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ASYMMETRIC INDUCTION IN THE 1,7 RING CLOSURE OF DIENE-CONJUGATED DIAZO-COMPOUNDS: A ROUTE TO CHIRAL 1H-2,3-BENZODIAZEPINES

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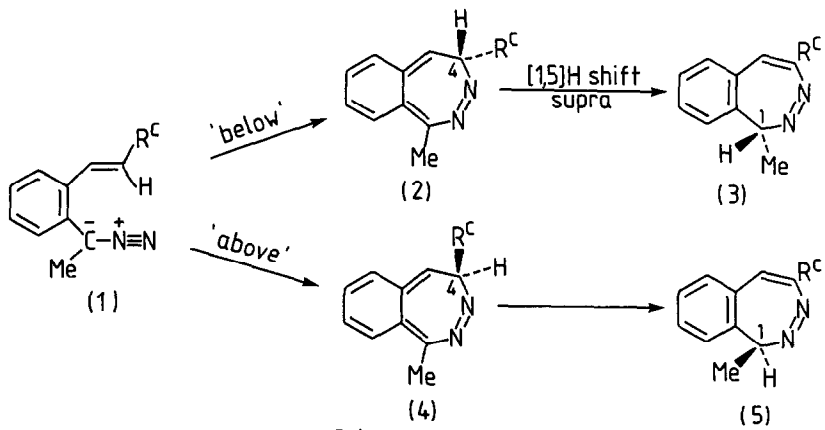
In the cyclisation of the diazo-compound (7) to give the diastereomeric pair of 1*H*-2,3-benzodiazepines (8) and (9), alkoxy groups, when present as the medium sized group M, show the opposite effect in promoting face selectivity to that of alkyl groups and the alkoxide ion. Thus when M=OMe the (8):(9) ratio is 92:8 while in contrast when M=O$^-$ the ratio is 15:85.

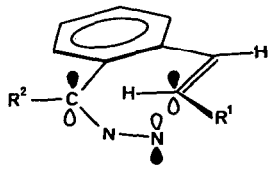
Studies on asymmetric induction have embraced many types of reaction since Cram's original work on nucleophilic addition to the carbonyl group. In particular there has been extensive work on the addition reactions of alkenes, both *via* electrophilic attack and *via* cycloaddition.[1,2,3] We now report the first study of asymmetric induction in the electrocyclisation reactions of conjugated 1,3-dipolar intermediates. Such reactions provide powerful synthetic routes to both 5- and 7-membered heterocyclic rings; the former by the 1,5 electrocyclisation of alkene-conjugated 1,3-dipoles,[4] and the latter by the 1,7 closure of diene-conjugated analogues.[5]

The reaction chosen for this study was the cyclisation of diazo-compounds of the type (1) to give 1*H*-2,3-benzodiazepines (Scheme 1).

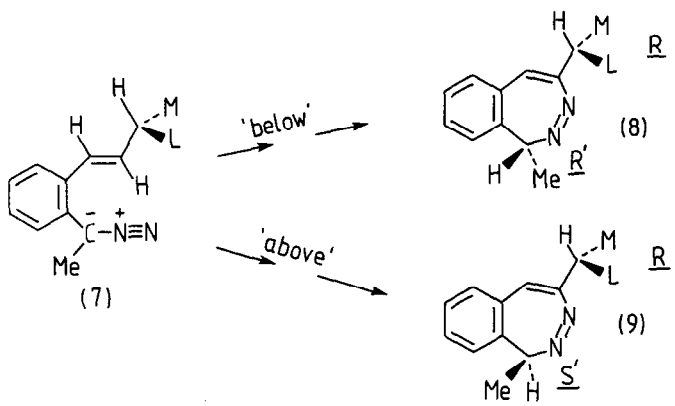


Scheme 1

It is thought that this conversion involves two steps, first a 1,7-electrocyclisation (8Π electron) in which orbital overlap at the termini of the Π system is achieved *via* a helical transition state (6); and second, an intramolecular sigmatropic [1,5] hydrogen shift (suprafacial) which converts, for example, (2) into (3).[6,7]

(6) 

The results reported here are concerned with the effect on the course of the reaction of the presence of a chiral substituent R^C in the *trans* position at the olefinic terminus of the conjugated system (Scheme 1). Cyclisation of (1) can occur *via* approach of the terminal nitrogen to either face of the double bond, so producing as the primary products a pair of diastereomers (2) and (4) which have a new chiral centre at C-4 adjacent to R^C. The suprafacial hydrogen migration in the second step will then transfer the chirality at C-4 stereospecifically to C-1 to produce the product pair of diastereomers (3) and (5) which have the new chiral centre remote from the original stereogenic group.



Scheme 2

The primary objective in this work was to vary the nature of R^C to determine the factors controlling stereoselectivity in the cyclisation step. We have looked at the cyclisation of compounds of the type (7) in which the largest group (L) is Ph or Bu^t; the medium sized group (M) is alkyl (Me or Et), alkoxy (OMe or $OSiMe_2Bu^t$), or alkoxide ion (O^-); and the smallest group is hydrogen. The cyclisations[6,7] were carried out at *ca* 80°C in aprotic solvents of various kinds (Table). The ratios of the diastereomers (8):(9) were measured by ^1H NMR and by HPLC on the crude reaction products before crystallisation or chromatography, and the relative configurations of the two chiral centres were determined by X-ray crystallography (cases a, b, d, e) or by comparison of NMR spectra.

Table Yields and diastereomer ratios for the products from Scheme 2

	(7)			(8):(9)		
				reaction solvent*		
	M	L	total yield %	CX	DME	DMF
(a)	Me	Ph	70	55:45	-	-
(b)	Me	But	85	58:42	55:45	57:43
(c)	Et	But	86	63:37	62:38	61:39
(d)	OMe	Ph	80	44:56	-	-
(e)	OMe	But	85	8:92	10:90	16:84
(f)	$OSiMe_2But$	But	92	9:91	-	-
(g)	O^-	But			85:15	-

* CX=cyclohexane, DME=1,2-dimethoxyethane, DMF=*N*,*N*-dimethylformamide

The results are shown in the Table. All cyclisations were carried out using racemates, but for illustration the results are presented and discussed for the enantiomer shown in structure (7). In the products (8) and (9) this is the *R* configuration of R^C for all the cases in the Table. The configuration of the new chiral centre at C-1 is given as R' or S'.

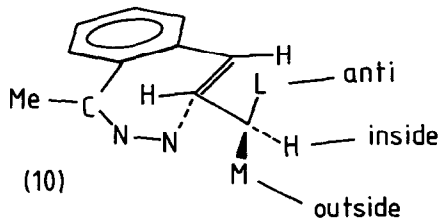
The most striking observation is that alkyl groups and the alkoxide ion, when present as the medium sized group M, have the opposite effect to that of alkoxy groups in inducing face selectivity. Thus (8) is the major product when M=Me or Et (cases a, b, c), and when $M=O^-$ (case g); but (9) is favoured when M=OMe or $OSiMe_2But$ (cases d, e, f). In the discussion following we make the assumption, based on Houk's earlier work on *cycloaddition* reactions, that in the transition states leading to both diastereomers the largest group L is in the position *anti* to the attacking N. This is illustrated in (10) and in the partial structures (11) and (12) which, respectively, represent attack from 'below' and 'above' the plane of the double bond.

In the cases where M is an alkoxy group, cyclisation at the 'upper' face predominates *via* the transition state (12) which has the alkoxy group in the 'inside' position. This 'inside' preference of alkoxy groups can be strong (cases e, f) giving a ratio of diastereomers of >90:10. In contrast there is a remarkable reversal of face selectivity when $M=O^-$. The cyclisation then shows a strong preference (85:15) for attack at the 'lower' face *via* (11). Alkyl groups show the same effect but to a much lesser degree. The transition state (11) has the O^- or alkyl group in the 'outside' position.

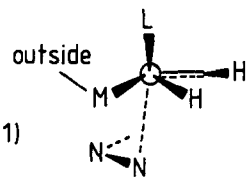
These results make an interesting comparison with those of Houk and others on the *cycloaddition* reactions of nitrile oxides to alkenes.[1,2,3] In these reactions alkyl and alkoxy groups *both* occupy the 'inside' position in the favoured transition state. The effect of having $M=O^-$ was not examined but hydroxyl groups showed a moderate 'outside' preference.

Further work is needed before a firm rationalisation of these

observations can be advanced. The facial selectivity obviously depends on the chemical nature of the medium sized group and not simply on its size. It must therefore arise from a combination of steric and stereoelectronic



(10)



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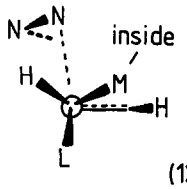

(12)

effects. The 'inside alkoxy' effect in cycloadditions has been attributed both to polar repulsion and to a stereoelectronic effect related to its interaction with the Π-system. In the latter explanation Houk has pointed out that this 'inside' position, close to the molecular plane of the alkene moiety, minimises electron withdrawal from the Π bond *via* σ^{*}_{C-O}/Π overlap.[1,2] In these diene-conjugated diazo compounds this position would be favoured since the Π system is already electron deficient because of the electron withdrawing diazo group and any further electron withdrawal at the other end of the Π system would be destabilising. If that is so then it may be that the 'outside' position for O^{-} and the alkyl groups is the one which best allows them to donate electrons into the Π-system.

Whatever the explanation it is clear that the 'inside alkoxy' effect and the 'outside alkoxide' effect manifested here give a degree of control of selectivity which is high enough to be potentially useful in the synthesis of chiral benzodiazepines. Similar studies on the cyclisation of other 1,3-dipolar intermediates are in progress.

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