449-32-4; **6**, 79449-31-3; **7**, 591-24-2; **8**, 38127-46-7; **9**, 85355-90-4; **10**, 22336-10-3; **11**, 15786-53-5; **12**, 933-17-5; **13**, 85355-91-5; **14**, 85355-92-6; **15**, 85355-93-7; **16**, 85355-94-8; **17**, 22460-44-2; **18**, 85355-97-1; **19**, 85355-98-2; **20**, 85355-95-9; **21**, 85355-96-0; **22**, 5452-36-8; **23**, 85355-99-3; **24**, 85356-00-9; $POCl_3$, 10025-87-3; dimethylformamide, 68-12-2; isopropenyl acetate, 108-24-7; acetic anhydride, 108-22-5.

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