Primary and Secondary Kinetic Isotope Effects in the Cope and Hofmann Elimination Reactions

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Summary: Primary and secondary kinetic isotope effects suggest that the Cope elimination affording apopinene at 120 °C has a later transition and greater rehybridization at carbon than the corresponding syn 1,2-Hofmann elimination in DMSO solvent.

The measurement of kinetic isotope effects (KIE) typically involve competitive rate studies or mass spectral analyses of isotopically labeled substrates.[1] Unfortunately, mass spectral analysis is not applicable for measuring secondary KIE. Secondary KIE effects are one of the few tools available to the experimentalist to probe the geometry of transition states for alkene formation in 1,2-elimination reactions. The change in out-of-plane bending frequency attending the rehybridization from sp^3 to sp^2 carbon is still thought to be largely responsible for the slightly lower rate of alkene formation when the alkene precursor is deuterated at C_α or C_β.[2] We recently reported a general method for measuring KIE that involved the relative rates of formation of "nominal enantiomers" from a single chiral isotopically labeled precursor.[3] We now demonstrate the utility of this differential polarimetric method for measuring both primary and secondary KIE in Cope and Hofmann elimination reactions.

The 3-substituted bicyclo[3.2.1] system 1 meets the essential criteria for successful application of this kinetic resolution. This generalized substrate has two pairs of diastereotopic β-hydrogens and possesses a plane of symmetry (C3–C6–C7) that may be formally removed by deuterium substitution and it affords either an enantiomer (–DX) or its isotopically labeled optical antipode ($-H_aX$) upon 1,2-elimination (Scheme I). Stereoselectivity due to reaction at an isotopically labeled center can potentially afford an observable KIE. Competitive base abstraction of hydrogen or deuterium and suprafacial elimination produces a pair of nominal enantiomers of opposite absolute configuration of the alkene chiral unit. A preferential syn elimination of H_a will give rise to an excess of stereoisomer (+)-(*R*)-4d_1 and the measurement of the optical purity of the resulting alkene affords the ratio of rate constants k_H/k_D. The chirality at C_4 as a result of deuterium substitution should have a negligible effect upon the final rotation ($[\alpha]_f$) of the product.

Both chiral elimination substrates 3 and 4 are readily derived from (–)-(*R*)-apopinene (2) by a series of chemical reactions of known stereochemistry.[4] The mechanism of the Cope elimination has been well established by both stereochemical[6] and isotopic labeling studies.[3b,c] A late transition state has been advocated for the thermal decomposition of amine oxides.[3,7] Despite these extensive

Scheme I

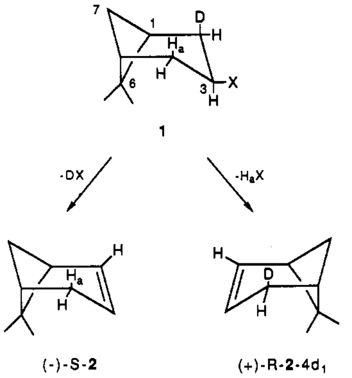
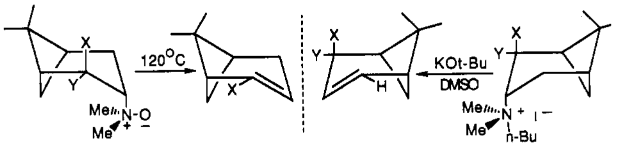


Table I. Kinetic Isotope Data for the Cope Elimination and E_2 Elimination Affording Apopinene



3 2a 2b 4

substrate	X	Y	temp (°C)	k_H/k_D[a]	$[\alpha]_f$[b]	k_H/k_D[c]
(2*R*,3*S*)-3	H	D[d]	120	2.23	17.10	2.22[e]
(2*S*,3*S*)-3	D[h]	H	121		1.333	1.061[f,g]
(2*R*,3*S*)-4	H	D[i]	25	1.22	5.24	1.27[f]
(2*S*,3*S*)-4	D	H	26		1.540[j]	1.072[f,g]

[a] Determined by mass spectroscopy. [b] Initial rotation $[\alpha]_i$ = –45.1° for 2 used in the formation of 3 and –44.3° for formation of 4. [c] Determined by optical rotation method. [d] Initial deuterium content = 80.0%. [e] Average of three experiments, ±0.03. [f] Average of two experiments, ±0.03. [g] Secondary KIE. [h] Initial deuterium content = 77.3%. [i] Initial deuterium content = 95.0%. [j] $[\alpha]_i$ = –44.1°.

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[4] (–)-(*R*)-2 ($[\alpha]_D$ –45.1°, 98% ee) was prepared from (–)-β-pinene ($[\alpha]_D$ –21.5°, 98% ee) by ozonolysis[5a] affording norpinone ($[\alpha]_D$ 33.0°, 97% ee)[5b] followed by a Shapiro reaction[5c] on the corresponding *p*-toluenesulfonylhydrazone. (–)-(*R*)-Apopinene-2d_1, $[\alpha]_D$ –44.7° (2a, X = D) was obtained by quenching the vinyl anion intermediate in the above Shapiro elimination with D_2O. Suprafacial deuterioboration[5d] of the more accessible *endo* face of the carbon–carbon double bond of (–)-(*R*)-2 and subsequent treatment with NH_2Cl afforded a mixture of the 2- and 3-amines in an 85:15 ratio. The desired 3-amine was purified by HPLC (90:9.5:0.5 hexane/ethyl acetate/acetic acid). A Clark–Eschweiler procedure[5e] on the primary amine afforded (2*S*,3*R*)-*N*,*N*,6,6-tetramethylbicyclo[3.2.1]hep-3-ylamine-2d_1 in 48% yield after purification. Oxidation of the tertiary amine with *m*-chloroperbenzoic acid in CH_2Cl_2 afforded 3 while treatment with *n*-butyl iodide in ether solvent gave 4 (99%).

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mechanistic studies, there have been no measurements of secondary KIE for this prototypical five-membered ring intramolecular elimination reaction. Pyrolysis of trans-deuterated *(2R,3R)*-**3** (X = D) at 120 °C *afforded (+)*-apopinene (**2**) that had $[\alpha]_f = +1.343°$, and a secondary KIE of 1.061 may be calculated from the relationship[3] $k_H/k_D = ([\alpha]_i - [\alpha]_f)/([\alpha]_i + [\alpha]_f)$ where $[\alpha]_i = -45.1°$ (Table I). No discernable loss of deuterium was observed by mass spectral analysis confirming the syn elimination pathway. In a duplicate experiment, the recovered (+)-(*S*)-apopinene exhibited a rotation of $[\alpha]_D = +1.323°$ and a secondary KIE of 1.060. Thus, the perturbations of the bending vibrations of the C-H bonds at C_β in the elimination process are significant at the transition state (TS) as evidenced by the appreciable secondary KIE.

Pyrolysis of the cis-deuterated amine oxide **3** (Y = D) afforded apopinene with an optical rotation of +17.1°. Since the initial rotation of the (-)-(*R*)-apopinene used in the synthesis of **3** was -45.1°, the primary syn KIE for the concerted Cope elimination is found to be 2.22. A temperature correction to 25 °C suggests a primary KIE of ~2.8. An accompanying mass spectral analysis using selective ion monitoring (SIMS) on this same cis-deuterated amine oxide showed that the recovered alkene contained 69.0% of its original deuterium content and a k_H/k_D of 2.23 may be calculated from this datum. These combined data, *for a rate-limiting nonlinear hydrogen transfer with discernible rehybridization at* C_β, are consistent with a transition state with extensive double-bond character.

Since the oxygen of an amine oxide is weakly basic and a relatively late TS should be anticipated, it is instructive to use a stronger base in order to assess the relative magnitudes of the secondary KIE in a comparable elimination process. Mass spectral analysis of the apopinene recovered from the trans-deuterated quaternary ammonium iodide **4** (X = D) showed no detectable loss of deuterium upon elimination with potassium *tert*-butoxide in DMSO solvent. This process is therefore a 100% syn 1,2-elimination under these reaction conditions reflecting the association of the alkoxide base with the cationic ammonium center.[8] Treatment of trans-deuterated (2*R*,3*R*)-**4** (X = D) at 26 °C under these conditions afforded (+)-**2** that had $[\alpha]_f$ 1.54° and a secondary KIE of 1.072. The magnitude of this KIE is smaller than that of the Cope elimination when corrected to 25 °C (~1.05). The primary KIE of 1.27 (Table I) is also very small suggesting a somewhat earlier transition state when KO-*t*-Bu is employed in DMSO solvent where the potassium cation is highly coordinated and the base strength of the oxyanion is markedly increased.

In summary, we have described a highly sensitive method for measuring both primary and secondary KIE in elimination reactions.[9] These data provide the first experimental evidence for extensive rehybridization at carbon in the Cope elimination. Recent ab initio calculations[10] (MP2/631G*) of secondary KIE in the Cope elimination suggests that the rehybridization at C_α (secondary KIE = 1.11) is even geater than that at C_β (secondary KIE = 1.04). *These combined data provide a unique explanation for the* fact that a Cope elimination in the cyclooctyl system (a late TS) affords exclusively *cis*-cyclooctene. However, much stronger bases that involve an earlier TS with much less double-bond character give predominantly the highly strained *trans*-cyclooctene despite the fact its ground-state energy is 9 kcal/mol higher in energy.[3]

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Synthesis of 1,4-Dicarbonyl Compounds via the Conjugate Addition of a Masked Activated Ester, $ROCH(CN)_2$

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Summary: A new acyl anion equivalent for the preparation of masked activated esters, the protected hydroxymalonitrile **1**, readily undergoes conjugate addition to α,β-unsaturated carbonyl derivatives **2** to give the masked 1,4-dicarbonyl compounds **3** in good to high yields. 1,4-Dicarbonyl compounds **4**, in which one of the two carbonyl groups has a reactivity different from the other, can be prepared selectively from **3**.

1,4-Dicarbonyl compounds are starting materials and intermediates in many important natural product syntheses, and a number of methods for their syntheses have appeared.[1] One of the most common approaches is the conjugate addition of acyl anion **5** or its equivalent to α,β-unsaturated carbonyl compounds.[1] Since the sub-

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