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RELATIONSHIP BETWEEN REGIOSELECTIVE REDUCTION OF CYCLIC ANHYDRIDES AND PATH OF NUCLEOPHILIC APPROACH TO THE ACTIVATED CARBONYL FUNCTION

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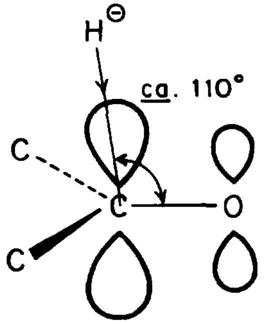
It has been demonstrated that the reduction of a carbonyl function with $LiAlH_4$ is catalyzed by Li^+ cation[1,2] and that stereoselection is fixed from the first step in the mechanism, namely, association of Li^+ cation with the oxygen atom of the carbonyl function[3]. The subsequent addition of AlH_4^- nucleophile to the activated carbonyl function[4] has been shown to proceed with strict stereochemical restraints[5,6]. It was theoretically predicted and experimentally confirmed that the approach vector of a nucleophile is not perpendicular to the C-O bond but forms an angle of *ca.* 110° with it (1). Baldwin[7] suggested that the path of nucleophilic attack may be further restricted in amide or ester functions due to the shift from the symmetric position, as in ketone 2, to a position in space away from the hetero atom (3).



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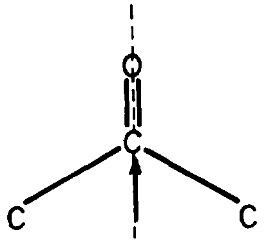

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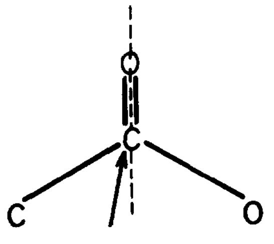

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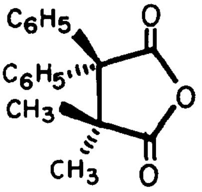
Taking into account the above restrictions we have been able to rationalize the regioselectivity observed in the metal hydride reduction of a number of cyclic anhydrides[8] and have also shown that a previously postulated mechanism involving both carbonyl groups sequentially must be incorrect. 2,2-Dimethylsuccinic anhydride and 2,2-diphenylsuccinic anhydride are both reduced in a highly regioselective manner at the carbonyl function adjacent to the fully substituted carbon atom. This was attributed to a combination of electronic and steric factors operating in the same direction. In this communication we report the results of metal hydride reduction of 2,2-dimethyl-3,3-diphenylsuccinic anhydride 4 and of *trans*-2-methyl-3-phenylsuccinic anhydride 9.

By analogy with previous results (reduction of 2,2-dimethyl- and 2,2-diphenylsuccinic anhydride) it might have been expected that reduction of 2,2-dimethyl-3,3-diphenylsuccinic anhydride 4 would lead to a mixture of isomeric lactones. However the only lactonic product



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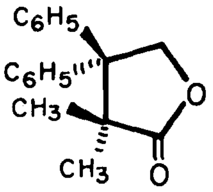

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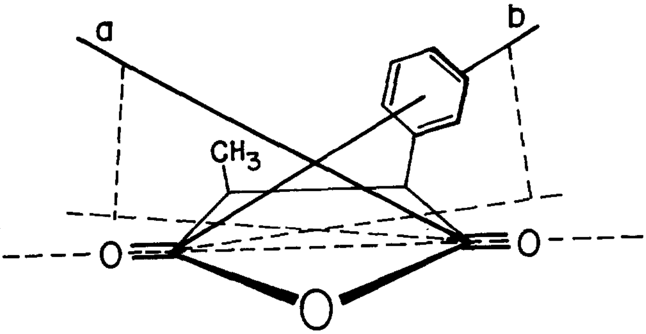
formed with both $LiAlH_4$ and $NaBH_4$ was found[9] to be 2,2-dimethyl-3,3-diphenyl-γ-butyrolactone 5 in yields ranging from 89 to 95%. The regiospecific nature of this reduction provides strong evidence for the validity of a restricted pathway[6,7] for nucleophilic attack.

In terms of the most favourable path of nucleophilic attack onto the plane of the trigonal carbon atom, the approach toward the carbonyl group α to the phenyl substituents (6, path a) is



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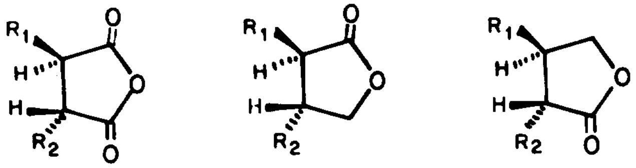
sterically less restricted than the approach toward the other carbonyl function (6, path b) which is obstructed by the phenyl groups. It now becomes clear that in situations where primarily steric effects (as in 4) are operative or in situations where both steric and electronic effects favour reduction of the same carbonyl function (2,2-dimethyl- and 2,2-diphenylsuccinic anhydride) one can expect regiospecific formation of only one lactone. On the other hand, when steric and electronic effects operate in opposite directions, mixtures of isomeric lactones are formed. The ratio of the two lactones obtained may reflect the dominance of steric or electronic effects. For example, reduction[10] of 2-methylsuccinic anhydride yielded a mixture of lactones **7a** and **7b** in a ratio of 1:2.2. The reduction of 2-phenylsuccinic anhydride **8** showed diminished preference for the more hindered carbonyl group (**8a** : **8b** = 1:1.5). From steric considerations alone, the opposite trend would be expected.



$R_1 = CH_3$, $R_2 = H$	7	7a	1 : 2.2	7b
$R_1 = C_6H_5$, $R_2 = H$	8	8a	1 : 1.5	8b
$R_1 = C_6H_5$, $R_2 = CH_3$	9	9a	1.5 : 1	9b

We were interested to observe which effect would be dominant in the reduction of *trans*-2-3-phenylsuccinic anhydride **9**. Here, the sterically more important phenyl group is in direct competition with the less bulky methyl group. The major product[11] of this reduction was found to be *trans*-2-phenyl-3-methyl-γ-butyrolactone **9a** (**9a** : **9b** = 1.5:1). This result suggests that the phenyl group, which promotes electron delocalization, lowers the basicity of the oxygen atom of the neighbouring carbonyl group relative to the carbonyl group adjacent to the methyl substituent. As a result, association with Li^+ cation is more likely to occur at the carbonyl function next to the methyl group and consequently this function is preferentially reduced.

In conclusion, we suggest that besides steric and torsional interactions, electronic effects appear to be an important factor controlling the regioselectivity of nucleophilic addition to carbonyl groups in cyclic anhydrides.

ACKNOWLEDGEMENT

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