STEREOSPECIFICITY IN DIELS-ALDER AND 1,3-DIPOLAR CYCLOADDITIONS DOES NOT PROVE THE CONCERTED MECHANISM

Raymond A. Firestone

Medicinal Chemistry - Immunology & Inflammation Dept., Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, N.J. 07065, U.S.A.

Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.

Abstract- The exceptionally high stereospecificites in some recent cycloaddition cases do not rule out diradical intermediates, because (1) rotation barriers for free radicals >0, (2) those for diradicals may exceed those for free radicals, and (3) strain-free cyclizations to 5- and 6-membered rings generally enjoy large rate advantages over their intermolecular counterparts.

A prime factor in mechanistic thinking about Diels-Alder and 1,3-dipolar cycloadditions is stereospecificity, which means that groups disposed cis or trans to each other in the dienophile or dipolarophile remain so in the cycloadduct. It is required by the concerted mechanism, and permitted by the diradical mechanism. Although it is often held to general, in most examples this is based on a mass balance of only 90-95%[1]. Recently, however, several papers have appeared describing examples of both reactions that are stereospecific to within very small error limits[2,3,4]. The authors say that these must be concerted, because if a diradical intervened, some rotation in the dieno/dipolarophile would have been observed. This paper is a reply to that argument.

Numerous reports of non-stereospecific Diels-Alder reactions already exist[5,6]. An important addition to this list is the cycloaddition of cis- and trans-2-butene to 1,3-cyclohexadiene, which occurs in both directions with a few percent rotation[7]. Two other investigations of this nature in progress are yet to be published[8]. Although no bona fide example of non-stereospecific 1,3-dipolar cycloaddition has been published, at least one phenomenon - hydrogen transfer - requires the intervention of extended diradicals[5], from which the existence of cyclo diradicals can reasonably be inferred. Therefore at least these cases must occur to some extent via diradicals[9]. Simultaneous concerted and diradical pathways have been postulated before[10], and the closeness on the reaction coordinate of concerted and diradical transition states has been pointed out[11].

Huisgen and co-workers report that diazomethane cycloadds to methyl angelate and tiglate with >99.94% and >99.997% stereospecificity[2]. Houk and co-workers found that cis- and trans-dideuterioethylene cycloadd to p-nitrobenzonitrile oxide with $\geq$98% stereospecificity[3], and to butadiene with

<1% rotation[4].They argue that since free radicals rotate with vanishingly small barriers[12], even if cyclization of the diradical occurred with Ea = 0 some rotation should have been observed. They conclude that the cycloadditions are concerted, and that if there is a diradical component its fraction is severely confined. Although Huisgen's diradical is tertiary in the dipolarophile component, and therefore expected to have a finite rotation barrier[5,13], Houk's are primary, for which barriers are lower but not zero. For example, the barrier for n-propyl radical, which is closest in structure among those in the literature to Houk's diradicals, is >0.4 Kcal/mole (3.1 Kcal/mole by another method of calculation)[12]. Other primary radicals (bonded to branched carbons) range from 0.38 to 1.17 Kcal/mole[14].

There are two important assumptions implicit in this argument. The first is that the radical center in the diradical that arises from the dieno/dipolarophile rotates just as easily as a monoradical, i.e. that the second radical does not affect the rotation of the first.However it could, if the two were to interact by hyperconjugation. While evidence for it is lacking[3], there is some theoretical support for the idea[15]. In addition to the sources cited, calculations by Lluch and Bertran for some 1,3-dipolar cycloadditions indicate that the bond order for the dipolarophile remains >1 in the diradical, so that the rotational barrier of that bond could be higher than that in monoradicals[16]. For extended 1,4-butane-diyl, Borden and Davidson calculate that rotation of the first radical center from the most stable (90,90) geometry to (0,90) costs 2.76 Kcal/mole, and rotation of the second to (0,0) costs an additional 1.19 Kcal/mole, so that through-bond coupling of the two radical centers by hyperconjugation is worth 1.57 Kcal/mole[17]. The fact that butane-1,4-diyls rotate extensively during cyclization[18] does not negate this concept because they were made by means other than cycloaddition (i.e. pyrolysis of diazenes), so that rotation during a prior stage of their existence cannot be conclusively ruled out, and also because closure to 4-membered rings is not strain-free, as it is to 5- and 6-rings, giving rotation a better chance to compete. Indeed, despite an entropic advantage, cyclization to 4-rings is generally the slowest of all ring sizes below 7[19,20].

The second implicit assumption is more interesting because it has never to my knowledge been discussed before in this context. It is that, since free radicals combine with Ea = 0, the cyclization of diradicals cannot go any faster.

However, cyclization reactions, especially to 5- and 6-rings, have long been known to proceed much faster than their intermolecular counterparts[19]. Perhaps the simplest example is the lactonization of 4-hydroxybutyric acid, which goes 79 times faster than esterification of acetic acid with ethanol[21]. In this heavily-studied field this is one of the smallest rate ratios, which frequently reach immense values. Even a very modest ratio is enough to explain Huisgen's and Houk's data. Speculation on the origin of the intra- vs. intermolecular rate ratios has centered on entropy[22].

For SN2, DeTar calculates the intra/intermolecular entropy advantage for 6-rings at 17.7, and 5-rings at 20.5 e.u.[23], which translate into rate factors of ca. 10^4. Nevertheless the reason for this phenomenon, which interests people because of its possible connection with enzymic catalysis, is by no means firmly established, and for the present purpose it does not matter. It simply means that one must consider it possible for a diradical to cyclize much faster than free radicals combine, even though Ea = 0 for both processes.

Probably every diradical case is poised closely between rotation that is or is not observable. It is not surprising, then, that non-stereospecific Diels-Alders, while not universal, are commonplace. Why is this not also true for 1,3-dipolar cycloadditions? Because in this reaction, rotation has a harder time competing with cyclization since 5-rings, as a rule, form faster than 6[19]. This might be an entropy effect; 5-ring cyclization requires one less bond rotation to be frozen out, and is favored over 6 in SN2 by 8.4 e.u.[23], equivalent to a rate factor of 63.

Therefore my conclusion, as before[5], is that stereospecificity cannot be used to rule out the diradical mechanism.

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