180 (29.4), 164 (13.6), 136 (14.5), 93 (9.2); NMR 7.52, (s, 1 H), 7.19 (s, 1 H), 4.05, (s, 3 H), 4.04 (s, 3 H).

Anal. Calcd for $C_{10}H_8O_3S_2$: C, 49.99; H, 3.36; S, 26.68. Found: C, 49.96; H, 3.36; S, 26.68.

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Registry No. 3, 3199-08-4; 5, 112270-93-6; 6, 32819-84-4; 7, 20687-95-0; 8, 112270-94-7; 5,6-dimethoxyphthalide, 531-88-4.

Ring Size Dependent Orientation in Dehydration of 1-[(Ethoxycarbonyl)methyl]cycloalkanols

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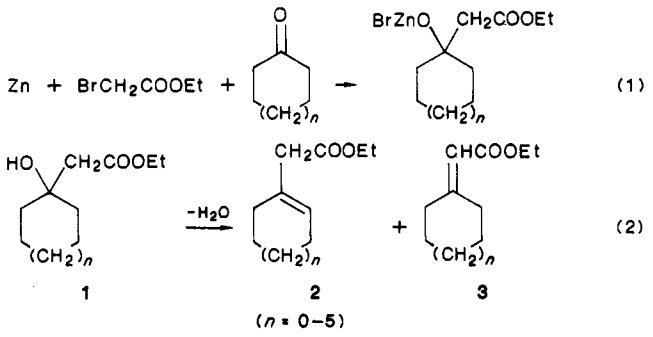
In connection with another research project, a series of ethyl cycloalken-1-ylacetates was needed for analytical standards. An attractive route to them appeared to be dehydration of the respective [(ethoxycarbonyl)methyl]-cycloalkanols,[1] which are readily accessible by the Reformatsky reaction,[2] eq 1.

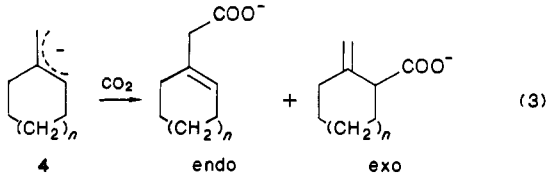


Information concerning the orientation of dehydration in this particular type of β-hydroxy acid ester appears to be very limited.[1] A special characteristic of this class of hydroxy esters is that the carbon bearing the nucleofuge (H_2O^+) is shared by a carbocyclic ring and, this being the case, one should reasonably expect that the conformational requirements of the ring should affect the orientation of dehydration of 1. If no special effects are operable, dehydration of 1 should give the statistical 2:1 mixture of endo and exo olefins, 2 and 3 respectively. On the other hand, the presence of the carboxy double bond should favor formation of the exo product, because the new double bond is conjugated with the already existing one.[1] Table I summarizes the results of acid-catalyzed dehydration of 1-[(ethoxycarbonyl)methyl]cycloalkanols, in which the ring size is varied from C5 to C10, including the special case of the 4-*tert*-butylcyclohexanol derivative. It can be seen that there is a strong dependence of the orientation of dehydration on the ring size. The relative yield of the endocyclic olefin increases rapidly (Figure 1) from C5 to C8 and less so from C8 to C10, where the reaction attains great selectivity. By extrapolating the linear segment from C8 to C10, we can predict that in the case of a C12 or larger ring dehydration will afford just one product, the endo one. Obviously, neither is the statistical mixture of the two possible products obtained, nor does the directive effect of the carboxy group double bond seem to operate.[1] The increasing relative yield of the endo product with increasing ring size may perhaps be associated with the respective decreasing conformational rigidity of the ring. However, this explanation fails to accommodate the result of the 4-*tert*-butylcyclohexanol derivative. In this case the relative yield of the endo product is 10% higher than in the less rigid unsubstituted cyclohexanol derivative. We have noted that a very similar distribution of olefinic products was obtained in the carbonation reaction of the allylic type organolithium reagents 4.[3] In fact, the relative yield of endo product from the dehydration reaction plots linearly against the respective yield of the carbonation reaction, eq 3, and the slope is nearly unity, Figure 2.

Table I. Relative Yields of Endo- and Exocyclic Olefinic Product from Dehydration of 1-[(Ethoxycarbonyl)methyl]cycloalkanols[a]

cycloalkanol	relative yield, % endo	exo
cyclopentanol	46.4	53.6
cyclohexanol	58.8	41.2
4-*tert*-butylcyclohexanol	68.3	31.7
cycloheptanol	77.4	22.6
cyclooctanol	90.7	9.3
cyclononanol	93.8	6.2
cyclodecanol	97.5	2.5

[a] By *p*-toluenesulfonic acid in refluxing benzene for 20 h. The product is a mixture of ethyl cycloalken-1-ylacetate and ethyl cycloalkylideneacetate.



Thus, two reactions, one electrophilic (eq 2) and the other nucleophilic (eq 3), with markedly different transition states lead to similar product distributions. It is felt that this points to the conclusion that in both reactions the factor that determines orientation in dehydration of 1 or site of attack in the carbanion 4 is the thermochemical stability of the product(s).

Experimental Section

Nuclear magnetic resonance spectra were recorded with a Varian FT80A NMR spectrometer, with $CDCl_3$ as solvent. Chemical shifts are reported in ppm to lower fields from TMS. The cycloalkanones that served as starting material were commercial products (Merck or Fluka), at least 98% pure, and were used as received. Activated zinc was prepared according to the literature.[4] The following experiments are exemplary.

1-[(Ethoxycarbonyl)methyl]-4-*tert*-butylcyclohexanol. A mixture of 1.54 g (10 mmol) of 4-*tert*-butylcyclohexanone, 3.5 mL (ca. 32 mmol) of ethyl bromoacetate, 6.0 g (ca. 92 mg-atom of activated zinc, 40 mL of anhydrous benzene, 20 mL of absolute ether, and a crystal of iodine was stirred at reflux temperature for 20 h. Excess zinc was separated by filtration, and the filtrate was hydrolyzed with 4 N sulfuric acid and ice. The organic layer

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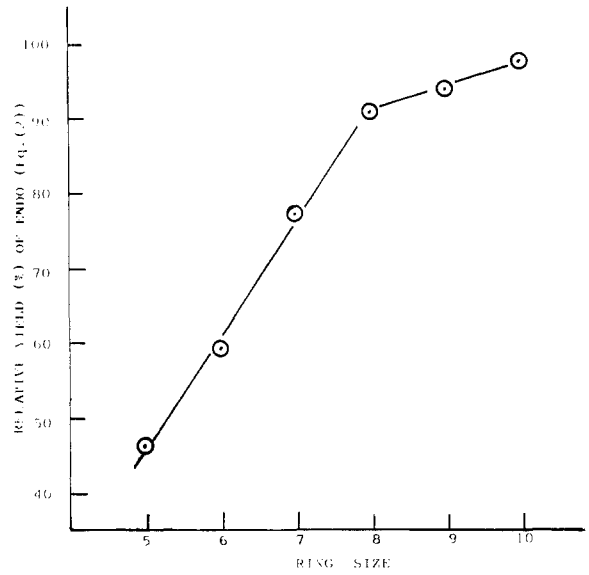

Figure 1. Relative yields of endo olefinic product from reaction 2 plotted against the number of carbon atoms in the carbocyclic ring (endo + exo = 100%).

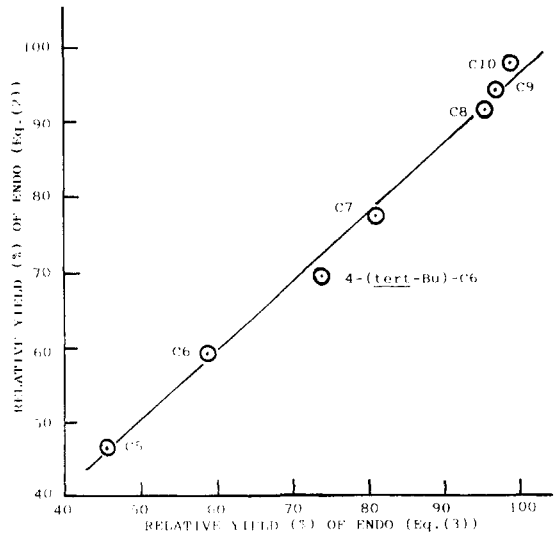

Figure 2. Relative yields of endo olefinic product from reaction 2 plotted against the respective yields of endo product from reaction 3.

was separated, the water layer was extracted with 2 × 70 mL of ether, and the ether extracts were combined with the organic layer. The latter mixture was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the solvent left 2.54 g (100%) of pure product. The mixture of the two epimeric alcohols was separated by gas chromatography, Apiezon L (14 ft × $^3/_8$ in.), and they were in the ratio equatorial/axial = 1.00/1.19. Axial alcohol: ^{1}H NMR δ 0.86 (s, 9 H), 1.28 (t, J = 7.14 Hz, 3 H), 1.75 (m, 9 H), 2.56 (s, 2 H), 3.75 (s, 1 H), 4.19 (q, J = 7.14 Hz, 2 H); ^{13}C NMR δ 70.87 (C(1)), 38.50 (C(2,6)), 24.42 (C(3,5)), 47.57 (C(4)), 40.82 (C(7)), 173.02 (C(8)), 60.65 (C(9)), 14.23 (C(10)), 32.29 (C(11)), 27.65 (C(12–14)). Equatorial alcohol: ^{1}H NMR 0.86 δ (s, 9 H), 1.27 (t, J = 7.13 Hz, 3 H), 1.51 (m, 9 H), 2.40 (s, 2 H), 3.17 (s, 1 H), 4.17 (q, J = 7.13 Hz, 2 H); ^{13}C NMR δ 69.19 (C(1)), 37.74 (C(2,6)), 22.27 (C(3,5)), 47.90 (C(4)), 47.03 (C(7)), 172.85 (C(8)), 60.49 (C(9)), 14.21 (C(10)), 32.12 (C(11)), 26.85 (C(12–14)).

1-[(Ethoxycarbonyl)methyl]cyclopentanol:[5] ^{1}H NMR δ 1.25 (t, J = 7.10 Hz, 3 H), 1.68 (m, 8 H), 2.57 (s, 2 H), 3.54 (br s, 1 H), 4.13 (q, J = 7.10 Hz, 2 H).

1-[(Ethoxycarbonyl)methyl]cyclohexanol:[5] ^{1}H NMR δ 1.24 (t, J = 7.20 Hz, 3 H), 1.50 (m, 10 H), 2.41 (s, 2 H), 3.37 (s, 1 H), 4.10 (q, J = 7.20 Hz).

1-[(Ethoxycarbonyl)methyl]cycloheptanol:[6] ^{1}H NMR δ 1.26 (t, J = 7.13 Hz, 3 H), 1.62 (br m, 12 H), 2.46 (q, J = 7.13 Hz, 2 H).

1-[(Ethoxycarbonyl)methyl]cyclooctanol:[7] ^{1}H NMR δ 1.26 (t, J = 7.13 Hz, 3 H), 1.55 (br m, 14 H), 2.45 (s, 2 H), 3.42 (s, 1 H), 4.16 (q, J = 7.13 Hz, 2 H).

1-[(Ethoxycarbonyl)methyl]cyclodecanol:[8] ^{1}H NMR δ 1.14 (t, J = 7.03 Hz, 3 H), 1.41 (br s, 18 H), 2.30 (s, 2 H), 3.37 (br s, 1 H), 4.03 (q, J = 7.03 Hz, 2 H).

Dehydration of 1-[(Ethoxycarbonyl)methyl]cyclopentanol. One gram of the title compound, 15 mL of dry benzene, and ca. 50 mg of *p*-toluenesulfonic acid were refluxed with stirring overnight. The mixture was diluted with 25 mL of toluene and then washed with 3 × 25 mL of distilled water, followed by 2 × 25 mL of saturated $NaHCO_3$ solution. Evaporation of the solvent, after drying over $MgSO_4$, afforded 0.75 g (83%) of a mixture of the endo and exo olefinic products. The two isomers were separated by preparative gas chromatography, Apiezon L (14 ft × $^3/_8$ in.). For the relative yields of the two olefinic products from the dehydration of this and other [(ethoxycarbonyl)methyl]-cycloalkanols, see Table I.

Ethyl cyclopentylideneacetate:[9] ^{1}H NMR δ 1.24 (t, J = 7.08 Hz, 3 H), 1.67 (m, 4 H), 2.40 (m, 2 H (syn to COO)), 2.75 (m, 2 H (anti to COO)), 4.08 (q, J = 7.08 Hz, 2 H), 5.73 (m, 1 H); ^{13}C NMR δ 166.75 (C(1/1)), 35.84, 32.52 (C(2,5/3)), 26.37, 25.44 (C-(3,4/3)), 111.71 (C(6/2)), 168.70 (C(7/1)).

Ethyl cyclohexylideneacetate:[10] ^{1}H NMR δ 1.27 (t, J = 7.00 Hz, 3 H), 1.62 (br s, 6 H), 2.10 (m, 2 H (syn to COO)), 2.78 (m, 2 H (anti to COO)), 4.10 (q, J = 7.00 Hz, 2 H), 5.55 (s, 1 H); ^{13}C NMR δ 163.43 (C(1)), 38.02, 29.91, 28.69, 27.86, 26.34 (C(2–6)), 113.12 (C(7)), 166.87 (C(8)), 59.45 (C(9)), 14.36 (C(10)).

Ethyl cycloheptylideneacetate: ^{1}H NMR δ 1.26 (t, J = 7.13 Hz, 3 H), 1.56 (s, 8 H), 2.34 (br m, 2 H (syn to COO)), 2.84 (br m, 2 H) (anti to COO)), 4.13 (q, J = 7.13 Hz, 2 H), 5.65 (m, 1 H); ^{13}C NMR δ 166.35 (C(1/1)), 39.01, 32.01, 29.79, 28.95, 28.02, 26.61 (C(2–7/3)), 115.1 (C(8/2)), 166.55 (C(9/1)), 59.27 (C(10/3)), 14.31 (C(11/4)).

Ethyl cyclooctylideneacetate: ^{1}H NMR δ 1.26 (t, J = 7.13 Hz, 3 H), 1.46 (m, 10 H), 2.31 (m, 2 H (syn to COO)), 2.76 (m, 2 H (anti to COO)), 4.13 (q, J = 7.13 Hz, 2 H), 5.70 (s, 1 H); ^{13}C NMR δ 166.35 (C(1)), 30.76 (C(2)), 27.83, 27.59, 26.57, 25.75, 25.49 (C(3–7)), 38.76 (C(8)), 115.76 (C(9)), 168.16 (C(10)), 59.30 (C(11)), 14.35 (C(12)).

Ethyl cyclodecylideneacetate: ^{1}H NMR δ 1.27 (t, J = 7.15 Hz, 3 H), 1.40 (m, 14 H), 2.38 (br m, 2 H (syn to COO)), 2.73 (m, 2 H (anti to COO), 4.15 (q, J = 7.15 Hz, 2 H), 5.70 (s, 1 H).

Ethyl (4-*tert*-butylcyclohexylidene)acetate: ^{1}H NMR δ 0.86 (s, 9 H), 1.25 (t, J = 7.12 Hz, 3 H), 1.95 (br m, 9 H), 4.12 (q, J = 7.12 Hz, 2 H), 5.53 (br s, 1 H); ^{13}C NMR δ 163.83 (C(1)), 37.89, 29.25, 29.64, 27.20 (C(2,3,5,6)), 47..0 (C(4)), 112.84 (C(7)), 167.21 (C(8)), 59.45 (C(9)), 14.33 (C(10)), 32.46 (C(11)), 27.57 (C(12–14)).

Registry No. **1** (n = 0), 3197-76-0; **1** (n = 1), 5326-50-1; **1** (n = 2), 95019-29-7; **1** (n = 3), 5095-70-5; **1** (n = 4), 112296-55-6; **1** (n = 5), 65426-84-8; **2** (n = 0), 57647-92-4; **2** (n = 1), 4709-59-5; **2** (n = 2), 92599-53-6; **2** (n = 3), 105540-55-4; **2** (n = 4), 112296-56-7; **2** (n = 5), 65462-07-9; **3** (n = 0), 1903-22-6; **3** (n = 1), 1552-92-7; **3** (n = 2), 1903-23-7; **3** (n = 3), 1903-24-8; **3** (n = 4), 112296-57-8; **3** (n = 5), 1903-25-9; ethyl bromoacetate, 105-36-2; 4-*tert*-butylcyclohexanone, 98-53-3; *cis*-1-[(ethoxycarbonyl)methyl]-4-*tert*-butylcyclohexanol, 25143-68-4; *trans*-1-[(ethoxycarbonyl)-methyl]-4-*tert*-butylcyclohexanol, 25143-70-8; 1-[(ethoxycarbonyl)methyl]-4-*tert*-butylcyclohexene, 54281-01-5; 1-[(ethoxycarbonyl)methylidene]-4-*tert*-butylcyclohexane, 13733-50-1.

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