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UNSATURATED CARBOXYLIC ACID DIENOLATES. ADDITION TO SUBSTITUTED CYCLOHEXANONES. INVERTED KINETIC AND THERMODYNAMIC STEREOSELECTIVITIES.

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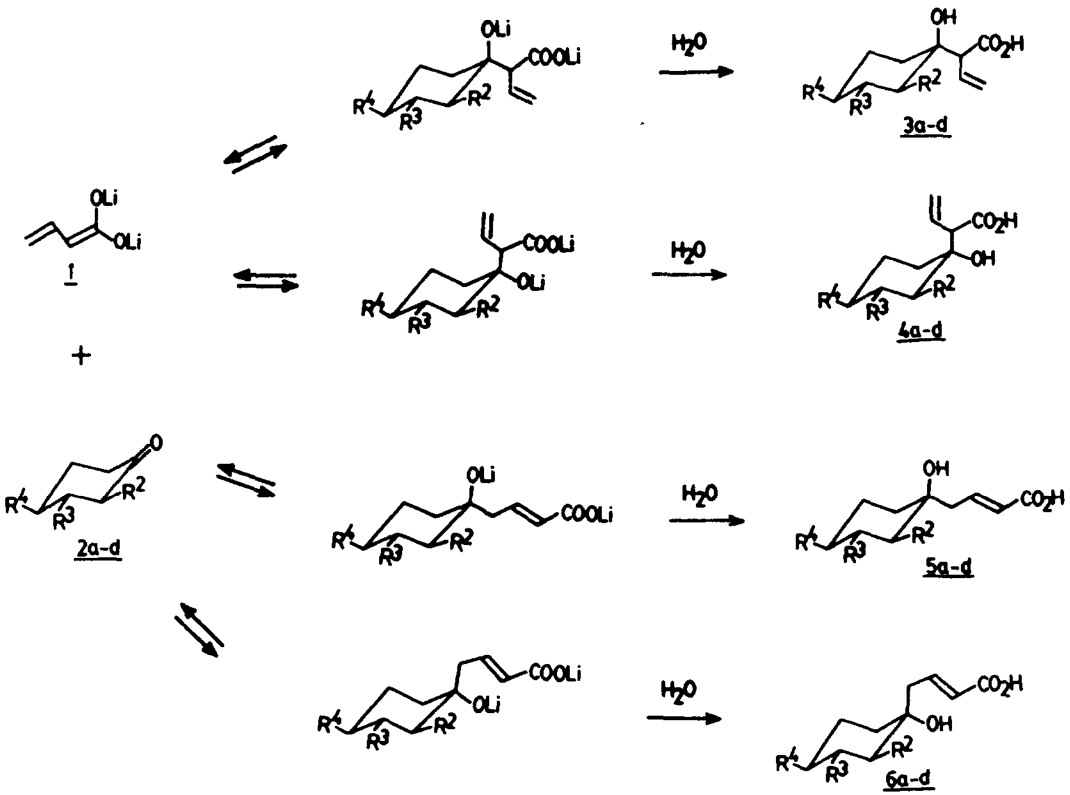
Abstract. Addition of the lithium dienolate derived from crotonic acid to monosubstituted cyclohexanones occurs through the α and γ carbon atoms of the dienolate in the cold and on heating, respectively. For any regioselectivity, equatorial approach is found under kinetic conditions, but equilibration favours products from axial attack and selectivity may be inverted.

The steric course of nucleophilic additions to cyclohexanones has been the object of much work and speculation along the past three decades since the first generalizations were disclosed by Barton and the concepts of steric approach control and product development control were introduced by Dauben and Noyce[1-4]. When attention is restricted to irreversible additions of carbanion nucleophiles, now standing theories assume early, reactant-like transition states. A late, product like transition state, as implied in the product development control would lead to the stable cyclohexanol as predominant isomer, but this is against published findings. Thus, allylic carbanions afford high amounts of the unstable cyclohexanol, namely that resulting from axial approach[5,6].

We have found that γ-additions of crotonic lithium dienolate 1 to substituted cyclohexanones 2 in THF show clearly discernible kinetic and thermodynamic stereochemical trends: equatorial attack is favoured in the cold and for short time, but the products of axial attack predominate on heating or after long reaction time. Once isolated, the more thermodynamically stable hydroxy acids are obtained from reactions performed under kinetic conditions, whereas the less thermodynamically stable compounds result from equilibration of the intermediate dilithium salts.

It had been found for other ketonic substrates that the dienolate 1 adds fast and reversibly through the γ-carbon, and more slowly through the γ-carbon atom. Short reaction times and low temperatures allow α-adducts to be obtained, whereas γ-adducts result from runs carried out for longer time at room temperature or on heating[7-9]. The present monosubstituted cyclohexanones 2 should not be exceptional, but α- and γ-adducts 3 to 6 derived from both equatorial and



2a to 6a, R^2= Me; 2b to 6b, R^3= Me; 2c to 6c, R^4= Me; 2d to 6d, R^4= t-Bu
Non specified R groups stand for H.

dithiane, and no selectivity nor changes for 2-lithium-1,3-dithiane[18].

When just unrefined steric factors are considered, similar requirements may be expected for α-carbon atom of both the dienolate 1 and the allylic reagents $|CH_2=CHCH_2|_nM$ in their approach to a substrate. As the latter reagents interact with carbonyl groups irreversibly[4,6], stereochemical ratios for their additions to substituted cyclohexanones should resemble those obtained now under kinetic conditions: equatorial approach should predominate. This is indeed observed for aluminium, cadmium and zinc reagents[6,19], but on the contrary the additions of lithium, sodium, and the poorly selective magnesium allylic reagents, rather parallel those of the dienolate after equilibration, as axial interactions predominates, and the adducts which we now presume being the more stable are obtained[4,6].

Wigfield has shown that reductions by sodium borohydride occur through a late transition state[3], and this may be the case for some of the refered allylic additions. We feel that further clarification of the position of the transition states in the reaction coordinates is needed before full understanding of the factors that control the steric course of nucleophilic additions to cyclohexanones is achieved.

axial attack to the substrates could result now.

Configurations of adducts have been unambigously established through both ^{13}C and ^{1}H-NMR spectra of pure isolated compounds. For each pair of stereoisomers the ^{13}C values are in agreement with those expected for cyclohexanes with axially and equatorially oriented hydroxyl groups[10,11]. Similar agreement is found for the proton signals of the methine and methylene groups of the α- and γ-crotonic chains[12-14].

The effect of temperature and time on regio- and stereo-selectivities for the addition of crotonic acid dienolate to cyclohexanones 2a to 2d are shown in Table I. All substrates afford two γ-adducts and, except for 2-methylcyclohexanone 2a, two α-adducts. In agreement with expectations, both α- and γ-adducts resulting from equatorial attack develop more rapidly than their diastereoisomers, but surprisingly, both α- and γ-adducts resulting from axial approach are favoured on equilibration, and occasionally become the major components of the mixtures, without decrease of yield. Especially significant are the inversions of stereoselectivity found for α-addition to 4-methylcyclohexanone 2c, and γ-additions to 2-methyl and 4-tertbutylcyclohexanone 2a and 2d. The α-adduct 4a has not been found. This is in keeping with the general observation of axial interactions with bulky groups being prevented by 2-equatorial substituents[2].

The occurrence of inversion of steric trends on equilibration shows that the relative stabilities of the adducts under the reaction conditions may differ strongly from those assumed for isolated compounds, and should be found for requirements than the nucleophile. Thus similar behaviour to that observed now has been described by Maroni-Barnaud for addition of ketone magnesium enolates[17], whereas the opposite trend has been found for the bulky 2-lithium-2-phenyl-1,3-

TABLE I. Regio- and stereoselectivity of crotonic lithium dienolate addition to substituted cyclohexanones.[15,16]

Ketone	Time	Temp.	Yield					Product ratios	
	(h)	(°C)	(%)	3	4	5	6	3:4	5:6
2a	0.5	-70	72	66	-	29	5	100:0	85:15
	2	0	96	16	-	62	22	100:0	74:26
	2	55	92	-	-	30	70	-	30:70
2b	0.5	-70	77	80	10	6	4	88:12	60:40
	16	20	85	8	44	37	11	15:85	77:23
	2	55	79	-	-	48	52	-	48:52
2c	1	-70	86	85	-	10	5	100:0	67:33
	14	20	83	24	60	10	4	28:72	72:28
	2	55	77	-	-	52	48	-	52:48
2d	2	0	84	75	10	15	-	88:12	100:0
	2	55	77	-	-	50	50	-	50:50
	100	37	84	-	-	25	75	-	25:75

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REFERENCES AND NOTES

1. A.V. Kamernitzky and A.A. Akhrem, Tetrahedron, 1962, 18, 705.
2. E.C. Ashby, and J.T. Leammle, Chem. Rev., 1975, 75, 521.
3. D.C. Wigfield, Tetrahedron, 1979, 35, 449.
4. M. Cherest, Tetrahedron, 1980, 36, 1593.
5. M. Cherest, H. Felkin, and C. Frajerman, Tetrahedron Lett., 1971, 383.
6. M. Gaudemar, Tetrahedron, 1976, 32, 1689.
7. I. Casinos, and R. Mestres, J.C.S. Perkin Trans. I, 1978, 1651.
8. P.R. Johnson, and J.D. White, J. Org. Chem., 1984, 49, 4424.
9. P. Ballester, A. García-Raso, and R. Mestres, Synthesis, 1985, 802.
10. H.O. Kalinoowski, S. Berger, and S. Braun, ^{13}C-NMR Spektroskopie, Georg Thieme Verlag, 1984, p.236.
11. E. Breitmeier, G. Haas, and W. Voelter, Atlas of Carbon-13 NMR Data, Vol. 1 and 2, Heyden and Son Ltd, 1979.
12. L.M. Jackman, and S. Sternhell, Applications of NMR Spectroscopy in Organic Chemistry, Pergamon Press, 1969.
13. Selected ^{1}H and ^{13}C-NMR data (δ, $CDCl_3$, as methyl esters):
    3c: 2.95 (d, 9.5 Hz, C$\underline{H}$COOMe);71.0 ($\underline{C}$-OH), 60.6 ($\underline{C}$HCOOMe);
    4c: 3.40 (d, 9 Hz, C$\underline{H}$COOMe); 71.7 ($\underline{C}$-OH), 54.1 ($\underline{C}$HCOOMe);
    5c: 2.33 (d, 7.7 Hz, $C\underline{H}_2C{=}C$); 70.0 ($\underline{C}$-OH), 46.4 ($\underline{C}H_2C{=}C$);
    6c: 2.43 (d, 7.6 Hz, $C\underline{H}_2C{=}C$); 71.4 ($\underline{C}$-OH), 40.1 ($\underline{C}H_2C{=}C$).
14. Conformations shown are those expected from A values (s, T.H. Lowry and K.S. Richardson, Mechanism and Theory in Organic Chemistry, Harper and Row Publishers, 1981, p. 126), and are in agreement with spectra.
15. Satisfactory analytical values were obtained for all new compounds.
16. Relative amounts of isomers in esterified reaction mixtures were determined through ^{1}H-NMR (α:γ , and 3:4 ratios) and GLC (5:6 ratios) integration curves. α-adducts decompose when introduced in the GLC column.
17. Y. Koudsi, and Y. Maroni-Barnaud, Comptes Rendus Acad. Sci., 1973, 280C, 399.
18. E. Juaristi, J.S. Cruz-Sánchez, and F.R. Ramos-Morales, J. Org. Chem., 1984, 49, 4912.
19. D. Abenhaïm, E. Henry-Basch, and P. Freon, Bull. Soc. Chim. France, 1969, 4038.

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