The Kinetics of Epimerization of Dimethyl *cis*- and *trans*-1,2-Cycloalkanedicarboxylates[1]

DAVID S. SEIGLER AND JORDAN J. BLOOMFIELD*[2]

Department of Chemistry, The University of Oklahoma, Norman, Oklahoma 70369

Received May 8, 1972

The kinetics, position of equilibrium, and related thermodynamic parameters have been determined for epimerization of a series of 1,2-dimethyl esters of cycloalkanes varying from cyclopropane through cycloheptane and for the related 1-methylcyclohexane, 1-methylcyclohex-4-ene systems. The trans isomer is always favored, with K (trans/cis) varying from 99 (cyclopropane) to 1.6 (1-methylcyclohexene). Insertion of a Δ^4 double bond in cyclohexane increases the amount of cis isomer (K changes from 11.7 to 2.8), but decreases the trans isomer in the 1-methyl derivative (K changes from 1.8 to 1.6). All of the equilibrium effects are accounted for in terms of decreased configurational or steric strain in the more stable isomer. The rate effects ($3 < 6 < 4 \simeq 7 < 5$) are explained in terms of steric strain or its relief in a trigonal transition state and relative ease of removal of the enolizable proton.

The relations between conformation, steric factors, and chemical reactivity have long posed problems of theoretical interest. Substituents in axial positions are more crowded, which is a principal factor controlling their reactivity. Thus reactions which proceed with relief of strain are generally facilitated, while those with transition states involving increase in strain are hindered.[3] Examples of this effect include the rates of hydrolysis of esters of cyclohexanol, cyclohexanecarboxylic acid, and *cis*- and *trans*-4-*tert*-butylcyclohexyl acetates.[4] In cases where a common intermediate is found the difference in reactivity becomes the difference between the free energies of the two ground states.[5]

Studies of the effect of ring size on solvolysis reactions have been conducted by several workers.[6-8] The configuration of cyclohexanedicarboxylic, cycloheptanedicarboxylic, and cyclopentanedicarboxylic esters greatly affects the rate of both acid- and base-catalyzed hydrolysis.[9-11]

Systems containing a carbonyl group and at least one α proton undergo enolization with either acidic or basic catalysts, a process which is greatly influenced by both steric and polar effects. In general the enols that are stronger acids are formed more rapidly than those that are weaker.[12]

Ring size plays an important role in the rate of enolization of alicyclic ketones and cycloalkyl phenyl ketones. Schechter concluded from data on base-catalyzed enolization that the rates are related to the amount of s character in the carbon orbital directed toward the enolizable hydrogen.[13a] In a later paper, describing the results of deuterium exchange studies on phenyl cyclopropyl ketone, it was pointed out that s character alone cannot account for exchange or lack of it.[13b]

The carbonyls of ester groups are, in general, not as effective in enolization reactions as are those of ketones. However, reactions such as the Claisen-type condensation do involve anions which are at least partially stabilized by ester carbonyl participation in enolization.[14] Base-catalyzed equilibrations of cyclic esters yield an equilibrium mixture which reflects the relative stabilities of the cis and trans isomers.[15-19]

In order to examine the combined effects of ring size, conformation, steric factors, and chemical reactivity, we initiated a combined kinetic and equilibration study of several dimethyl 1,2-cycloalkanedicarboxylates. This approach was chosen for several reasons: (i) relative ease of synthesis; (ii) simple analytical method (glc); (iii) synthetic value of the reaction; (iv) convenient rates of epimerization; (v) a minimum of side reactions.

Experimental Section

All melting points and boiling points are uncorrected. Gas chromatographic analyses were conducted on a MicroTek GC-1600 instrument with a flame ionization detector. Separations were made on stainless steel columns 3.2 mm o.d. and 3.3 m long packed with 20% Carbowax 20M or 20% QF-1 on Anakrom ABS (80-100 mesh) and operated isothermally at temperatures between 115 and 140° with helium as the carrier gas. Known mixtures were prepared from gas chromatographically pure esters and analyzed. The gas chromatographically determined percentages corresponded within experimental error (±1%) to those of known analytical samples, and no correction factors for the relative responses were necessary. The relative percentages of epimers were calculated using the method of half peak heights. Samples of dimethyl 1,2-cyclohexanedicarboxylate which contained less than 12% of the cis ester were determined by the ratio of peak heights, which were compared with the relative heights of known samples.

The syntheses, appropriate physical constants, and gas-liquid chromatographic data for the substrates used in this study are summarized in Table I.

Preparation of Samples for Kinetic Determinations.—Solutions of the esters were prepared to be 0.25 M, by weighing the required amount of ester into a previously tared volumetric

---

(1) Abstracted from the Doctoral Dissertation of D. S. S., University of Oklahoma, 1967.

(2) Corporate Research Department, Monsanto Company, St. Louis, Missouri 63166.

(3) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(4) N. B. Chapman, R. E. Parker, and D. J. A. Smith, *J. Chem. Soc.*, 3634 (1960).

(5) S. W. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

(6) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).

(7) R. Heck and V. Prelog, *Helv. Chim. Acta*, **38**, 1541 (1955).

(8) H. C. Brown and M. Borkowski, *J. Amer. Chem. Soc.*, **74**, 1894 (1952).

(9) N. B. Chapman, J. Shorter, and K. J. Toyne, *J. Chem. Soc.*, 2543 (1961).

(10) C. K. Ingold and H. G. G. Mohrhenn, *ibid.*, **138**, 1482 (1935).

(11) H. A. Smith and T. Fort, Jr., *J. Amer. Chem. Soc.*, **78**, 4000 (1956).

(12) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 380.

(13) (a) H. Schechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Amer. Chem. Soc.*, **84**, 2905 (1962). (b) H. W. Amburn, K. C. Kauffmann, and H. Schechter, *ibid.*, **91**, 530 (1969). We are grateful to a referee for pointing out this important reference, which was not published when the thesis was written or when we first started this manuscript.

(14) J. Kenyon and D. P. Young, *J. Chem. Soc.*, **143**, 216 (1940).

(15) For an early synthetic example see W. Hückel and E. Goth, *Ber.*, **58**, 447 (1925).

(16) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

(17) J. W. McFarland, *J. Org. Chem.*, **30**, 3298 (1965).

(18) G. J. Fonken and S. Shiengthong, *J. Org. Chem.*, **28**, 3435 (1963).

(19) S. Shiengthong, M.S. Thesis (Chemistry), The University of Texas, Austin, 1963.

TABLE I

THE SYNTHESES AND SEPARATION OF DICARBOXYLIC ESTERS FOR THE EPIMERIZATION STUDIES

Registry no.	Dicarboxylate (dimethyl)	Yield, %[a]	n_D (°C)	Lit. n_D (°C)	Ref	Bp, °C (mm)	Lit. bp, °C (mm)	Ref	Retention time, min (temp,[g] °C)
826-34-6	*cis*-1,2-Cyclopropane-	97.5[b,i]	1.4434 (27)			59 (0.6)	200–202	*t*	4.0 (180)[e]
826-35-7	*trans*-1,2-Cyclopropane-	64.0[d,j]	1.4523 (26)	1.4472 (18)	*w*	61–63 (0.5)	219–220	*w*	2.4 (180)[e]
2607-03-6	*cis*-1,2-Cyclobutane-	88.5[b,k]	1.4453 (27)	1.4430 (18)	*q*	56 (0.5)	85 (3)	*k*	7.4 (160)[f]
7371-67-7	*trans*-1,2-Cyclobutane-	58.0[d,k]	1.4430 (25)			53 (0.4)	114 (20)	*q*	5.8 (160)[f]
4841-91-2	*cis*-1,2-Cyclopentane-	91.5[b,l]	1.4512 (27)	1.4528 (21)	*r*	68–70 (0.7)	116–117 (12)	*y*	11.3 (150)[f]
941-75-3	*trans*-1,2-Cyclopentane-	54.0[d,l,m]	1.4482 (25)	1.4491 (20)	*r*	59 (0.7)	119–120 (16)	*y*	8.3 (150)[f]
1687-29-2	*cis*-1,2-Cyclohexane-	64.0[c,d]	1.4578 (25)	1.4570 (25)	*s*	73–75 (1.3)	136.2 (18)	*z*	12.6 (170)[f]
3205-35-4	*trans*-1,2-Cyclohexane-	80.0[d,x]	1.4518 (25)	1.4539 (24)	*v*	58 (1.3) Mp 33.5–35	72–75 (0.5–0.8) Mp 33°	*v* *x*	11.6 (170)[f]
38312-27-5	*cis*-1,2-Cycloheptane-	82.0[b,p]	1.4651 (26)	1.4659 (20)	*i*	85 (0.4)	143–144 (15)	*i*	8.3 (150)[f]
38312-28-6	*trans*-1,2-Cycloheptane-	*b, p*	1.4546 (28)	1.4630 (20)	*i*	110–120 (3.5)	140–141 (10 mm)	*i*	7.0 (150)[f]
14679-33-5	*cis*-1-Methyl-1,2-cyclohexane-	90.0[b,o]	1.4588 (27)	1.4635 (20)	*n*	69–71 (0.5)	95 (2)	*n*	21.4 (130)[e]
38312-30-0	*trans*-Methyl-1,2-cyclohexane-	92.5[b,o]	1.4594 (25)	1.4636 (20)	*n*	54–55 (0.2)	95 (2)	*n*	23.7 (130)[e]
2305-26-2	*cis*-1,2-Cyclohex-4-ene-	94.0[b,c]	1.4708 (26)	1.4700 (25)	*s*	77 (0.7)	110–113 (3)	*u*	13.3 (165)[f]
17673-68-6	*trans*-1,2-Cyclohex-4-ene-	*h, o*							11.8 (165)[f]
14679-33-5	*cis*-1-Methyl-1,2-cyclohex-4-ene-	*h, n, o*							18.8 (115)[e]
38312-30-0	*trans*-1-Methyl-1,2-cyclohex-4-ene-	*h, n, o*							20.3 (115)[e]

[a] References are to syntheses of the acids or anhydrides. [b] Acids esterified by diazomethane. [c] Anhydride obtained commercially. [d] Acids esterified by Fischer method. [e] On QF-1 column. [f] On Carbowax 20M column. [g] See experimental conditions. [h] Ester prepared as described in ref *o;* all physical constants identical with those reported there. [i] J. Sicher, F. Sipos, and J. Jonas, *Collect. Czech. Chem. Commun.*, **26**, 262 (1961). [j] L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568 (1958). [k] E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *ibid.*, **64**, 2696 (1942). [l] S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **20**, 1178 (1955). [m] W. J. Bailey and W. R. Sorenson, *J. Amer. Chem. Soc.*, **76**, 5421 (1954). [n] I. N. Nazarov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 289 (1952); *Chem. Abstr.*, **47**, 5363c (1953). [o] J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967). [p] K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963). [q] W. A. Roth and G. J. Östling, *Chem. Ber.*, **46**, 309 (1913). [r] L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 2383 (1955). [s] A. C. Cope and E. C. Herrick, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 306. [t] H. von Pechman, *Chem. Ber.*, **27**, 1888 (1894). [u] F. V. Brutcher, Jr., and D. D. Rosenfeld, *J. Org. Chem.*, **29**, 3154 (1964). [v] L. Bauer and C. N. V. Nambury, *ibid.*, **26**, 1106 (1961). [w] G. J. Östling, *J. Chem. Soc.*, **101**, 457 (1912). [x] A. von Baeyer, *Justus Liebigs Ann. Chem.*, **258**, 145 (1890). [y] Reference 10. [z] Reference 11.

flask. The solution was made to volume with methanol. All methanol used in the kinetic studies was specially dried by reaction with magnesium followed by distillation, and was stored over molecular sieve (3A) under a drying tube.

Sodium methoxide solutions were prepared approximately 0.25 *M* by dissolving hexane-washed sodium metal in methanol, treated as above, in a dried volumetric flask. The solution was made to volume by addition of methanol. Each solution was standardized by titration of weighed portions of potassium acid phthalate dissolved in water, using phenolphthalein as indicator. These stock solutions were prepared several times in the course of the work to avoid the use of sodium methoxide samples contaminated with sodium hydroxide.

Aliquots of the standard ester and base solutions necessary to prepare the desired concentrations were pipetted into dried volumetric flasks. These flasks were filled to volume with methanol and a septum was placed in the neck of the flask. The solution was agitated and placed in a constant-temperature bath. In cases where the reaction was reasonably fast the ester solution and methanol were added and the mixture was allowed to reach temperature equilibrium. The base solution was then added and the solution quickly agitated.

Duplicate kinetic samples were run in each case and equilibrium was approached with both cis and trans samples at 50 ± 0.02°, 35 ± 0.05°, and 25 ± 0.05°.

Removal of Samples and Work-up for Kinetic Runs.—Samples (1 ml) were removed with a syringe and quenched with 0.1 *N* hydrochloric acid. Saturated sodium chloride solution (1 ml) and ether (1 ml) were added to the quenched sample in a 3-in. test tube. The tube was shaken and the phases were allowed to separate. The ethereal phase was removed and dried with anhydrous magnesium sulfate. Samples prepared in this manner were used for gas chromatography directly. Each sample was analyzed three times and the average of the three values of relative percentages was used in subsequent calculations. The relative percentages of samples of known ester composition worked up in the above manner showed no significant deviations from the known values.

The kinetics of a first-order reversible reaction of the type

$$A \underset{k_t}{\overset{k_c}{\rightleftarrows}} B$$

where $K = k_c/k_t$, may be expressed as[20]

$$\ln (AK - B) = \ln (A_0K - B_0) - (k_t + k_c)t \qquad (1)$$

---

(20) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p 96.

where A_0 and B_0 are the initial concentrations of the cis and trans esters, respectively. The rates of the base-catalyzed epimerization reactions of *cis*- and *trans*-1,2-cycloalkanedicarboxylates were observed to obey this equation and to have pseudo-first-order, reversible kinetics. The values of the equilibrium constants, K, were measured from analysis of the equilibrium concentrations. Dimethyl *cis*- and *trans*-1,2-cyclopropanedicarboxylate did not attain equilibrium in a reasonable time; so the values reported by Shiengthong were used.[19] The concentration of the esters, A and B, was calculated from the relative percentages a and b, which were measured by gas chromatography and the initial concentration, A_0, by the relations

$$A = aA_0(0.01)$$

$$B = bA_0(0.01)$$

Equation 1 is linear; therefore plots of ln $(AK - B) = Y_i$ *vs.* t (time) have a slope of $-(k_t + k_c)$ and a y intercept of ln $(A_0K - B_0)$.

The least squares equations for the slope, S, and the y intercept are as follows.

$$S = -(k_c + k_t) = \frac{N\Sigma t_iY_i - \Sigma t_i\Sigma Y_i}{N\Sigma t_i^2 - (\Sigma t_i)^2}$$

$$\ln (A_0K - B_0) = \frac{\Sigma t_i^2Y_i - \Sigma t_i\Sigma t_iY_i}{N\Sigma t_i^2 - (\Sigma t_i)^2}$$

Because the reliability of the data decreases as equilibrium is approached, the above equations were modified so that a weighted least squares treatment could be used to calculate the rate constant. The data were weighted in the following manner: the deviation of each value of Y [ln $(AK - B)$] was calculated from the least squares line by the equation.

$$DY = [K(DA) - DB]/AK - B$$

where DA and DB are the errors in A and B, respectively. The error in A is assumed to be the same for all values with a corresponding relative percentage greater than 97.0% and for B with a value less than 3.0%.

The weighting factors, w_i, were calculated by the following arbitrary relation.

$$w_i = 1.0/[DY]$$

The factors were then normalized so that $\Sigma w_i = 1.0$. With the inclusion of weighting factors the least squares equations become[21]

$$S = \frac{\Sigma w_it_iY_i - \Sigma w_it_i\Sigma w_iY_i}{\Sigma(w_it_i)^2 - (\Sigma w_it_i)^2}$$

and

$$\ln (A_0K - B_0) = \frac{\Sigma w_iY_i\Sigma(w_it_i)^2 - \Sigma w_it_iY_i\Sigma w_it_i}{\Sigma(w_it_i)^2 - (\Sigma w_it_i)^2}$$

The pseudo-first-order rate constants obtained were corrected for base concentration by the relation

$$k_c = k_c \text{ (pseudo)/base concentration}$$

The free energy of each reaction was calculated by the relation

$$\Delta G° = -RT \ln K$$

The activation parameters $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$ were calculated by standard relationships.[22]

The rate calculations described above were executed on an IBM 1410 computer. The program used calculated the least squares slope, the rate constants, and their associated errors, as well as a statistical analysis of the equilibrium constant values.[23] Values for the standard deviations and related error functions have been tabulated.[23]

Discussion

Our kinetic and equilibration study of the base-catalyzed epimerization of an homologous series of *cis*- and *trans*-1,2-cycloalkanedicarboxylates, from three to seven carbon rings, also included the 1-methylcyclohex-4-ene and cyclohex-4-ene systems. Dimethyl *cis*- and *trans*-1,2-cycloalkanedicarboxylates were equilibrated from both directions with sodium methoxide in methanol. By measurements of the relative percentages of each pair of esters at equilibrium, the equilibrium constant and the free energy value may be calculated for the epimerization reaction (Table III, columns 1 and 2). The effect of ring size on the equilibrium position in epimerization reactions of the preceding type has been studied by Fonken and Shiengthong.[18,19]

The rates of epimerization, k_c and k_t, were measured for the epimerizations of both cis and trans esters (Table II). As the trans runs involve small changes of concentration, in most cases the data derived from them is less accurate. Plots of log k_c *vs.* ring size for the homologous series of esters, Figure 1, resemble those for solvolysis reactions.[8,9,23]

Table II

Equilibrium and Kinetic Data for the Epimerization of Esters

Temp, °C	K (trans/cis)[a]	k_c, l. sec^{-1} mol^{-1} [b]	k_t, l. sec^{-1} mol^{-1} [b]
Dimethyl *cis*-1,2-Cyclopropanedicarboxylate			
25	99[c]	7.06×10^{-8}	7.11×10^{-10}
35	99[c]	2.42×10^{-7}	2.44×10^{-9}
50	99[c]	2.09×10^{-6}	2.12×10^{-8}
Dimethyl *cis*-1,2-Cyclobutanedicarboxylate			
25	8.40	1.32×10^{-4}	1.57×10^{-5}
35	7.67	3.00×10^{-4}	3.92×10^{-5}
50	8.58	1.71×10^{-3}	2.42×10^{-4}
Dimethyl *cis*-1,2-Cyclopentanedicarboxylate			
25	9.53	1.76×10^{-4}	1.84×10^{-5}
35	7.37	5.72×10^{-4}	7.78×10^{-5}
50	6.08	2.55×10^{-3}	4.17×10^{-4}
Dimethyl *cis*-1,2-Cyclohexanedicarboxylate			
25	13.5	6.72×10^{-6}	4.97×10^{-7}
35	9.71	2.36×10^{-5}	2.43×10^{-6}
50	11.7	1.41×10^{-4}	1.20×10^{-5}
Dimethyl *cis*-1,2-Cycloheptanedicarboxylate			
25	3.74	6.06×10^{-5}	1.61×10^{-5}
35	4.51	2.02×10^{-4}	4.78×10^{-5}
50	3.90	9.11×10^{-4}	2.33×10^{-5}
Dimethyl *cis*-1-Methyl-1,2-cyclohexanedicarboxylate			
25	1.84	4.42×10^{-7}	2.41×10^{-7}
35	1.84	1.26×10^{-6}	6.83×10^{-7}
50	1.75	7.00×10^{-6}	3.81×10^{-6}
Dimethyl *cis*-1,2-Cyclohex-4-enedicarboxylate			
25	2.68	2.42×10^{-7}	9.06×10^{-6}
35	3.19	5.50×10^{-5}	1.72×10^{-5}
50	2.82	2.47×10^{-4}	8.78×10^{-5}
Dimethyl *cis*-1-Methyl-1,2-cyclohex-4-enedicarboxylate			
25	1.60	1.35×10^{-6}	8.44×10^{-7}
35	1.60	4.33×10^{-6}	2.71×10^{-6}
50	1.70	1.76×10^{-5}	1.03×10^{-5}

[a] Equilibrium constants, unless otherwise noted, are obtained by measuring percentages of equilibrated mixtures. [b] The second-order rate constants k_c and k_t are all taken from runs with a base concentration of 0.05 M. [c] Values taken from ref 18 and 19.

The effect of ring size in reactions of various types has been the subject of many studies. In small rings (3, 4) the principal rate-determining factor is angular strain. In normal rings (5, 6, 7) bond opposition strains play a large role but angular strain is still

---

(21) H. D. Young, "Statistical Treatment of Experimental Data," McGraw-Hill, New York, N. Y., 1962.

(22) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961.

(23) D. S. Seigler, Ph.D. Dissertation (Chemistry), The University of Oklahoma, Norman, Okla., 1967.

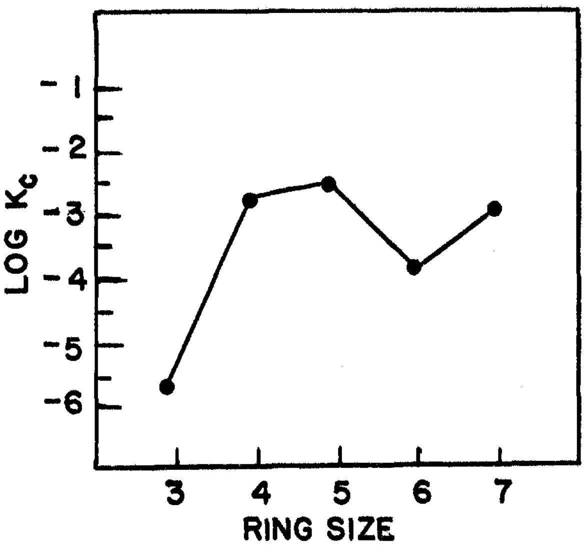

Figure 1.—Log K_c *vs.* ring size for epimerization of *cis*-1,2-cycloalkanedicarboxylates at 50°.

important. In seven-membered rings transannular effects become a factor to be considered.

The epimerization must involve a change from one tetrahedral configuration to another *via* trigonal bonding. Solvolyses of cycloalkyl tosylates[8] and halides[9] show similar trends of reactivity, and similar effects of ring size are observed.

The equilibrium percentages for the different esters are rather similar, except for the cyclopropane case, where the trans epimer is overwhelmingly preferred. This is not unexpected, for in the cis epimer the carbomethoxy groups are eclipsed and this strain is relieved in the trans epimer. The rate of epimerization is slow because the reaction involves change from an already distorted tetrahedral angle (60°) to a trigonal angle (120°) which introduces even more strain into the ring (*cf.* ref 13b).

The position of equilibrium for the cyclobutane system is similar to those of the cyclopentane and cyclohexane systems. This provides evidence for the nonplanarity of the cyclobutane ring. If this ring were planar the *cis*-carbomethoxy groups would be eclipsed as in the *cis*-cyclopropane ester and a substantially different position of equilibrium would be observed. The epimerization of planar cyclobutyl esters should be rather slow by the same assumptions. However, the cyclobutyl system is nonplanar,[24] and the rates more closely resemble those observed for the cyclopentane system.

The cyclopentane esters also exist in a nonplanar form, allowing a partial relief of interactions in the cis epimer. This is again reflected in the equilibrium constant for the epimerization reaction.

Formation of a trigonal carbon atom is facilitated by the relief of bond eclipsing. This relief of bond opposition strains is easily enough to offset the change from a tetrahedral to a trigonal configuration.

Similar considerations apply to the cycloheptyl system, which contains many bond oppositions, and this epimerization is also observed to be rapid. The cis diester in this system is stabilized relative to that of the corresponding cyclohexane system (see below) because of a degree of flexibility in the ring which allows the substituents to decrease 1,3-diaxial and gauche butane interactions. The trans ester is affected less by this flexibility, although some gauche butane interactions are undoubtedly relieved.

In cyclohexane systems a much greater amount of puckering exists than in cyclopentane and other factors, such as 1,3-axial interactions, become important. The position of equilibrium for 1,2-cyclohexanedicarboxylates indicates a destabilization of the cis epimer with respect to the trans. The situation is made more complex by the possibility of conformers of each of the epimeric esters. Dimethyl *cis*-1,2-cyclohexanedicarboxylate must contain one equatorial and one axial carbomethoxy group. The corresponding trans ester, by analogy with 1,2-dimethylcyclohexane, should largely exist in the diequatorial conformation.[20]

The rate is slower in cyclohexane systems because the ground state has no angle strains and no bond opposition strains. Any attempt to change the hybridization of a ring atom is resisted, as it increases eclipsings (and introduces some angular strain, although in this case angle strain is probably a minor factor).

Comparison of 1,2-disubstituted cyclohexanes with 1,2-disubstituted cyclohex-4-ene shows that an axial position for a substituent is relatively more stable in the olefin because of loss of a 1,3 interaction[25] Therefore the cis ester should be more stable in cyclohexene than in cyclohexane. This stabilization is observed, with a decrease in the trans/cis ratio from 11.7 to 2.8.

The rate of epimerization of dimethyl *cis*-1,2-cyclohex-4-enedicarboxylate is 1.8 times faster than that of the corresponding saturated compound. The approach to the hydrogen atom is easier, as there are less steric effects, *i.e.*, less crowding in the unsaturated systems.

The introduction of a methyl group into the 1 position of 1,2-cyclohexanedicarboxylates produces an appreciable effect on the relative stabilities of the two epimers. In dimethyl *trans*-1-methyl-1,2-cyclohexanedicarboxylate the diequatorial conformation (carbomethoxy groups) should again be preferred. The cis ester may exist in two conformations. The carbomethoxy groups are axial and equatorial and the methyl group may be either axial or equatorial. Examination of all possible 1,3 and gauche butane interactions indicates that the preferred conformation has the methyl group in an equatorial position. Similar conformational analysis reveals that the cis and trans isomers will differ only slightly. There is a difference of two 1,3 interactions and two gauche butane interactions with the methyl group in the trans isomer, whereas in the cis isomer these interactions are with a carbomethoxy group. As the interactions of a carbomethoxy group and a methyl group are similar,[16] the cis isomer should be stabilized relative to the trans in this system (when compared to cyclohexanedicarboxylate). Again the prediction is borne out by the experimental results, as K is the lowest for any of the saturated systems studied.

If a double bond is introduced into the system at the 4 position the trans-diequatorial conformer becomes

---

[24] See J. J. Bloomfield and R. Fuchs, *J. Chem. Soc., B*, 363 (1970), and references cited therein.

[25] *Cf.* H. Peters, R. A. Archer, and H. S. Moser, *J. Org. Chem.*, **32**, 1382 (1967).

TABLE III

FREE ENERGY AND ACTIVATION PARAMETERS FOR THE EPIMERIZATION OF DIMETHYL 1,2-CYCLOALKANEDICARBOXYLATES AT 50°

Ester	K (trans/cis)[a]	$\Delta G°$, kcal/mol[a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$ eu
Cyclopropane	99 (99)[b]	−2.62 (−3.1)[b]	20.2 (±0.3)	27.1 (±0.1)	−23 (±0.1)
Cyclobutane	8.58 (8.1)[b]	−1.27 (−1.5)[b]	81.7	22.7	−10
Cyclopentane	6.08 (8.8)[b]	−1.06 (−1.5)[b]	19.4	22.5	−10
Cyclohexane	11.7 (13.7)[b]	−1.45 (1.7)[b]	21.7	28.6	−23
Cycloheptane	3.99	−0.82	19.8	23.1	−11
1-Methylcyclohexane	1.84	−0.36	20.2	26.0	−20
Cyclohex-4-ene	2.82	−0.61	19.3	23.7	−15
1-Methylcyclohex-4-ene	1.60	−0.30	23.7	25.4	−6

[a] This work, measured at 50°. [b] Fonken and Shiengthong (ref 18, 19), measured at 67°.

stabilized with respect to that of the saturated 1-methyl ester by a factor of one methyl/ring gauche butane interaction and one 1,3-carbomethoxy–hydrogen interaction. Since the interactions of carbomethoxy groups are only slightly different from those of methyl groups, the effect should be small. In fact, a very slight decrease in the trans/cis ratio is observed to produce the lowest ratio found in this study.

The rates of the 1-methylcyclohexyl and 1-methylcyclohexenyl dicarboxylates are more difficult to explain. Even assuming that a statistical factor (only one acidic proton) will decrease the rate of epimerization by one-half, the 1-methyl ester is still slower by a factor of ten than the unsubstituted ester. This effect may be partially related to the added steric effects of the methyl group.

Variations in the equilibrium constants were observed for changes in temperature and concentration. The equilibrium is generally shifted toward the less stable cis isomer by an increase in temperature (Table II). Changes produced by concentration were also observed. This effect increased the cis isomer in some systems and reduced it in others.

The mechanism of the epimerization reaction has not been examined closely. The removal of an acidic proton may be the rate-controlling step and involves enolization. A similar mechanism has been proposed by Shechter for the base-catalyzed enolization of cycloalkanones and phenyl cycloalkyl ketones.[13] The transition states are fairly close to the enolate ion in character, and it is of interest to note that the energies of activation of this reaction are all nearly the same (±2 kcal). In the epimerization reaction of 1,2-cycloalkanedicarboxylates a similar situation is observed. The activation parameters are given in Table III. Large negative entropies of activation are observed in both Shechter's and the present study.

A negative entropy of activation is predicted for a reaction in which two substrates are brought together in the rate-controlling step. However, the rather large differences between some of the esters indicate a decided increase in ordering necessary in the transition state for certain esters.

The combination of a constant enthalpy of activation (or energy of activation) reflects a balance of the entropy and free energy factors, which may be expressed as

$$\text{constant} = \Delta H^{\ddagger} = \Delta\,(\Delta G^{\ddagger}) + T\Delta\,(\Delta S^{\ddagger})$$

Based on these assumptions, the rates will be chiefly determined by the entropy factor. A plot of $\Delta S^{\ddagger}$ *vs.* ring size, (Figure 2) is quite similar to the plot of log k_c *vs.* ring size (*cf.* Figure 1).

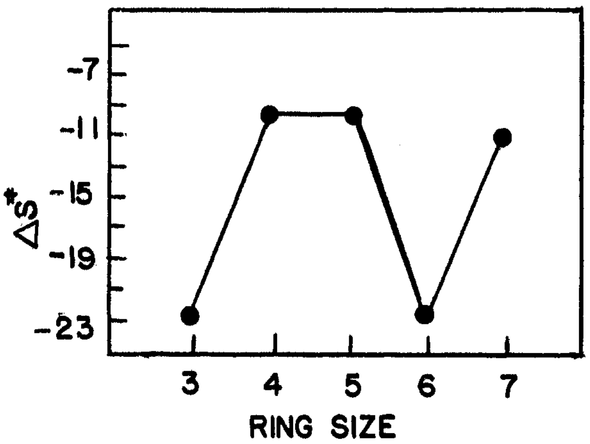

Figure 2.—$\Delta S^{\ddagger}$ *vs.* ring size for epimerization of 1,2-cycloalkanedicarboxylates at 50°.