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STEREOCHEMICAL CONTROL OF MICHEAL CONDENSATION BY MACROCYCLIC POLYETHERS

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Many researchers[1-3] have reported that the reaction of α-halo esters with α,β-unsaturated esters in the presence of base gives cyclopropane derivatives. The general feature of the condensation is that the thermodynamically less stable cis-isomer in solvents of low dielectric constant predominates in the cyclopropane products. Attempts have been made to elucidate the course of the cis and/or trans formation of this reaction and a tentative interpretation has been proposed by McCoy[1] and Inoue et al.[2]. Inoue et al. have reported that the stereochemical results were explicable in terms of electrostatic stabilization and non-bonded interaction in the postulated transition state conformations stabilized by the orbital overlap in the rate- and, therefore, stereochemistry-determining cyclization. Furthermore they pointed out that the metal-chelation of the conformation as shown in eq. 1 plays an important role in determining the cis-isomer formation process. It is well known that separation of ion-pairs and thus anionic activation can be obtained through the selective complexation of cations by organic ligands. This is dramatically shown by the enhancement in reaction rates obtained by addition of crown ethers[4] and of cryptands to a homogeneous reaction medium. It might be expected that in the presence of these macrocyclic polyethers the Micheal condensation in solvents having low dielectric constants results in predominant formation of the trans-isomer of the cyclization product. Therefore, we have now investigated the effect of 18-crown-6 (1) and [2.2.2]cryptand (2) on the cis/trans ratios of cyclopropane products in the reaction of α-chloro esters (3) with α,β-unsaturated esters (4) in various solvents.

As a typical example, the reaction of methyl α-chloroacetate (3a) with methyl acrylate (4a) will be mentioned. A mixture of methyl α-chloroacetate (8 mmol), methyl acrylate (10 mmol), NaH (10 mmol) as a dispersion in oil, 18-crown-6 (0.8 mmol), and 10 ml of THF was stirred at 22°C for about 10 h. After the usual work-up, the reaction mixture was analysed by GLC.

The yield of the cyclopropane products and percentages of the trans-isomers are listed in Table 1. As the data show, the reaction of α-chloro esters (3) with α,β-unsaturated esters (4) in benzene, THF or dichloromethane which has a relatively low dielectric constant yields the cis-isomer, whereas in DMF and acetonitrile the trans-isomer formation occurs to a substantial extent. The addition of macrocyclic polyethers to the reaction mixture did not affect the product ratio in DMSO, but caused a remarkable increase in the trans-isomer formation for the reactions in other solvents used. When 18-crown-6 was absent, these results (runs 1,4,8 and 12) are nearly consistent with previous findings in similar reactions of this type by other workers[1-3]. They suggest that the cis/trans ratios of the resulting dimethyl ester increase with decreasing solvent polarity, i.e. the trans-isomer predominates in a more polar medium DMF, whereas the cis-isomer in a less polar medium benzene.

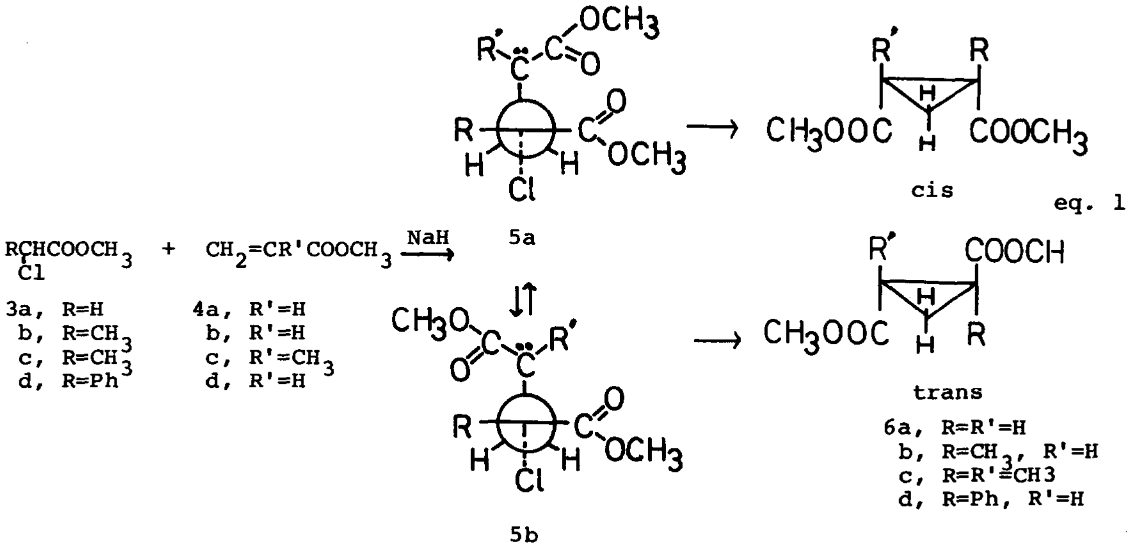
However, from our more detailed examination, it is obvious that the cis/trans ratio of cyclopropane products is dependent upon both the polarity and the solvating ability of solvents. For example, in spite of the fact that dielectric constants of DMF and acetonitrile are nearly the same, the reaction of 3 with in DMF gives the trans-isomer alone, whereas in acetonitrile under otherwise the same conditions gave trans-isomer as a main product. Because DMF is superior to acetonitrile in the solvation of sodium cation[5], the result may be interpreted on the basis of the difference in the solvating abilities of these two solvents. Although Inoue et al.[2] have explained the preference of cis-isomer formation in less polar solvents from the orbital overlap as a main reason, the present authors are tempted to consider that the chelation of sodium cation with the transition intermediate is the most important factor on the cis-isomer formation. If the intermediate carbanion exists as the free, 5b due to repulsion of the two carbonyl groups of the intermediate would be more favored than 5a. However, in the nonpolar solvents the tight chelation of sodium cation with the intermediate carbanion stabilizes 5a which leads to the cis-isomer formation as shown eq 1.

As the data (runs 2,5,9 and 13) in Table 1 show, the addition of catalytic amount of 18-crown-6 to the reaction mixture affect the cis/trans ratios of the products to remarkable extents in the solvents except DMF. The most pronounced effect was found in the solvents of low dielectric constants benzene, THF and dichloromethane. In the absence of 18-crown-6 the cis-isomer formation is the overwhelming process. On the other hand, when the crown ether is present it is the trans-isomer formation in the corresponding reactions. These results are explicable as follows. In an aprotic solvent having a low dielectric constant, the intermediate carbanion (5a)[2] is likely to exist as ion aggregates. However, when 18-crown-6 is added to the reaction mixture, sodium cation forms a complex with the crown ether and the intermediate carbanion exists as a free or loose ion pair[4]. Therefore the intermediate free carbanion 5b would be sterically more favored than 5a. In support of this view of the chelate stabilization, the reaction in DMF, in which the dissociation of the intermediate takes place, fails to show any effect of the crown ether on the product ratio. Further support for favoring the interpretation is given by the effect of [2.2.2]cryptand upon the cis/trans ratios of cyclization products. From these results (runs 3,7,11 and 15),

Table 1. Yield and Percentage of trans-isomer

Run	Product	Solvent	benzene	THF	CH_2Cl_2	DMF	CH_3CN
		Cat \ ε	2.3(20°)	7.6(25°)	9.1(20)	36.7(25°)	37.5(20°)
1	6a	—	2(32)[a]	27(34)	2(30)	58(ca.100)	17(53)
2	"	1	21(67)	25(66)	68(88)	14(ca.100)	72(68)
3	"	2	25(80)	24(81)	15(71)	27(ca.100)	50(74)
4	6b	—	1(9)	74(12)	1(15)	76(92)	65(70)
5	"	1	11(66)	63(89)	97(87)	74(92)	84(90)
6	"	1[b]		65(14)			
7	"	2	66(96)	26(96)	45(96)	32(95)	60(96)
8	6c	—	24(3)	93(6)	7(7)	91(67)	52(38)
9	"	1	80(47)	60(56)	84(65)	84(69)	54(70)
10	"	1[b]		59(11)			
11	"	2	58(60)	26(73)	23(70)	25(71)	38(80)
12	6d	—	4(3)	35(7)	3(16)	92(85)	19(55)
13	"	1	20(38)	52(54)	100(58)	68(86)	100(65)
14	"	1[b]		44(9)			
15	"	2	26(47)	48(53)	78(63)	100(85)	69(89)

a) The first number is the yield, based on α-chloroester of mixed isomeric esters. The number in parentheses is the percentage of trans isomer in the ester mixture, the remainder being the cis-isomer; these results were obtained by GLC. Gas chromatographic analysis was performed on 1m x 3mm stainless steal column of 10% Polyester on Chromosorb W at ambident temperature. Neither conversion was optimized so the values reported are minimum yield. b) Eight-fold amount of sodium thiocyanate over sodium hydride was dissolved in the reaction mixture prior to the reaction.



$\underset{\text{Cl}}{\text{RCHCOOCH}_3}$ + CH_2=CR'COOCH$_3$ $\xrightarrow{\text{NaH}}$

eq. 1

5a

5b

3a, R=H
b, $R=CH_3$
c, $R=CH_3$
d, R=Ph

4a, R'=H
b, R'=H
c, $R'=CH_3$
d, R'=H

6a, R=R'=H
b, $R=CH_3$, R'=H
c, R=R'=CH3
d, R=Ph, R'=H

it is obvious that [2.2.2]cryptand shows a remarkable increase in the trans-isomer in all the solvents examined. It is known[6)] that [2.2.2]cryptand is able to surround the cation completely and is a powerful anionic activator. Therefore the differences in catalytic efficiency of 18-crown-6 and [2.2.2]cryptand on the cis/trans ratios of cyclization products can be pictured as arising from the differences in the equilibrium between the aggregated and the macrocyclic polyether separated ion pair species. Thus it is reasonable to assume that the degree of the separation of the intermediate carbanion ion pair plays an important role on the cis/trans isomer ratio. The effect of common salts (runs 6,10 and 14) on the cis/trans ratio of the cyclization products in THF supports the idea also: a large excess of sodium cation can convert the intermediate carbanion 5b to 5a because the sodium cation not captured by the crown ether contributes to the stabilization of the latter.

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References

1)L. L. McCoy, J. Amer. Chem. Soc., 80 6568 (1958), J. Org. Chem., 25 2078 (1960), J. Amer. Chem. Soc., 82 6416 (1960), J. Amer. Chem. Soc., 84 2246 (1962)
2)Y. Inoue, S. Inamasa, M. Horiike, M. Ohno and H. M. Walborsky, Tetrahedron, 24 2907 (1968), Y. Inoue, S. Inamasa, M. Ohno, T. Sugita and H. M. Walborsky, J. Amer. Chem. Soc., 83 2962 (1961)
3)R. Fraisser and R. Jacquir, Bull. soc. chim. France, 986 (1957), M. Mousseron, R. Fraisser, R. Jacquier and G. Bonavent, Compt. rend., 248 1465 (1959), D. T. Warner and C. E. Morreal, J. Amer. Chem. Soc., 82 439 (1960), O. Widman, Ber., 51 533, 907 (1918)
4)C. J. Pedersen and H. K. Frensdorff, Angew. Chem. Int. Ed., 11 16 (1972), J. J. Christensen, D. J. Eatough and R. M. Izatt., Chem. Rew., 74 351 (1974)
5)H. E. Zaugg, J. Amer. Chem. Soc., 82 2903 (1960)
6)B. Dietlich, J. M. Lehn, J. P. Sauvage and J. Blanzat, Tetrahedron, 29 1629 (1973), B. Dietlich, J. M. Lehn and J. P. Sauvage, ibid, 29 1467 (1973), B. Dietlich and J. M. Lehn, Tetrahedron Letters, 1225 (1973)

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