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The Claisen Rearrangement of Allyl Phenyl Ether: Heavy-Atom Kinetic Isotope Effects and Bond Orders in the Transition Structure

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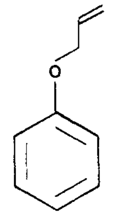
Abstract: Kinetic isotope effects (KIE) were measured for the rearrangement at 220 °C of allyl phenyl ether (**1**) which was labeled successively at its oxygen atom ([^{18}O]-**1**), α-carbon atom ([α-^{14}C]-**1**), γ-carbon atom ([γ-^{14}C]-**1**), and ortho-carbon atom ([2-^{14}C]-**1**). The KIE were 1.0297 (^{18}O), 1.0306 (α-^{14}C), 1.0362 (γ-^{14}C), and 1.0375 (2-^{14}C). KIE were determined from isotopic abundances in the product, *o*-allylphenol (**2**), which were measured by multiscan mass spectrometry (^{18}O) and scintillation counting (^{14}C). A model of the transition structure was then developed, whose bond orders gave calculated KIE in reasonably good agreement not only with the experimentally determined heavy-atom KIE but also with the deuterium KIE reported earlier by McMichael and Korver.[13] A loose transition structure was thus found for the rearrangement of **1** into **2**. In this transition structure the C_α–O bond is 50–60% broken while the C_γ–C_{ortho} bond is only 10–20% complete. The results thus define this concerted, nonsynchronous rearrangement more explicitly than hitherto possible.

The Claisen rearrangement of allyl phenyl ether and its homologues is probably the most thoroughly studied and best documented thermal, sigmatropic rearrangement known.[4] Even before the clarifying classification of pericyclic reactions was made, according to the principle of the conservation of orbital symmetry,[5–7] the concerted nature of the aromatic Claisen rearrangement had been deduced. The isotopic labeling and kinetic and stereochemical studies that led to this deduction have been summarized in a number of reviews.[8–10] Much interest, furthermore, has been shown in the nature and geometry of the transition structure[11] of the rearrangement. In broad terms, a chair-like transition structure (**4**) is now well-accepted for the rearrangement of allyl phenyl ether (**1**) into the dienone precursor (**3**) of the final product, *o*-allylphenol (**2**), as well as for analogous, structurally uncomplicated rearrangements.[9,12] Interest has also been shown in a more explicit description of the transition state, particularly as to the timing of the concerted breaking and forming of the σ bonds. In this respect, McMichael and Korver[13] measured the deuterium kinetic isotope effects (KIE) for rearrangements of α-dideuterio- and γ-dideuterioallyl phenyl ether. They concluded that in the transition state of this rearrangement breaking of the C_α–O bond was advanced as compared with forming of the C_γ–C_{ortho} bond. Specifically, the bond orders of these bonds in the transition structure were calculated to be respectively ≃0.23–0.43 and 0.22–0.62. This picture, then, is of a nonsynchronous rearrangement with an unsymmetrical transition structure. Nonsynchronous rearrangement of allyl vinyl ether into 5-pentenal was deduced by Gajewski and Conrad, also on the basis of deuterium KIE.[14] The use of deuterium KIE in such rearrangements (the Claisen and Cope) has been discounted by Dewar as being incapable of throwing light on their synchronicity.[15] On the other hand, Dewar and Healy[16,17] have characterized the rearrangements of allyl vinyl ether and some of its derivatives as concerted but nonsynchronous[18] on the basis of MNDO calculations. Thus, the nature of the transition structures in these rearrangements commands a lively interest.[20]



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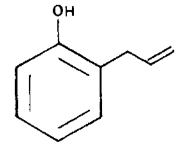

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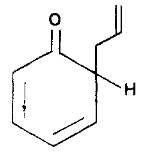

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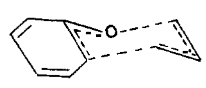

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Substitution of a heavy isotope for one or both of the atoms between which a bond is being broken or formed may give rise to a heavy-atom KIE. In that case, the magnitude of the KIE reflects the magnitudes of the vibrational frequencies, and hence the bond orders, in the transition structure relative to the reactant. With this in mind we have set out to obtain a measure of the bond order of the σ bond which is breaking and of the one which is

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(4) The term Claisen rearrangement is often taken to mean the rearrangement of allyl aryl ethers and aryl ethers containing extended unsaturated groups such as pentadienyl. More recently, the term has been applied also to allyl vinyl ether and its derivatives. The rearrangement of allyl vinyl ether is sometimes also called an oxa-Cope rearrangement. In this paper, therefore, when it is useful or necessary to use general terminology, we will call the rearrangement of allyl aryl ethers the aromatic Claisen rearrangement.

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(11) We use the term *transition structure* to describe the structure of the reacting system as it passes through the *transition state*, which is the highest point on the minimum-energy path between reactant and product.

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Table I Kinetic Isotope Effects (KIE) for the Thermal Rearrangement of Allyl Phenyl Ether (**1**) to *o*-Allylphenol at 220 °C in Diphenyl Ether

run no.	isotope	conv.	KIE[a]
1	^{18}O	0.11	1.0315 ± 0.0041
2	^{18}O	0.14	1.0300 ± 0.0022
3	^{18}O	0.15	1.0298 ± 0.0018
4	^{18}O	0.16	1.0282 ± 0.0027
5	^{18}O	0.165	1.0272 ± 0.0022
6	^{18}O	0.26	1.0316 ± 0.0024
7	α-^{14}C	0.009	1.0350 ± 0.0006
8	α-^{14}C	0.15	1.0274 ± 0.0024
9	α-^{14}C	0.16	1.0288 ± 0.0007
10	α-^{14}C	0.18	1.0348 ± 0.0016
11	α-^{14}C	0.19	1.0236 ± 0.0019
12	α-^{14}C	0.25	1.0341 ± 0.0021
13	γ-^{14}C	0.157	1.0351 ± 0.0006
14	λ-^{14}C	0.158	1.0390 ± 0.0014
15	γ-^{14}C	0.165	1.0358 ± 0.0013
16	γ-^{14}C	0.165	1.0342 ± 0.0014
17	γ-^{14}C	0.184	1.0355 ± 0.0005
18	γ-^{14}C	0.221	1.0374 ± 0.0028
19	2-^{14}C	0.08	1.0421 ± 0.0023
20	2-^{14}C	0.13	1.0358 ± 0.0025
21	2-^{14}C	0.13	1.0389 ± 0.0015
22	2-^{14}C	0.16	1.0352 ± 0.0026
23	2-^{14}C	0.24	1.0342 ± 0.0038
24	2-^{14}C	0.25	1.0385 ± 0.0023

[a] KIE for [2^{14}C]-**1** have been corrected for intramolecular competition between ^{12}C and ^{14}C.

forming in the transition structure of the aromatic Claisen rearrangement. For this purpose we have chosen the classical rearrangement of allyl phenyl ether (**1**) itself into *o*-allylphenol (**2**) and have measured KIE for substitution at each of the four atoms of the σ bonds involved. That is, we have prepared **1** labeled with ^{18}O and with ^{14}C at its α-C, γ-C, and C_{ortho} positions. We refer to the isotopically labeled compounds as [^{18}O]-**1**, [α-^{14}C]-**1**, [γ-^{14}C]-**1**, and [2-^{14}C]-**1**, respectively. We have then constructed models of the transition structure and have computed bond orders that accommodate not only the heavy-atom but also the earlier deuterium KIE.

Results and Discussion

Kinetic Isotope Effects. We have described the syntheses of [α-^{14}C]-**1** and [γ-^{14}C]-**1** earlier.[21] Syntheses of [^{18}O]-**1** and [2-^{14}C]-**1** were from 4-nitroaniline and from 2-nitro[1-^{14}C]aniline by adaptation of routine methods.

Initially, we tried to carry out rearrangements of **1** in carbitol, but we were unable to isolate **2** cleanly for isotopic assay. Rearrangements, therefore, were carried out in diphenyl ether solution at 220 °C. The rate constant at 197 °C ($k = 3.86 \times 10^{-5}\ s^{-1}$) and activation energy ($E_a = 31.6$ kcal/mol) for rearrangement of **1** in this solvent have been reported by Goering and Jacobson,[22] from which the rate constant ($k = 1.87 \times 10^{-4}\ s^{-1}$) for rearrangement at 220 °C was calculated. Timing for stopping rearrangement, by cooling, for specified low conversions was calculated from this rate constant. However, the extent of conversion needed for use in calculating KIE was measured in the diphenyl ether solution by ^1H NMR spectroscopy before beginning isolation of **2**. 100% conversions were also confirmed with ^1H NMR before beginning isolation of **2**. Product **2** was not itself used for measuring isotopic abundances. For ^{14}C KIE measurements by scintillation counting, **2** was converted into its phenylurethane, for better handling and for purifying by sublimation. For ^{18}O KIE measurements by multiscan mass spectrometry, **2** was first methylated and next oxidized, ending in *o*-methoxybenzoic acid. The reason for this was that **2** itself, and its methyl ether, had a very low parent-ion mass-spectrometric abundance. In contrast, *o*-methoxybenzoic acid gave a substantial parent ion and a negligible M − 1 ion abundance, thus making calculation of KIE simple.

Table II. Averaged KIE

isotope	KIE
^{18}O	1.0297
α-^{14}C	1.0306
γ-^{14}C	1.0362
2-^{14}C	1.0375

Table III. Assumed Force Constants

type	value, mdyn Å^{-1}	type	value, mdyn Å^{-1}
C–H str	4.5	H–C–O bd	0.67
C–O str	5.0	H–C(C)$_2$ oop bd	0.2
C–H str	4.7	O–C(C)$_2$ oop bd	0.2
C–C–H bd	0.67	C–C–O–C tors	0.044
H–C–H bd	0.55	C–C–C–O tors	0.066
C–C–C bd	0.83	C–C–C–H tors	0.09
C–O–C bd	0.7	C–C–C–C tors	0.071
C–C–O bd	0.7		

Rearrangements were clean, giving rise, however, to small amounts of higher (assumed) molecular weight products from which **2** was separated by column chromatography. In the total of eight 100% conversions that were carried out, the yield of **2** isolated by column chromatography averaged 93.8%, while byproducts, isolated in two successive chromatographic elutions (see Experimental Section), averaged a total of 6.1%. In this connection, small amounts of higher molecular weight product(s) have been reported by others, e.g., in the rearrangement of allyl *p*-tolyl ether.[23]

KIE are listed in detail in Table I and are summarized in Table II. They are substantial for all of the four positions and are consistent with the long-held view of a concerted process in the aromatic Claisen rearrangement.

Calculations of Bond Orders in the Transition Structure. The Claisen rearrangement presents a considerable challenge to isotope effect calculations. There are few reactions in the literature for which isotope effects at so many positions are available. Even though the number of disposable parameters in this complex system still exceeds greatly the number of experimental data, it proved difficult to arrive at models that predicted all of the observed isotope effects.

The models do not include all the atoms of the complete reactant (**1**) and transition structure (**4**) but follow the Wolfsberg–Stern cutoff procedures, in which atoms more than two bonds from the site(s) of isotopic substitution are omitted.[24,25] These procedures reduce considerably the number of parameters that must be assigned, and the resulting models have been shown to give results differing little from those obtained with full models. Initially we worked with four different cutoff models so as to explore most economically the influence of force constants and bond orders on the various calculated isotope effects. In the final calculations reported here, we still use two different models, **5** → **6** for the $^{16}O/^{18}O$, α-$^{12}C/^{14}C$, and α-H_2/D_2 effects, and **7** → **8** for the γ-$^{12}C/^{14}C$, γ-H_2/D_2, and *o*-$^{12}C/^{14}C$ effects. These models were chosen in preference to a single model for all isotope effects so as to avoid the problems encountered with redundancies when cyclic transition structures are involved.[26]

The calculations on these models were performed by using the Bebovib-IV program.[27,28] Standard single-bond lengths (r_{CO} = 1.43 Å, r_{CC} = 1.54 Å, r_{CH} = 1.09 Å) were used and adjusted by

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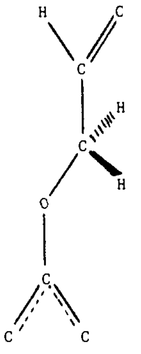
the program according to the bond orders in a particular model. Geometry was taken as tetrahedral for sp^3 and trigonal for sp^2 atoms. At first the geometry of atoms that change hybridization in the reaction was varied for different transition structures. This variation was found to have little influence on the isotope effects, however, so fixed intermediate geometries were adopted for such atoms in the transition structures **6** and **8**. The force constants used are listed in Table III. They are taken from or estimated from standard compilations[29-31] and are adjusted by the program according to the bond orders in particular models.



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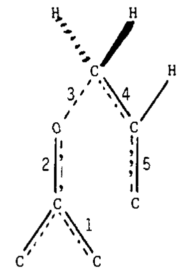

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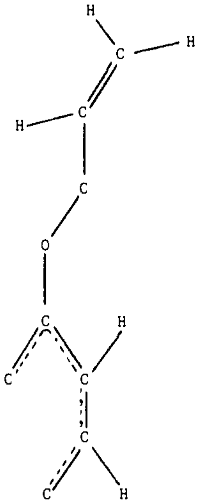

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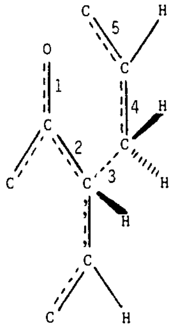

8 (TS)

Diagonal force fields were used for the reactants. In the transition structures **6** and **8**, off-diagonal **F** matrix elements for stretches of the reacting bonds were introduced by the usual procedure,[32] where (eq 1)

$$F_{mn} = a_{mn}(F_{mm}F_{nn})^{1/2} \tag{1}$$

and the a_{mn} values are given (eq 2) by

$$1 - a_{12}^2 - a_{23}^2 - a_{34}^2 - a_{45}^2 + a_{12}^2a_{34}^2 + a_{12}^2a_{45}^2 + a_{23}^2a_{45}^2 = D \tag{2}$$

where the subscripts indicate the bonds denoted by the corresponding numbers in the structures. The parameters a_{mn} measure the strength of the coupling between the stretching motions of bonds m and n. A positive value signifies that bond n contracts as m stretches (and vice versa) in the motion along the reaction coordinate. The curvature parameter, D, was generally assigned a value of ca. −0.05, which gave imaginary reaction coordinate frequencies of a few hundred cm^{-1}. Force constants of reacting bonds in the transition structures were assumed to be directly proportional to the bond order, n, of the reacting bonds. Tunnel corrections from the first term of the Bell equation[33] are included in all calculated isotope effects, but the corrections are small enough to be within the experimental errors of the observed isotope effects.

Table IV. Calculated Isotope Effects for Model **5** → **6**. The Role of Off-Diagonal **F** Matrix Elements

		k_{light}/k_{heavy} for		
n_{CO}/n_{CC}[a]	a_{mn}[b]	$^{16}O/^{18}O$[c]	α-H_2/D_2[d]	α-$^{12}C/^{14}C$[c]
0.9/0.1	a_{12}	1.0130	1.0341	1.0070
0.7/0.3		1.0126	1.0842	1.0085
0.5/0.5		1.0130	1.1388	1.0110
0.3/0.7		1.0141	1.1983	1.0143
0.1/0.9		1.0165	1.2622	1.0180
0.9/0.1	a_{23}	1.0536	1.0305	1.0100
0.7/0.3		1.0516	1.0851	1.0158
0.5/0.5		1.0478	1.1459	1.0228
0.3/0.7		1.0418	1.2132	1.0307
0.1/0.9		1.0320	1.2871	1.0384
0.9/0.1	a_{34}	1.0057	1.0600	1.0425
0.7/0.3		1.0071	1.1131	1.0451
0.5/0.5		1.0091	1.1704	1.0475
0.3/0.7		1.0120	1.2323	1.0491
0.1/0.9		1.0160	1.2978	1.0484
0.9/0.1	a_{45}	1.0040	1.0364	1.0144
0.7/0.3		1.0038	1.0863	1.0156
0.5/0.5		1.0041	1.1406	1.0176
0.3/0.7		1.0051	1.1999	1.0206
0.1/0.9		1.0066	1.2651	1.0247
exptl		1.0297	1.18	1.0306

[a] All bond changes synchronous as follows (bond, bond order change): 1, 1.5 → 1.0; 2, 1.0 → 2.0; 3, 1.0 → 0.0; 4, 1.0 → 2.0; 5, 2.0 → 1.0. C–O refers to C_α–O and C–C to C_γ–C_{ortho}. [b] See eq 1 and 2. The designated a_{mn} = 1.025. All other a_{mn} = 0. [c] At 220 °C. [d] At 180 °C.

Until the present work, the only isotope effects available for the Claisen rearrangement of allyl phenyl ether were for the α-d_2 (1.18 ± 0.02) and γ-d_2 (0.95 ± 0.02) species in the temperature range 170–195 °C.[13] They were interpreted as resulting from a concerted reaction with a transition structure in which bond breaking had proceeded to a greater extent than bond making.[13,20] One of the aims of our calculations was to determine whether such a transition structure also fits the heavy-atom isotope effects. The most obvious feature of the observed $^{12}C/^{14}C$ and $^{16}O/^{18}O$ effects is that they are fairly large and all in the normal (light faster than heavy) direction. Simple qualitative reasoning based on zero-point energy effects would make one expect quite small normal or even inverse heavy-atom isotope effects in a concerted rearrangement, for new bonds are being made to the isotopic atoms at the same time as old bonds are being broken. This should result in little net change in bonding to these atoms, and in zero-point energies associated with the vibrations involving them.

Our first task was to decide what factors were most important in determining the magnitudes of the various primary and secondary isotope effects. We tried a synchronous concerted model in which no change in total bond order to any atom was allowed: the C_α–C_β and C_β–C_γ bond orders of the allyl group were respectively 1.1, 1.9; 1.3, 1.7; 1.5, 1.5; 1.7, 1.3; 1.9, 1.1, and bond orders varied analogously for the other reacting bonds. In order to explore the role of the off-diagonal **F** matrix elements, we carried out four separate sets of calculations in each of which one pair (F_{mn} and F_{nm}, eq 1 and 2) was assigned a finite value and the other three pairs were zero. The results are shown in Tables IV and V.

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Table V. Calculated Isotope Effects for Model **7** → **8**. The Role of Off-Diagonal **F** Matrix Elements

		k_{light}/k_{heavy} for		
n_{CO}/n_{CC}[a]	a_{mn}[b]	γ-$^{12}C/^{14}C$[c]	γ-H_2/D_2[d]	o-$^{12}C/^{14}C$[c]
0.9/0.1	a_{12}	0.9960	0.9273	1.0098
0.7/0.3		0.9916	0.8836	1.0085
0.5/0.5		0.9880	0.8432	1.0080
0.3/0.7		0.9854	0.8058	1.0081
0.1/0.9		0.9837	0.7712	1.0087
0.9/0.1	a_{23}	1.0183	0.9492	1.0117
0.7/0.3		1.0100	0.8994	1.0160
0.5/0.5		1.0031	0.8546	1.0180
0.3/0.7		0.9978	0.8140	1.0195
0.1/0.9		0.9938	0.7770	1.0209
0.9/0.1	a_{34}	1.0297	0.9580	1.0062
0.7/0.3		1.0305	0.9148	1.0059
0.5/0.5		1.0285	0.8726	1.0048
0.3/0.7		1.0255	0.8326	1.0036
0.1/0.9		1.0218	0.7948	1.0028
0.9/0.1	a_{45}	1.0045	0.9311	0.9982
0.7/0.3		0.9999	0.8870	0.9971
0.5/0.5		0.9964	0.8463	0.9965
0.3/0.7		0.9937	0.8088	0.9965
0.1/0.9		0.9918	0.7740	0.9970
exptl		1.0362	0.95	1.0375

[a] All bond changes synchronous as follows (bond, bond order change): 1, 1.5 → 1.0; 2, 1.0 → 2.0; 3, 1.0 → 0.0; 4, 1.0 → 2.0; 5, 2.0 → 1.0. C–O refers to C_α–O and C–C to C_γ–$C_{orth.}$ [b] See eq 1 and 2. The designated a_{mn} = 1.025. All other a_{mn} = 0. [c] At 220 °C. [d] At 180 °C.

The secondary deuterium isotope effects are most easily interpreted. They show little dependence, barely beyond experimental error, on the magnitudes of the off-diagonal **F** matrix elements. In addition, they vary steadily with progress from reactant-like to product-like transition structures and support the earlier conclusion[13,20] that breaking of the C_α–O bond has proceeded farther than formation of the C_γ–C_{ortho} bond in the transition state.

The calculated heavy-atom isotope effects present a more complex picture. They appear to be of little use as measures of progress along the reaction coordinate; some decrease, and some do not even change monotonically. The most striking feature is that the effects tend to be small or even inverse unless the isotopically substituted atom is between two bonds whose stretches are coupled by off-diagonal **F** matrix elements. It has previously been noted that isotope effects can be significantly enhanced over those expected from zero-point energy effects if motion of the isotopically substituted atom contributes to the motion along the reaction coordinate.[34] The fairly large normal values of the experimental heavy-atom isotope effects thus mean that the process is concerted and the bonding changes are rather strongly coupled. None of the models of Tables IV and V, however, satisfactorily reproduces all of the experimental isotope effects.

The next logical step was to go to models in which all bonding changes are strongly and equally coupled. Table VI reports the results of calculations in which all a_{mn} = 0.6 for both models. The first five entries refer to completely synchronous processes in which the total bond order to each atom remains constant from the most reactant-like to the most product-like transition structure. In the remaining entries, the formation of the C_γ–C_{ortho} bond lags behind the breaking of the C_α–O bond but other bonding changes remain synchronous.

It is immediately obvious that no one of the completely synchronous transition structures gives isotope effects that agree with the experimental ones. The looser transition structures improve the situation. Those with n_{CO}/n_{CC} = 0.5/0.2, 0.5/0.1, 0.4/0.3, and 0.4/0.2 give tolerable fits to four of the isotope effects, but the calculated α-carbon effect is too large, and the ortho-carbon effect too small. The model with n_{CO}/n_{CC} = 0.3/0.3 fits best overall, but the α-carbon effect is much too large, and the secondary deuterium effects are off by somewhat more than experimental error.

Table VI. Calculated Isotope Effects for Models **6** → **7** and **7** → **8** with Equal Coupling of Bond Changes[a]

	k_{light}/k_{heavy} for					
$n_{CO}/$ n_{CC}[b]	$^{16}O/$ ^{18}O[c]	α-$H_2/$ D_2[d]	α-$^{12}C/$ ^{14}C[c]	γ-$^{12}C/$ ^{14}C[c]	γ-$H_2/$ D_2[d]	o-$^{12}C/$ ^{14}C[c]
0.9/0.1	1.0360	1.0456	1.0297	1.0294	0.9583	1.0130
0.7/0.3	1.0354	1.0995	1.0338	1.0243	0.9084	1.0166
0.5/0.5	1.0343	1.1591	1.0387	1.0197	0.8640	1.0181
0.3/0.7	1.0325	1.2256	1.0443	1.0159	0.8239	1.0193
0.1/0.9	1.0284	1.3000	1.0492	1.0129	0.7873	1.0205
0.7/0.2	1.0354	1.0995	1.0338	1.0314	0.9328	1.0209
0.7/0.1	1.0354	1.0995	1.0338	1.0365	0.9595	1.0217
0.6/0.3	1.0349	1.1285	1.0361	1.0272	0.9087	1.0211
0.6/0.2	1.0349	1.1285	1.0361	1.0326	0.9332	1.0242
0.6/0.1	1.0349	1.1285	1.0361	1.0393	0.9597	1.0256
0.5/0.4	1.0343	1.1591	1.0387	1.0249	0.8858	1.0220
0.5/0.3	1.0343	1.1591	1.0387	1.0302	0.9089	1.0256
0.5/0.2	1.0343	1.1591	1.0387	1.0356	0.9335	1.0287
0.5/0.1	1.0343	1.1591	1.0387	1.0409	0.9598	1.0305
0.4/0.3	1.0335	1.1914	1.0414	1.0336	0.9090	1.0301
0.4/0.2	1.0335	1.1914	1.0414	1.0391	0.9336	1.0332
0.4/0.1	1.0335	1.1914	1.0414	1.0440	0.9601	1.0349
0.3/0.3	1.0325	1.2256	1.0443	1.0375	0.9088	1.0346
0.3/0.2	1.0325	1.2256	1.0443	1.0427	0.9336	1.0369
0.3/0.1	1.0325	1.2256	1.0443	1.0473	0.9605	1.0394
exptl	1.0297	1.18	1.0306	1.0362	0.95	1.0375

[a] Bond changes are synchronous as defined in footnotes *a* of Tables IV and V, except when $n_{CO} + n_{CC} < 1$, the formation of the C_γ–C_{ortho} bond lags behind the rest of the bonding changes. All a_{mn} = 0.6 (eq 1 and 2). [b] C–O refers to C_α–O and C–C to C_γ–C_{ortho}. [c] At 220 °C. [d] At 180 °C.

There is, of course, no a priori reason why the couplings of the stretching motions of all reactive bonds (the a_{mn} in eq 1 and 2) need be equal. The results so far suggest a rather loose transition structure in which the C_γ–C_{ortho} and C_α–O bond orders add up to considerably less than unity. Following this line of thought, one might guess that coupling of bond stretches within the allylic and phenoxy moieties should be stronger than the coupling between them. To simulate this situation, we assigned values of 0.5 to all a_{mn} in which one bond was the forming C_γ–C_{ortho} or the breaking C_α–O bond and values of 0.8 to all other a_{mn}. Results for these models are given in Table VII. The models are otherwise identical with those of Table VI.

Not surprisingly, the completely synchronous models still fail to account for the experimental effects. The looser models do much better. Those with n_{CO}/n_{CC} = 0.5/0.2 and 0.5/0.1, especially the latter, predict all experimental isotope effects if a generous but not unlikely margin of error is assumed. The model with n_{CO}/n_{CC} = 0.4/0.2 predicts isotope effects in excellent agreement with the experimental values except for a 0.5% discrepancy on the α-carbon effect.

Further minor adjustments of parameters could undoubtedly lead to a still better fit, but the important characteristics of the transition structure are already apparent. The phenoxy and allylic fragments are rather loosely bonded (total $n_{CO} + n_{CC}$ = 0.6–0.7), and breaking of the C_α–O bond has proceeded to the extent of 50–60%, while formation of the C_γ–C_{ortho} bond is only 10–20% complete. In addition, the stretching motions of the reacting bonds are strongly coupled even though the rearrangement is not synchronous.

No SCF–MO calculations have been reported on the allyl phenyl ether rearrangement, but the allyl vinyl ether rearrangement has been treated by MNDO[16] and ab initio[35] methods. For

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Table VII. Calculated Isotope Effects for Models **6** → **7** and **7** → **8** with Unequal Coupling of Bond Changes[a]

n_{CO}/ n_{CC}[b]	k_{light}/k_{heavy} for					
	^{16}O/ ^{18}O[c]	α-H_2/ D_2[d]	α-^{12}C/ ^{14}C[c]	γ-^{12}C/ ^{14}C[c]	γ-H_2/ D_2[d]	*o*-^{12}C/ ^{14}C[c]
0.9/0.1	1.0313	1.0403	1.0251	1.0280	0.9538	1.0168
0.7/0.3	1.0311	1.0925	1.0283	1.0200	0.9012	1.0184
0.5/0.5	1.0311	1.1502	1.0328	1.0151	0.8575	1.0187
0.3/0.7	1.0311	1.2154	1.0389	1.0116	0.8185	1.0192
0.1/0.9	1.0297	1.2942	1.0478	1.0090	0.7829	1.0201
0.7/0.2	1.0311	1.0925	1.0283	1.0263	0.9261	1.0228
0.7/0.1	1.0311	1.0925	1.0283	1.0336	0.9544	1.0260
0.6/0.3	1.0311	1.1206	1.0304	1.0231	0.9016	1.0232
0.6/0.2	1.0311	1.1206	1.0304	1.0293	0.9264	1.0276
0.6/0.1	1.0311	1.1206	1.0304	1.0365	0.9547	1.0306
0.5/0.4	1.0311	1.1502	1.0328	1.0205	0.8790	1.0234
0.5/0.3	1.0311	1.1502	1.0328	1.0262	0.9019	1.0280
0.5/0.2	1.0311	1.1502	1.0328	1.0323	0.9267	1.0323
0.5/0.1	1.0311	1.1502	1.0328	1.0395	0.9550	1.0353
0.4/0.3	1.0311	1.1817	1.0356	1.0293	0.9022	1.0328
0.4/0.2	1.0311	1.1817	1.0356	1.0354	0.9270	1.0370
0.4/0.1	1.0311	1.1817	1.0356	1.0354	0.9552	1.0399
0.3/0.3	1.0311	1.2154	1.0401	1.0325	0.9026	1.0375
0.3/0.2	1.0311	1.2154	1.0401	1.0386	0.9273	1.0417
0.3/0.1	1.0311	1.2154	1.0401	1.0457	0.9555	1.0446
exptl	1.0297	1.18	1.0306	1.0362	0.95	1.0375

[a] Bond changes are synchronous as defined in footnotes of Tables IV and V, except when $n_{CO} + n_{CC} < 1$, the formation of the C_γ–C_{ortho} bond lags behind the rest of the bonding changes. For **5** → **6**, a_{12} = 0.8, a_{23} = 0.5, a_{34} = 0.5, a_{45} = 0.8; for **7** → **8**, a_{12} = 0.8, a_{23} = 0.5, a_{34} = 0.5, a_{45} = 0.8 (eq 1 and 2). [b] See footnote *b*, Table VI. [c] At 220 °C. [d] At 180 °C.

comparison with our conclusions, bond lengths from these calculations are translated into bond orders using the Pauling relation[28]

$$r_i = r_i^0 - 0.3 \ln n_i$$

where r_i is the actual bond length, r_i^0 is the bond length for the corresponding single bond, and n_i is the bond order. The MNDO calculations then predict the C–C bond to be 32% formed and the C–O bond to be 15% broken in the transition structure, so that the allyl and vinyloxy fragments are rather tightly bound. In contrast, the ab initio calculations predict a very loose transition structure, with the C–O bond 82% broken and the C–C bond only 9% formed (for the chair structure). Qualitatively we are in much better agreement with the ab initio results, though our transition structure is not as loose (50–60% bond breaking, 10–20% bond formation). At least part of the quantitative discrepancy could be illusory, for it is quite possible that the empirical Pauling relation underestimates bond orders at the considerable bond extensions of the ab initio model. Isotope effects were calculated for neither the MNDO nor the ab initio models, so the ability of either to predict them remains untested. There is, of course, no reason that transition structures need be the same for the allyl phenyl and allyl vinyl ether rearrangements, and the α-secondary deuterium isotope effects (1.18 at 170–195 °C[13] and 1.092 at 160 °C,[14] respectively) suggest that they may differ.

The temperature dependence has been measured experimentally only for the secondary isotope effects. No significant variation of k_H/k_D with temperature over the range 170–195 °C was found for either the α- or γ-deuterium effects.[13] Our calculations (Table VIII) show the expected normal temperature dependence for the α-deuterium effect and inverse temperature dependence for the γ-deuterium effect, but the range is small. Over a 30° range, k_H/k_D changes by 0.02 or less, the reported experimental error.

Table VIII. Temperature Dependence of Isotope Effects for Models **6** → **7** and **7** → **8** with Unequal Coupling of Bond Changes[a]

	Arrhenius parameters for					
	^{16}O/ ^{18}O	α-H_2/ D_2	α-^{12}C/ ^{14}C	γ-^{12}C/ ^{14}C	γ-H_2/ D_2	*o*-^{12}C/ ^{14}C
			n_{CO}/n_{CC}[b] = 0.5/0.2			
ΔE_a[c]	0.0204	0.1752	0.0246	0.0041	−0.1730	0.0187
A_l/A_h	1.0099	0.9468	1.0072	1.0280	1.1228	1.0130
k_l/k_h[d]	1.0311	1.1502	1.0328	1.0323	0.9267	1.0323
			n_{CO}/n_{CC}[b] = 0.5/0.1			
ΔE_a[c]	0.0204	0.1752	0.0246	0.0102	−0.1338	0.0217
A_l/A_h	1.0099	0.9468	1.0072	1.0288	1.1079	1.0126
k_l/k_h[d]	1.0311	1.1502	1.0328	1.0328	0.9550	1.0353
			n_{CO}/n_{CC}[b] = 0.4/0.2			
ΔE_a[c]	0.0212	0.2140	0.0279	0.0082	−0.1729	0.0217
A_l/A_h	1.0090	0.9318	1.0065	1.0268	1.1231	1.0143
k_l/k_h[d]	1.0311	1.1817	1.0356	1.0354	0.9270	1.0370

[a] See footnote *a*, Table VII. Calculations at 160, 180, 200, and 220 °C. [b] See footnote *b*, Table VI. [c] $E_{heavy} - E_{light}$ in kcal mol^{-1}. [d] From Table VII.

Experimental temperature dependences are not available for the heavy-atom isotope effects, but values of Arrhenius parameters from the calculated isotope effects are listed in Table VIII for the three best-fit models. All temperature dependences are normal (decreasing isotope effect with increasing temperature). The oxygen and α-carbon isotope effects reside mainly in the exponential factor ($E_{heavy} - E_{light}$). The zero-point energy factor might be expected to be dominant when a bond is loosened by 50–60% at the transition state. The γ-carbon isotope effect is, however, determined mainly by the Arrhenius pre-exponential factor, A_{light}/A_{heavy}. The pre-exponential factor also makes a sizable, though not dominant, contribution to the ortho-carbon isotope effect. The C_γ–C_{ortho} bond is just beginning to form at the transition state, so it is reasonable that the motion of the two atoms toward each other should be an important process at the transition state. Such a process is reflected in the effective mass along the reaction coordinate, which is temperature independent. In contrast, zero-point energy effects are expected to be small when a bond is only 10–20% formed at the transition state.

Discussion and Conclusion

To our knowledge no other measurements of heavy-atom KIE in Claisen rearrangements have been reported. Insofar as ring-labeled KIE are concerned, White and co-workers compared the rates of rearrangement of allyl *p*-tolyl and allyl *p*-[2,6-$^2H_2$]tolyl ethers, searching, in fact, for a primary deuterium KIE.[36] No difference in rates was found, within experimental error. This aromatic Claisen rearrangement should lead to a small secondary deuterium KIE, such as has been found in another concerted rearrangement, the benzidine rearrangement.[37] However, the method of measuring rates in the Claisen rearrangement[36] was not precise enough to detect a secondary deuterium KIE. Thus, our KIE are the first unquestionable definitions of a Claisen rearrangement in which significant bond breaking and bond making occur in the transition structure. The results do not define the *shape* of the transition structure, such as is shown in **4**. However, our computations of bond orders allow for a closer defintion of the extents of breaking and making of bonds in the transition structure than possible hitherto. Further, the question of the suitability of deuterium KIE to making decisions on synchronicity cannot be applied to the heavy-atom KIE. That such KIE are substantial for all labeled positions cannot be said to be accommodated by *any* mechanism of rearrangement[15] but is attributable only to a concerted one. Our conclusion is that our experimental data define the rearrangement of **1** into **2** as being nonsynchronous and that our calculations accommodate also the earlier deuterium KIE.[13] The isotope effects thus provide a consistent picture of bonding in the transition structure and of the dynamics of the system as it passes through the transition state.

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Experimental Section

Solvent Diphenyl Ether. Commercial diphenyl ether (500 g) was stirred and heated with metallic sodium for 4 h. A precipitate was filtered off, and the diphenyl ether was washed successively with dilute hydrochloric acid, sodium hydroxide solution, and water and dried with calcium chloride before being distilled under reduced pressure.

Preparation of Labeled Substrates. The preparation of [3-^{14}C]allyl phenyl ether ([α-^{14}C]-**1**) and [1-^{14}C]allyl phenyl ether ([γ-^{14}C]-**1**) has been described earlier.[12]

Allyl Phenyl [^{18}O]Ether. To a stirred suspension of 8.0 g (41.7 mmol) of benzenediazonium tetrafluoroborate in 8.0 mL of water (enriched in ^{18}O to the extent of 10.5 mol·%) was added dropwise 2 mL of concentrated sulfuric acid. The mixture was heated until the evolution of nitrogen ceased. The acid solution was extracted with ether several times, and the combined ether solution was extracted with 10% sodium hydroxide solution. The cooled alkaline aqueous solution was acidified with concentrated hydrochloric acid, and the acid solution was extracted several times with ether. Workup of the ether solution gave crude [^{18}O]phenol, which was distilled under reduced pressure to give 1.6 g (17 mmol, 41%) of product with a calculated enrichment of 8.3%. This preparation was repeated several times. To a solution of 5.5 g (58.5 mmol) of [^{18}O]phenol and 7.1 g (58.5 mmol) of allyl bromide was added 8 g of anhydrous potassium carbonate. The mixture was stirred and boiled for 6 h, cooled, diluted with water, and extracted with ether several times. The combined ether solution was extracted with 10% sodium hydroxide solution and dried over potassium carbonate. Workup gave 6.3 g (47 mmol, 81%) of [^{18}O]-**1**. GC–MS in the selected ion monitoring (SIM) mode showed that the product was enriched with ^{18}O to the extent of 7.3%. The product was mixed with 2.9 g of unenriched allyl phenyl ether and the mixture was distilled at 85–86 °C (15 mmHg) to give 8.7 g of [^{18}O]-**1** containing a calculated enrichment of 5%.

Allyl [2-^{14}C]Phenyl Ether ([2-^{14}C]-1). A mixture of 168 mg of 2-nitro[1-^{14}C]aniline (Hoechst, Frankfurt, FRG; 30.7 mCi/g) and 40 g (290 mmol) of 2-nitroaniline was dissolved in 200 mL of 50% hypophosphorous acid. A small amount of Cu_2O was added and to the mixture at 0 °C was added dropwise a solution of 25 g (360 mmol) of sodium nitrite in 80 mL of water. The solution was made alkaline with 40% sodium hydroxide solution, and nitrobenzene was extracted several times with ether. The dried ether solution was evaporated, and the nitrobenzene was washed with ether through a column of alumina, giving 30.4 g (247 mmol, 83%) of [2-^{14}C]nitrobenzene, having a calculated activity of 17 mCi/mol. The nitrobenzene (5.0 g, 40.7 mmol) was reduced by stirring and boiling for 3 h with 17.4 g (17 mmol) of triethylamine, 6.6 g of 90.5% formic acid, and 250 mg of 10% Pd/C. The catalyst was removed after diluting the mixture with 100 mL of methylene chloride. The methylene chloride solution was dried and evaporated, and the residue was distilled under reduced pressure to give 2.9 g (31.4 mmol, 77%) of [2-^{14}C]aniline. The labeled aniline was diazotized in cold aqueous sulfuric acid and the cold diazonium solution was added dropwise to boiling 5% sulfuric acid. [2-^{14}C]Phenol was extracted with ether and distilled under reduced pressure to give 2.4 g (2.6 mmol, 82%) of slightly yellow product. This product was mixed with 2.3 g of unlabeled phenol and the mixture was distilled under reduced pressure to give 4.2 g of [2-^{14}C]phenol with a calculated activity of 8 mCi/mol. The product was converted into [2-^{14}C]-**1** as described above with [^{18}O]-**1**.

Thermal Rearrangement of Labeled 1. A standard procedure was used for all of the rearrangements up to the stage of isolating the product *o*-allylphenol. Thereafter the treatment of the product depended on the isotopic label and the method of isotope assay. In the case of ^{14}C labeling the product was converted into its phenylurethane. In the case of ^{18}O labeling the product was converted into *o*-methoxybenzoic acid. Examples of procedures follow.

Rearrangement of [α-^{14}C]-1. Low Conversion. A solution of 611 mg (4.56 mmol) of [α-^{14}C]-**1** in 13.7 g of diphenyl ether was sealed under argon in a snap-neck ampule. The ampule was placed in a thermostatically controlled oven at 220 °C. The ampule was removed after 55 min, cooled quickly, and opened. A sample of the solution was used, neat, for ^{1}H NMR spectroscopy from which the extent of rearrangement was calculated to be 8.8%. Assay of **1** was made by using the doublet for $-OCH_2-$ at 4.4 ppm and of **2** by using the doublet for ring-attached CH_2 at 3.3 ppm. All of the diphenyl ether solution was then taken up in 50 mL of petroleum ether and the phenolic product was extracted with 5 × 25 mL of 10% aqueous sodium hydroxide solution. The sodium hydroxide solution was washed once with petroleum ether and acidified with concentrated hydrochloric acid. The acidic solution was extracted with 5 × 50 mL of ether, and the combined ether solution was dried over magnesium sulfate and evaporated. The residue (56.3 mg) was chromatographed on a column of silica gel (J. T. Baker, 60–200 mesh). Elution with 50-mL portions of benzene:petroleum ether, 8:3, was continued until TLC showed that *o*-allylphenol was no longer being extracted. Workup of these eluates gave 54.4 mg (8.9% conversion) of *o*-[1-^{14}C]allylphenol ([γ-^{14}C]-**2**). The column was washed with ether to give, after evaporation of the ether, 2 mg of unidentified material. Finally, the column was washed with methanol to give 2.5 mg of unidentified material.

High Conversion. A solution of 158 mg of [α-^{14}C]-**1** in 3.5 g of diphenyl ether was heated similarly for 24 h. ^{1}H NMR spectroscopy showed that conversion into *o*-allylphenol was complete. Workup as described above gave 157 mg of residue, from which chromatography gave 150.4 mg (96%) of [γ-^{14}C]-**2** and 3.4 mg (ether) and 4.2 mg (methanol) of unidentified products.

In all, six low-conversion rearrangements of [α-^{14}C]-**1** were carried out in two sets of three ampules. For each set of three low-conversion ampules one high-conversion ampule was used. The data for all runs are listed in Table I.

Conversion of *o*-Allylphenol (2) into Its Phenylurethane. To a solution of 95.3 mg (71.1 mmol) of isolated [γ-^{14}C]-**2** and 84.7 mg (71.1 mmol) of freshly distilled phenyl isocyanate in 5 mL of dry benzene was added 1 drop of pyridine. The mixture was boiled for 1 h, after which the benzene was evaporated. The residue was chromatographed on a column of silica gel, eluting with ether:petroleum ether, 1:1, to give 175 mg (69.3 mmol, 97.5%) of the phenylurethane of *o*-allylphenol. The product was sublimed four times, yielding 114 mg (45.1 mmol, 63%), mp 106–107 °C (lit. mp 106–107 °C[38]). The phenylurethane was used for scintillation counting with the use of a Beckman Instruments counter, Model LS 7000. A sample of 3.000 ± 0.001 mg was weighed on a Cahn balance and was dissolved in 10 mL of cocktail (Packard SCINT-0 6013183). The cocktail was counted 12 times. Three such samples were weighed and counted in this way. The average of each 12 counts was in the range of 32290–33390 with a standard deviation of 0.03 to 0.19%. All counts were then averaged and expressed as counts/mg of phenylurethane for calculation of the KIE. Thus, six measurements of KIE were obtained from two sets, each consisting of three low-conversion rearrangements and one high-conversion rearrangement.

Analogous rearrangements of [γ-^{14}C]-**1** into [α-^{14}C]-**2** and of [2-^{14}C]-**1** into [2-^{14}C]-**2** were carried out. Conversions into the phenylurethane and counting followed in the same way.

KIE were calculated with the use of eq 3.[39]

$$R_p/R_o = [1 - (1 - F)^{k_2/k_1}]/F \tag{3}$$

Rearrangements of [^{18}O]-**1** into [^{18}O]-**2** were carried out in the way described. The [^{18}O]-**2** was prepared for multiscan mass spectrometry as follows.

Conversion of [^{18}O]-2 into *o*-[^{18}O]Methoxybenzoic Acid. An excess (5 mL) of dimethyl sulfate was added dropwise to a solution of 179 mg (1.33 mmol) of [^{18}O]-**1** in 5 mL of 10% potassium hydroxide solution. The mixture was heated at 90 °C for 1 h and left at room temperature for 12 h. The product was extracted with petroleum ether, which was washed once with 10% sodium hydroxide solution and worked up to give 183 mg (1.24 mmol, 93%) of *o*-allyl[^{18}O]anisole. This product was suspended in 5 mL of 10% potassium hydroxide solution to which was added 1.95 g (12.4 mmol) of potassium permanganate. The mixture was stirred at room temperature for 3 days, after which a small amount of sodium bisulfite was added. Manganese dioxide was removed by filtration, and to the filtrate was added 5 mL of saturated calcium chloride solution. The mixture was allowed to stand 5 h, after which the precipitate of calcium oxalate was filtered. The filtrate was acidified with hydrochloric acid and was extracted with ether several times. The combined ether solution was dried over magnesium sulfate and evaporated to give *o*-[^{18}O]methoxybenzoic acid. The product was sublimed twice and gave 71.5 mg (0.47 mmol, 38%), mp 99–100.5 °C, for mass spectrometry.

Relative abundances of the ions *m/e* 152 and 154 were measured by multiscan mass spectrometry. A Hewlett-Packard quadrupole mass spectrometer, Model 5995, was used in the SIM mode. Samples were introduced via the solid sample inlet with a direct insertion probe. Approximately 1500 scans were made per sample and were analyzed in 25 blocks of 60 scans each. Details of the method and of calculating KIE have been described earlier.[40]

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Registry No. 1, 1746-13-0; $[^{18}O]$-**1**, 102430-96-6; $[2\text{-}^{14}C]$-**1**, 115942-44-4; **2**, 1745-81-9; $[\delta\text{-}^{14}C]$-**2**, 115942-45-5; $[\alpha\text{-}^{14}C]$-**2** PhNHCO$_2$H ester, 115942-46-6; $[2\text{-}^{14}C]$-**2** PhNHCO$_2$H ester, 115942-47-7; $[\gamma\text{-}^{14}C]$-**2**, 115942-48-8; $[\alpha\text{-}^{14}C]$-**2**, 115942-49-9; $[2\text{-}^{14}C]$-**2**, 115942-50-2; $[^{18}O]$-**2**, 115942-51-3; ^{14}C, 14762-75-5; ^{18}O, 14797-71-8; ^{2}H, 7782-39-0; $[^{18}O]$phenol, 1739-18-0; benzenediazonium tetrafluoroborate, 369-57-3; allyl bromide, 106-95-6; 2-nitro$[1\text{-}^{14}C]$aniline, 98703-87-8; $[2\text{-}^{14}C]$nitrobenzene, 98703-86-7; $[2\text{-}^{14}C]$aniline, 83548-27-0; $[2\text{-}^{14}C]$phenol, 115942-43-3; *o*-allyl$[^{18}O]$anisole, 115942-52-4; *o*-$[^{18}O]$methoxybenzoic acid, 115942-53-5.

Synthesis of CMP-NeuAc from *N*-Acetylglucosamine: Generation of CTP from CMP Using Adenylate Kinase[1,2]

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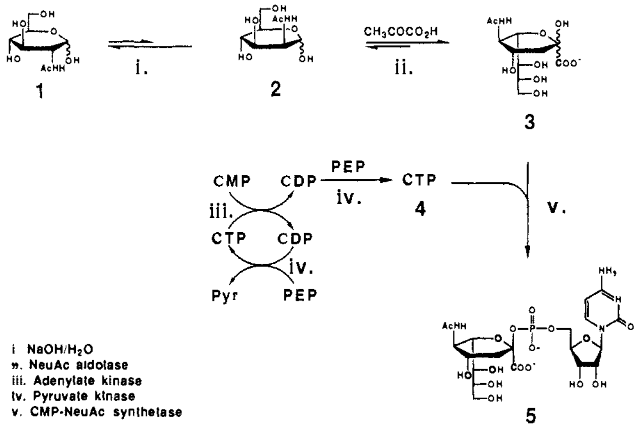
Abstract: This paper describes a multigram-scale synthesis of cytidine 5′-monophospho-*N*-acetylneuraminic acid (CMP-NeuAc) from *N*-acetylmannosamine, pyruvate, cytidine 5′-monophosphate (CMP), and phosphenolpyruvate (PEP) using three enzymes. *N*-Acetylmannosamine (produced in mole quantities by base-catalyzed epimerization of *N*-acetylglucosamine) and sodium pyuvate react to form *N*-acetylneuraminic acid (NeuAc) in a reaction catalyzed by NeuAc aldolase enclosed in a dialysis membrane. CTP is generated in situ from CMP by using adenylate kinase, pyruvate kinase, and PEP. The only purification step in the synthesis is the final separation of CMP-NeuAc from the reaction mixture by ion-exchange chromatography. CMP-NeuAc generated by this procedure was used to form sialic acid terminated glycoconjugates in reactions catalyzed by sialyltransferases.

Sialic acids (derivatives of neuraminic acid) are components of glycoproteins and glycolipids.[5-9] These compounds play an important role in biological recognition. Cell-surface glycoconjugates can serve as binding sites for antibodies, enzymes, hormones, toxins, lectins, bacteria, drugs, and viruses.[10-16] They also can function as cellular labels, sorting newly synthesized proteins between cellular compartments and influencing growth through intercellular contact.[17] Transformed and malignant cells often have modified glycolipids.[18-20]

Scheme I. Generation of CMP-NeuAc from *N*-Acetylglucosamine



Many of the glycoconjugates found in mammalian biochemistry share a similar structural motif: Their terminal carbohydrate residue is a derivative of *N*-acetylneuraminic acid (NeuAc, *N*-acetyl-5-amino-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid). NeuAc[21-26] and its glycosides[27] have been synthesized chemically and NeuAc has been isolated from natural sources;[28-31] analogues of NeuAc have been synthesized chemically.[32] Glycosides of NeuAc pose several synthetic problems in addition to the usual need for procedures for protection and

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(4) American Cancer Society postdoctoral fellow, Grant PF-2762; 1987.

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