Borchardt and Saunders[60] examined the influence of ion association upon the syn–anti dichotomy (*vide supra*) for eliminations from quaternary ammonium salts. In order to provide substantial, but not exclusive, formation of trans olefin by syn elimination[65] and the possibility for base strength variation, reactions of 3-hexyl-*4-d*-trimethylammonium iodide with alkali metal phenoxides in *t*-BuOH–Me_2SO mixtures were studied (Table VII).

That the proportion of *trans*-3-hexene resulting from syn elimination decreases as the phenoxide cation is varied (Li ~ NMe_4 > Na > K (Table VII, entries 1–4)) may be understood by considering eq 10 and structure **24.** For $PhONMe_4$, the equilibrium in eq 10 is shifted to the right and the high concentration of dissociated base favors syn elimination. If this interpretation is correct, entries 1–3 indicate increases in the dissociated base concentration in the order Li > Na > K for alkali metal phenoxides. This ordering may be rationalized if the stability of M^+X^- is assumed to control the equilibrium position in eq 10. An alternative explanation involves decreased reactivity of the associated base in the order PhOK > PhONa > PhOLi so that the proportion of reaction with dissociated phenoxide decreases in the same order.

Data for substituted potassium phenoxides (entries 5–7) are interpreted in similar fashion. The equilibrium in eq 10 would be farther to the right for the more weakly associated bases, such as *p*-nitrophenoxide, enhancing syn elimination.

Table VII
Percent *trans*-3-Hexene Formed by Syn Elimination from 3-Hexyl-*4-d*-trimethylammonium Iodide

Entry	Base	Solvent	% syn elimination
1	PhOLi	*a*	74
2	PhONa	*a*	55
3	PhOK	*a*	34
4	$PhONMe_4$	*a*	67
5	PhOK	*b*	38
6	*o*-$NO_2C_6H_4OK$	*b*	59
7	*p*-$NO_2C_6H_4OK$	*b*	69

[a] 80% *t*-BuOH–20% Me_2SO. [b] 5% *t*-BuOH–95% Me_2SO.

These results are all compatible with a mechanism in which associated phenoxide favors anti elimination, but dissociated phenoxide facilitates syn elimination, in agreement with the predictions of Závada and Sicher.[62,63]

Summary

The investigations described above amply illustrate an important influence of ionic association upon orientation and stereochemistry in base-promoted β elimination. Dependence of these effects upon the charge type of the leaving group is underscored. Recognition of these factors will provide new mechanistic insight into base-induced β-elimination reactions and may lead to improved reagents for alkene synthesis.

The author is indebted to his coworkers, whose names appear in the cited literature. Financial support from the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and the Society of Sigma Xi is gratefully acknowledged.

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[65] Reactions of 3-hexyl-*4-d*-trimethylammonium iodide with PhOK in *t*-BuOH and *t*-BuOH–Me_2SO form *cis*-3-hexene by 94–98% anti elimination. However, *trans*-3-hexene originates via both syn and anti elimination processes.[60]

Too Many Rearrangements of Cyclohexadienones

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Molecular rearrangements have long entranced the romantic spirits among organic chemists. While their colleagues plodded away, measuring minute rate differences and defining the structures of transition states for common reactions ever more precisely, students of molecular rearrangements raced ahead, happily anticipating that molecules would turn themselves inside out, rings would shrink or expand, chains would entwine and rearrange, all apparently at the whim of an imaginative and unfettered nature.

This undisciplined license was abhorrent to chemical puritans, who determined to restrict organic molecules to a small set of allowed reactions, and to forbid all others. The puritans have largely prevailed. Their rules, "thou shalt not undergo suprafacial [1,3] shifts; thou shalt not undergo antarafacial [3,3] shifts . . .",[1] are now among the familiar bedrocks of the theory of organic chemistry.

Bernard Miller received his Ph.D. from Columbia University, where he worked on free-radical halogenations. Finding these reactions insufficiently radical, he accepted a postdoctoral fellowship in steroid synthesis at the University of Wisconsin. This invaluable experience having taught him that his talents did not lie in natural product chemistry, he joined the American Cyanamid Co., synthesizing insecticides. Finding insects unexpectedly tough adversaries, he entered the academic life at the University of Massachusetts, where he is presently Professor of Chemistry. In addition to his research papers, he is the author of some 20 patents, none of which has ever increased his income. His present research interests lie principally in the fields of molecular rearrangements and the reactions of blocked aromatic molecules.

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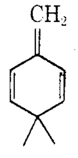
[1] R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1971; see also, M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10**, 761 (1971).

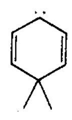
Organic molecules appear to chafe under these restrictions, and increasing numbers of examples of devious or blatant defiance of the rules are appearing.[2] No class of compounds exhibits more varied types of rearrangements, both allowed and (apparently) forbidden, than cyclohexadienones. Thus far, examples of apparent [1,2], [1,3], [1,4], [1,5], [3,3], [3,4], [3,5], and [5,5] sigmatropic shifts have been observed in the rearrangements of cyclohexadienones. This Account describes some of these rearrangements and attempts to consider the reasons for the existence of such an overabundance of types of migrations.

Thermal Rearrangements

Cyclohexadienones are "blocked aromatic molecules" in which the migration of a single bond can convert a nonaromatic molecule to an aromatic one. Other members of this class include the methylenecyclohexadienes (semibenzenes) such as **1**,[3] the recently discovered cyclohexadienyl carbenes (**2**),[4] and the still unknown cyclohexa-1,2,4-trienes (**3**). Cyclohexadienones constitute the least reactive of this series of molecules, since the greater stability of a carbonyl over an enol structure tempers the normal driving force for aromatization of the molecule. However, cyclohexadienones do rearrange quite rapidly compared to acyclic analogs, presumably because the transition states for their rearrangements attain a degree of aromatic character.



1



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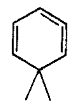
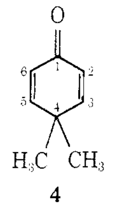


3

The most varied group of rearrangements of cyclohexadienones are those induced by acid catalysis. Before going on to the acid-catalyzed reactions, however, it is worth briefly reviewing the thermally induced rearrangements of cyclohexadienones. These form a comparatively docile, well-behaved set of rearrangements, which will form a useful benchmark against which to compare the acid-catalyzed reactions.

Simple cross-conjugated cyclohexadienones such as **4** (para dienones), in which only alkyl groups can migrate, are stable to heat, and no thermal reactions of such compounds have been reported. The linearly conjugated isomers (ortho dienones) such as **5** dimerize readily at relatively mild temperatures,[5,6] although more substituted analogs are more stable. No thermal rearrangements of the monomers, even at the temperatures necessary for cleavage of the Diels–Alder adducts, have been reported.[7]



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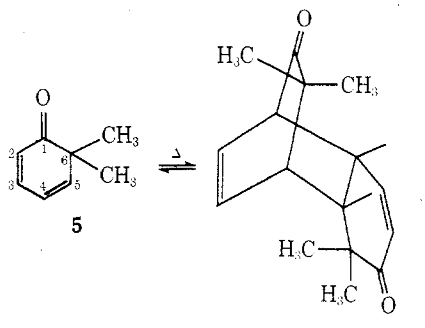
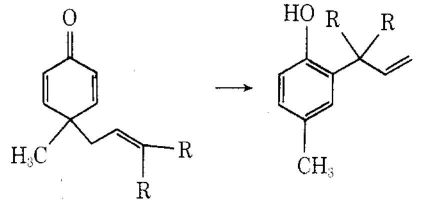
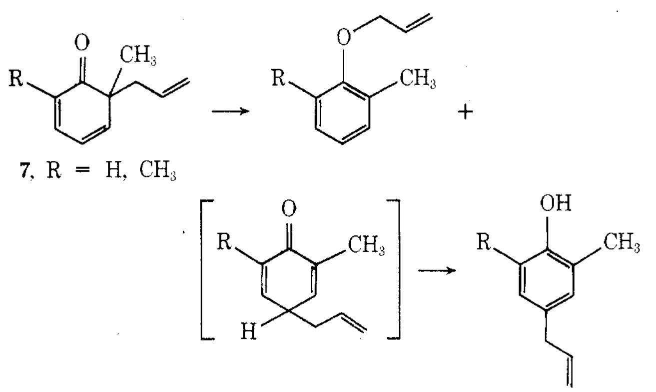


5

In contrast, migrations of allyl groups in cyclohexadienones occur readily at low temperatures. Rearrangements of dienone **6a** occurs smoothly at temperatures as low as 80°, while **6b** is reported to rearrange "slowly" at room temperature.[8] Cope rearrangements of comparably substituted acyclic molecules normally require temperatures of approximately 200°. Rearrangements of ortho dienones such as **7** give mixtures of *p*-allylphenols and ethers.[9,10] Although the more stable phenols are formed in higher yields than the less stable phenyl ethers, formation of the phenols must proceed in two steps, the initial step leading to cross-conjugated cyclohexadienones (which may be isolated in some cases).[11,12] Thus, allylic migrations in ortho dienones give rise initially to the less stable of the two observed products. A satisfactory explanation for this phenomenon has not yet been advanced.



6a, R = H
b, R = CH3



7, R = H, CH3

[3,3] shifts of benzyl groups would be highly endothermic, since the aromatic rings would be disrupted, and no such rearrangements occur. Instead, benzyl groups in ortho dienones undergo thermally allowed [1,5] migrations when such migrations are feasible. Although higher temperatures are required than for the [3,3] shifts of allyl groups, these rearrangements still proceed under relatively mild conditions. Dienone **11**, for instance, rearranges in a clean

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[2] R. C. Cookson and J. E. Kemp, *Chem. Commun.*, 385 (1971); J. A. Berson and P. B. Dervan, *J. Am. Chem. Soc.*, **95**, 269 (1973); J. A. Berson and R. W. Holder, *ibid.*, **95**, 2037 (1973).

[3] H. Hart and J. D. DeVrieze, *Tetrahedron Lett.*, 4259 (1968); see also, B. Miller and K.-H. Lai, *J. Am. Chem. Soc.*, **94**, 3472 (1972).

[4] M. Jones, Jr., A. M. Harrison, and K. R. Rettig, *J. Am. Chem. Soc.*, **91**, 7462 (1969); T. R. Berdick, R. H. Levin, A. D. Wolf, and M. Jones, Jr., *ibid.*, **95**, 5087 (1973).

[5] K. Alder, F. H. Flock, and H. Lessenich, *Chem. Ber.*, **90**, 1709 (1955).

[6] D. Y. Curtin and A. R. Stein, *Org. Synth.*, **46**, 115 (1966).

[7] Pyrolysis of **5** at 500° was reported to give "a little" 2,6-dimethylphenol in addition to the predominant *o*-cresol.[5]

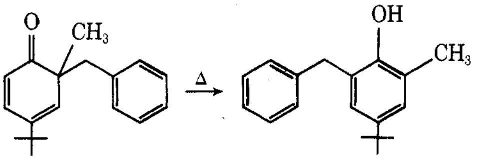
[8] R. Barner, A. Boller, J. Borgulya, E. G. Herzog, W. von Phillipsborn, C. von Planta, A. Fürst, and H. Schmid, *Helv. Chim. Acta*, **48**, 94 (1965).

[9] D. Y. Curtin and R. J. Crawford, *J. Am. Chem. Soc.*, **79**, 3156 (1957).

[10] B. Miller, *J. Am. Chem. Soc.*, **87**, 5115 (1965).

[11] B. Miller, *J. Am. Chem. Soc.*, **89**, 1685 (1967).

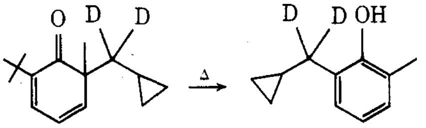
[12] B. Miller, *J. Org. Chem.*, **35**, 4262 (1970).



11

first-order process with a half-life of 200 min in diglyme solution at 165°.[13] Interestingly, the presence of a *tert*-butyl group at the migration terminus does not prevent or even markedly slow down the [1,5] shift. Instead, migration occurs with loss of the *tert*-butyl group.[14] It should be noted that *o*-benzylphenols are the only products of the rearrangements, with no detectable yields of ethers or *p*-benzylphenols, which would be likely to arise from free-radical or ionic intermediates.[13]

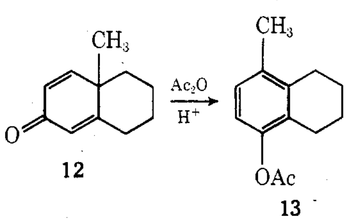
Cyclopropylmethyl groups migrate much more slowly than benzyl groups, but similarly give exclusively the products of [1,5] migration. Deuterium labeling shows that rearrangement occurs without any rearrangement in the migrating cyclopropylmethyl group.[15]



Thermal rearrangements of cyclohexadienones, therefore, proceed in conformance with the rules for thermal rearrangements.[1] Allyl groups migrate by allowed [3,3] sigmatropic shifts. Rearrangement occurs preferentially to the para position (in ortho dienones) and to a lesser extent to oxygen. When [3,3] migration is not possible, the allowed [1,5] migrations occur, though at significantly higher temperatures.

Acid-Catalyzed Rearrangements

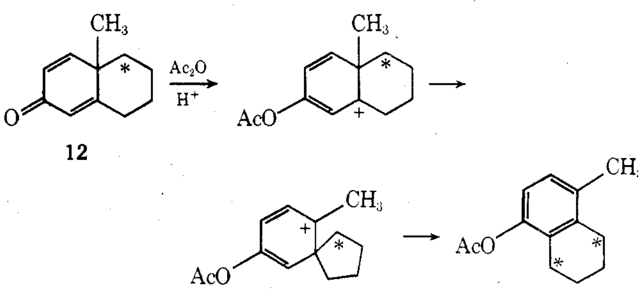
Acid-catalyzed migrations of alkyl groups in cyclohexadienones have been intensively studied since the first recognition of the nature of the rearrangement nearly half a century ago.[16] Many such "dienone–phenol rearrangements" result in apparent [1,3] migrations of alkyl groups (e.g., **12** → **13**).[17] It seems probable, however, that all such apparent [1,3] migrations actually proceed by sequences of [1,2] shifts.



12

13

Typical of the evidence for this statement is the demonstration by Fukati that **12**, in which the methylene at C-4 of the dienone ring is labeled with ^{14}C, gives **13** in which the radioactive label is equally distributed between the two benzylic methylene groups.[18] This result demonstrates the existence of the symmetrical intermediate **14**.[19]

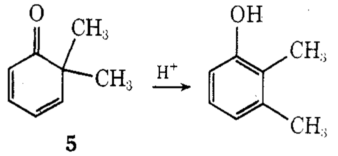


12

14

13

Migrations of alkyl groups in ortho dienones have been far less thoroughly investigated than those in para dienones. However, it has been shown that migration of a methyl group in **5** proceeds exclusively by a [1,2] process, either in acetic acid[20] or in acetic anhydride solution.[21]

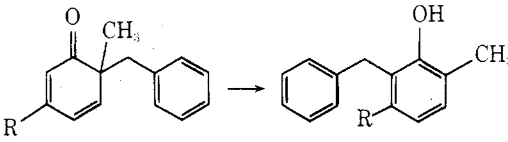


5

It appears, therefore, that all acid-catalyzed migrations of alkyl groups in cyclohexadienones proceed by [1,2] shifts or by sequences of [1,2] shifts.[22,23]

Migrations of Benzyl Groups

In dramatic contrast to the exclusive [1,2] migration of a methyl group in **5**, acid-catalyzed rearrangement of **15** gives exclusively the product of [1,5] benzyl migration.[14,20] Rearrangement of **15** occurs some millions of times more rapidly than that of **5**.



15, R = H or CH_3

When a [1,5] migration of the benzyl group is impossible (or would simply give a degenerate rearrangement), as in dienone **16a**, [1,2] benzyl migration

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(13) L. Lewis, unpublished work at the University of Massachusetts.

(14) K.-H. Lai, unpublished work at the University of Massachusetts.

(15) B. Miller and K.-H. Lai, *Tetrahedron Lett.*, 517 (1972).

(16) G. R. Clemo, R. D. Haworth, and E. Walton, *J. Chem. Soc.*, 1110 (1930).

(17) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72,** 494 (1950).

(18) R. Fukati, *Tetrahedron Lett.*, 3159 (1964).

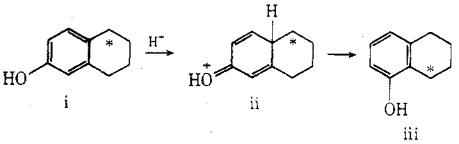
(19) For other demonstrations of the presence of intermediates in 1,3 shifts, see R. B. Woodward in "Perspectives in Organic Chemistry", A. Todd, Ed., Interscience, New York, N.Y., 1956, p 178; S. M. Bloom, *J. Am. Chem. Soc.*, **80,** 6280 (1958); P. J. Kropp, *Tetrahedron Lett.*, 1671 (1963).

(20) B. Miller, *J. Am. Chem. Soc.*, **92,** 6252 (1970).

(21) E. N. Marvell and E. Magoon, *J. Am. Chem. Soc.*, **77,** 2542 (1955).

(22) Migrations of carbomethoxy groups similarly proceed exclusively by [1,2] shifts [J. N. Marx, J. C. Argyle, and L. R. Norman, *J. Am. Chem. Soc.*, **96,** 2121 (1974)].

(23) R. Fukati [*Tetrahedron Lett.*, 6245 (1968)] has found that rearrangement of i in perchloric acid, which undoubtedly proceeds via dienone ii, gives iii in which the radioactive label is located exclusively on the ortho methylene groups. It seems probable that this apparent [1,3] migration proceeds by attack of water (or perchlorate) at the radioactive carbon to give a monocyclic intermediate, which then recyclizes at the ortho position. A similar mechanism for rearrangement of 12 would be inhibited by the neopentyl-like character of the radioactive methylene group.

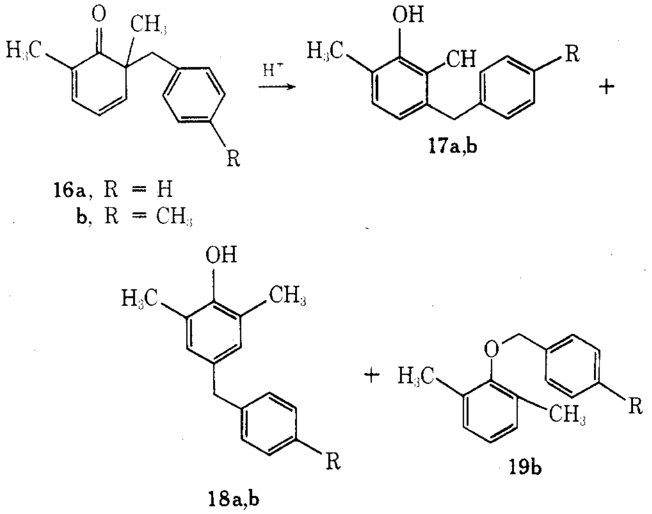


i

ii

iii

does occur. However, a [1,3] migration of the benzyl group is also observed.[24] In the rearrangement of dienone **16b**, which has been more thoroughly studied than that of **16a**, **17b** constitutes ca. 55% of the total rearrangement products and **18b** ca. 40%. A small amount (ca. 7% of the total rearrangement products) of the ether **19b** is also obtained.[25]



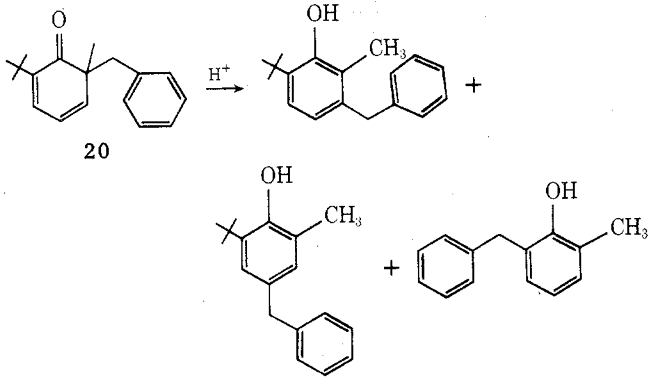
16a, R = H
b, R = CH_3

17a,b

18a,b

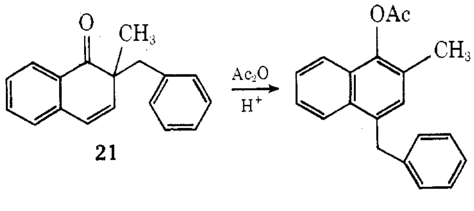
19b

Rearrangement of **20** gives a mixture of products resulting from [1,2], [1,3], and [1,5] migrations. No migration to oxygen was observed.[20]



20

Since [1,5] or normal [1,2] migration in naphthalenone **21** would result in disruption of an aromatic ring, only the [1,3] migration is observed.[26] This contrasts with the rearrangement of **22**, which gives only the product of [1,2] migration of the methyl group to the carbonyl carbon.[27]



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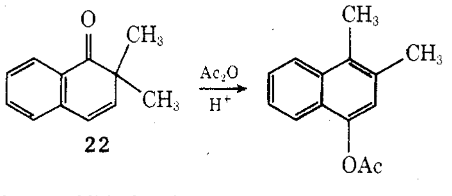
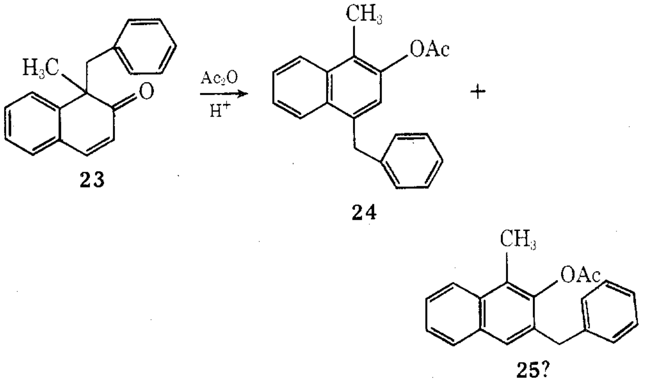


22

Finally, rearrangement of naphthalenone **23** in acetic anhydride gives principally **24**, formally resulting from a [1,4] benzyl shift, accompanied by a smaller amount of a product believed to be **25**.[26]



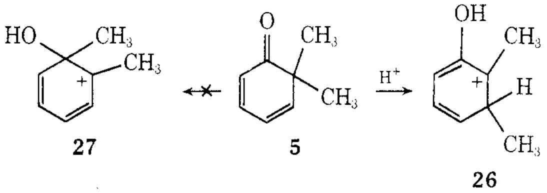
23

24

25?

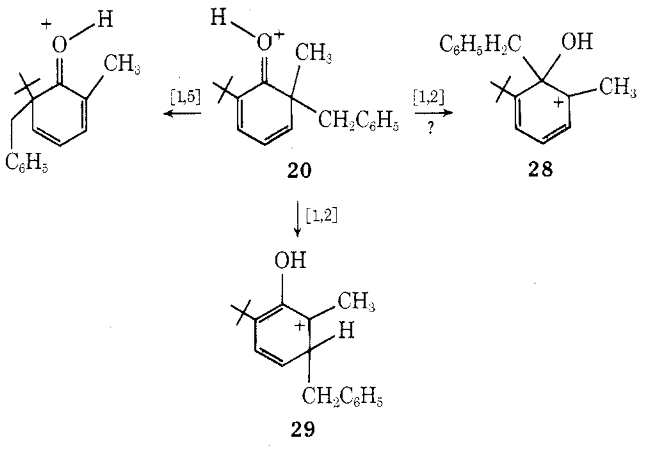
Before we conclude that benzyl groups undergo novel [1,3], [1,4], and [1,5] sigmatropic shifts, however, other possible mechanisms leading to the observed products must be eliminated.

One explanation for apparent [1,5] shifts, for instance, is that the benzyl group undergoes an initial [1,2] shift to the carbonyl carbon, followed by a second shift to the ortho position. However, as we have seen, a methyl group in **5** undergoes *solely* [1,2] migration to C-5 rather than to the carbonyl carbon.



27 **5** **26**

This is quite reasonable, since the resulting carbonium ion **26** should be several kilocalories per mole more stable, due to enolic resonance,[28] than **27**. It is hard to see why the benzyl group, in contrast, should migrate *exclusively* so as to give the less stable product. Migration of a benzyl group to the carbonyl carbon of **20** to give carbonium ion **28** seems particularly unlikely, since formation of **28** should be subject to strong steric interference from the adjacent *tert*-butyl group. Yet formation of **28** would have to proceed almost as rapidly as formation of the unhin-



20 **28**

29

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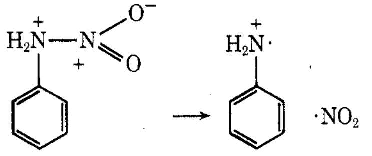
[24] B. Miller, unpublished work.
[25] B. Miller, *J. Am. Chem. Soc.*, **96**, 7155 (1974).
[26] B. Miller and M. R. Saidi, *Tetrahedron Lett.*, 1365 (1975).
[27] E. N. Marvell and A. O. Geiszler, *J. Am. Chem. Soc.*, **74**, 1259 (1952).
[28] Substitution of a methoxy group for a hydrogen atom stabilizes a double bond by ca. 5 kcal/mol [J. Hine and N. W. Flachskam, *J. Am. Chem. Soc.*, **95**, 1179 (1973)].

dered, enolic carbonium ion **29**, if the [1,5] rearrangement did proceed via a sequence of [1,2] shifts.

It seems far less unlikely that benzyl groups migrate in single-step [1,5] shifts leading directly to protonated cyclohexadienones, rather than the less stable carbonium ions. (The question of why benzyl groups give [1,5] shifts while methyl groups give [1,2] shifts will be ignored for the time being.)

An alternative possible mechanism is that protonated dienones dissociate to benzyl radicals and phenoxy radical cations which then recombine to form the *o*-benzylphenols. Schmid and his group at the University of Zurich[29] have supported this mechanism by analogy with the acid-catalyzed rearrangements of nitramines to nitroanilines, which have been proposed to proceed by a similar mechanism.[30]



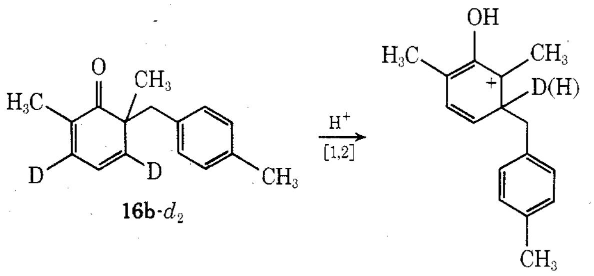
30

However, combination of benzyl and phenoxy radicals should occur at the oxygen and para carbon atoms of the phenoxy radical, rather than simply at the ortho position. (The nitramine rearrangement properly gives both *o*- and *p*-nitroanilines.[30]) Furthermore, the dissociation energy of a protonated nitramine (**30**) should be below 20 kcal/mol.[31] In contrast, dissociation of dienones such as **15** to benzyl and phenoxy radicals should require activation energies greater than 40 kcal/mol. The high temperatures necessary for thermal rearrangements of these dienones[13] accord with this estimate. The acid-catalyzed dissociation would require several additional kcal/mol for protonation of the ketone, and would require fission of an even stronger, polar bond. Since rearrangement of **15** in 1 *N* sulfuric acid in acetic acid is complete in a few hours at room temperature,[13] the activation energy must be much lower than 40 kcal/mol.

Thus, a direct sigmatropic shift appears to be the only acceptable mechanism for the acid-catalyzed [1,5] migrations of benzyl groups in cyclohexadienones.

Convincing evidence similarly eliminates all mechanisms other than direct [1,3] sigmatropic shifts for formation of **18b** and **19b** from **16b**.[25] Energy considerations similar to those above eliminate free-radical dissociation–recombination mechanisms, while lack of effect of free-radical initiators or inhibitors on the reaction rates or products are inconsistent with possible mechanisms involving free-radical chains. The rearrangements are first order in dienone, and therefore cannot proceed by intermolecular interchange of benzyl groups between two dienone molecules. Changes in the nucleophilicities of the solvents employed for the rearrangements, or addition of strong nucleophiles to the reaction mixtures, have no effect on the ratios of products of [1,2] and [1,3] migration. This eliminates the possibility that the [1,3] migration products arise from realkylation of 2,6-dimethylphenol by *p*-methylbenzyl carbonium ions, since the carbonium ions should be intercepted by solvent or added nucleophiles.

The possibility that **18b** might be formed by two consecutive [1,2] shifts of the migrating group was tested by rearranging the deuterium-labeled dienone **16b**-d_2. Rearrangement of the labeled dienone, either in methanol or acetic acid, gave almost exactly the same ratio of [1,2] to [1,3] rearrangement products as did rearrangement of **16b**. Since loss of a proton in the intermediate carbonium ion **31** should be ca. four to five times as fast as loss of a deuteron, the [1,2] shift mechanism for formation of **18b** can be discounted.[25]



16b-d_2

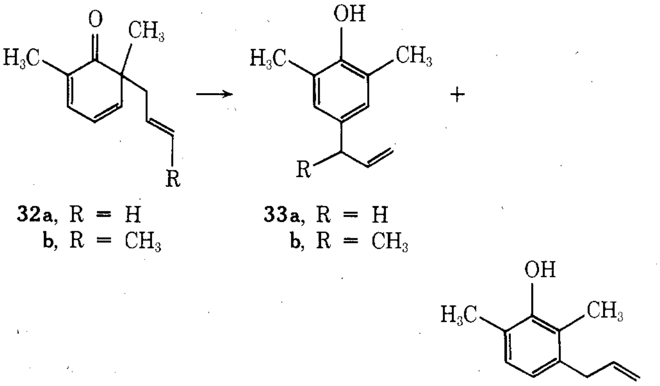
31

Since all obvious alternative mechanisms have been eliminated, the [1,3] migrations of 4-methylbenzyl groups, at least, apparently must proceed through concerted [1,3] sigmatropic shifts.

The mechanism for the apparent [1,4] benzyl shift in **23** remains unclear. We can eliminate intermolecular mechanisms, since alkylation of 1-methyl-2-naphthol would take place at C-3 or C-6, rather than C-4.[32] However, the possibility that the benzyl group migrates to the carbonyl carbon, and then undergoes a [1,3] migration to C-4, cannot be excluded.

Migrations of Allyl Groups

In the early 1960's, it was observed that allylic groups migrate principally by [3,3] shifts rather than the "normal" [1,2] shifts, in the acid-catalyzed rearrangements of *o*-cyclohexadienones.[33] Indeed, migration of the crotyl group in **32b** proceeded solely by the [3,3] path to give **33b**.[10]



32a, R = H
b, R = CH_3

33a, R = H
b, R = CH_3

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[29] U. Widmer, J. Zsindely, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 75 (1973).

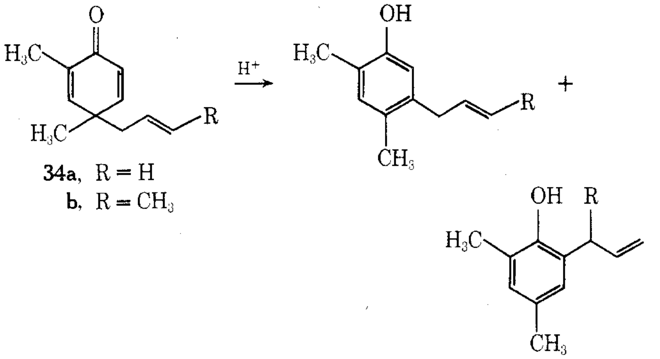
[30] W. N. White in "Mechanisms of Molecular Migrations", Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 109–137.

[31] Some dissociation energies for bonds between nitrogens bearing electronegative substituents are: $ON\text{-}NO_2$, 9.5 kcal/mol; $O_2N\text{-}NO_2$, 12.9 kcal/mol; $F_2N\text{-}NF_2$, 19.9 kcal/mol [J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966)].

[32] K. Fries and K. Schimmelschmidt, *Justus Liebigs Ann. Chem.*, **484**, 245 (1930).

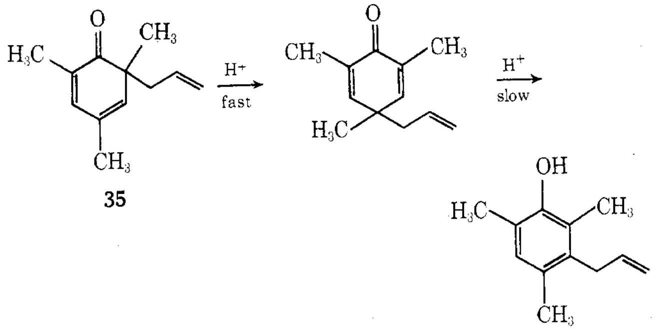
[33] (a) P. Fahrni, A. Habich, and H. Schmid, *Helv. Chim. Acta*, **43**, 448 (1960); (b) J. Leitich, *Monatsh. Chem.*, **92**, 1167 (1961).

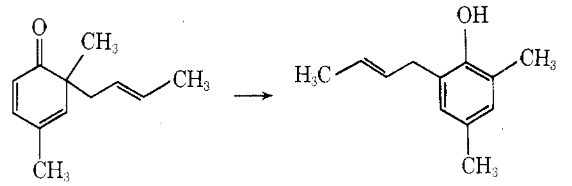
Rearrangements of the para dienones **34a** and **34b** similarly gave mixtures of the [1,2] and [3,3] migration products, with the proportion of [3,3] migration greater in the rearrangement of **34b.**[10]


34a, R = H
b, R = CH$_3$

These rearrangements are astonishingly rapid compared to most acid-catalyzed carbon skeleton rearrangements. Dienone **34b,** for instance, rearranges with a half-life of approximately 3 hr in 0.01 *N* HCl in methanol. Rearrangements of ortho dienones appear to occur at least one power of ten more rapidly.[34]

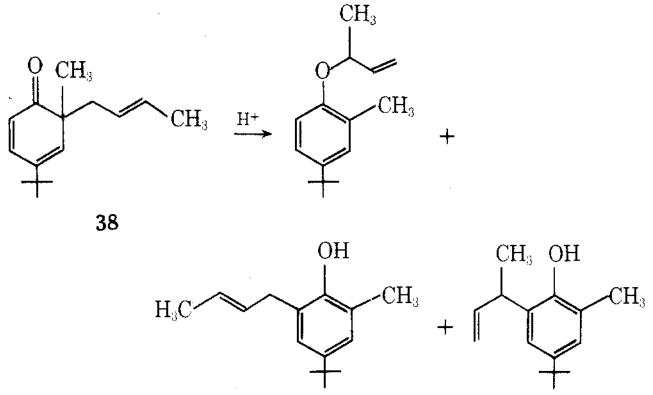
When the migration terminus at C-4 is blocked by a methyl group as in **35,** allyl groups still undergo [3,3] shifts, with no more than a trace of the [1,2] shift product.[35] However, migration of a crotyl group in **36** gives only **37,** resulting from apparent [1,5] migration.[35]

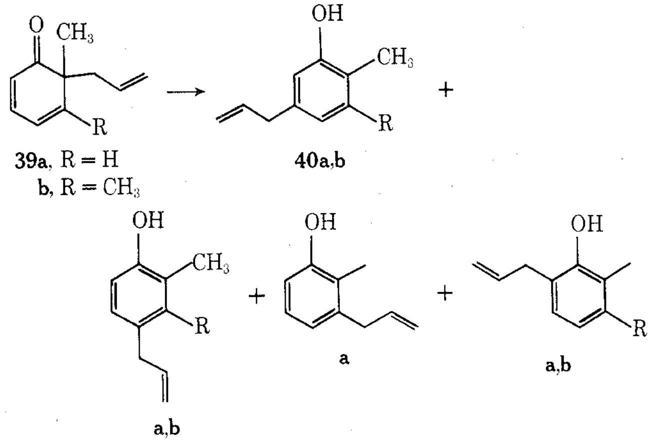

35


36 **37**

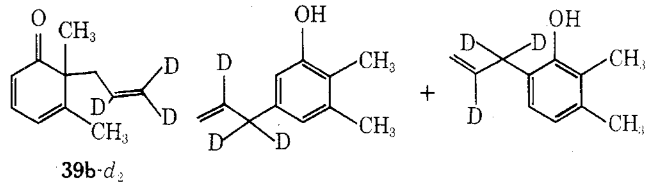
Finally, rearrangement of **38** in methanolic HCl gives products resulting from apparent [3,3] shifts to oxygen and [1,5] and [3,5] shifts to C-2.[35,36]

Changing the medium in which a rearrangement is carried out can have major effects on the types of products obtained. Rearrangements of dienones **39a** and **39b** in protic acids, for instance, give almost entirely the products of [3,3] migrations of the allyl groups.[29,33b] In a solution of trifluoroacetic anhydride in hexane, on the other hand, phenols **40a** and **40b,** resulting from apparent [1,4] migrations of the allyl groups, are obtained (after hydrolysis) together with products of [1,2], [3,3], and (apparently) [1,5] shifts.[29]

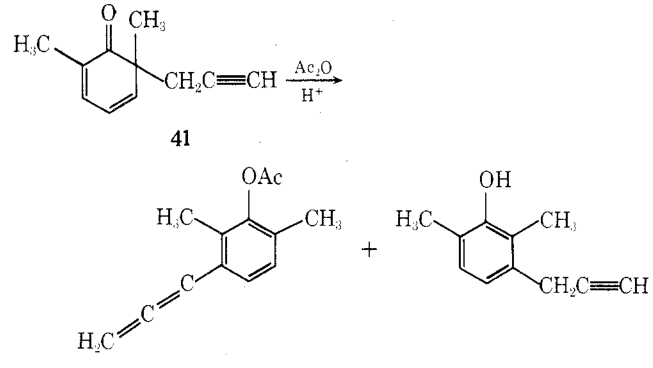

38


39a, R = H
b, R = CH$_3$
40a,b
a,b a a,b

Rearrangement of the deuterium-labeled dienone **39b**-d_2 demonstrated that the apparent [1,4] and [1,5] products from rearrangement of **39b** actually resulted from overall [3,4] and [3,5] shifts, respectively.


39b-d_2

A [3,4] shift of a propargyl group is observed in the acid-catalyzed rearrangement of **41** in acetic anhydride. A [1,2] shift is also observed, but, surprisingly, no [3,3] shift.[37]


41

Migrations of allyl groups in β-naphthalenones vary remarkably with changes in migrating groups or reaction conditions. Rearrangement of **42,** catalyzed by sulfuric acid in acetic acid[38a] or boron trichloride

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[34] B. Miller, unpublished observations.

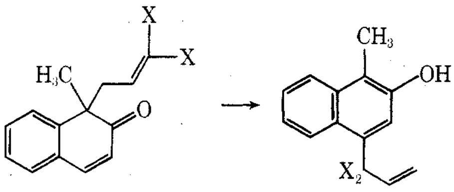
[35] B. Miller, *J. Am. Chem. Soc.*, **92,** 6246 (1970).

[36] B. Miller, *J. Am. Chem. Soc.*, **91,** 2170 (1969).

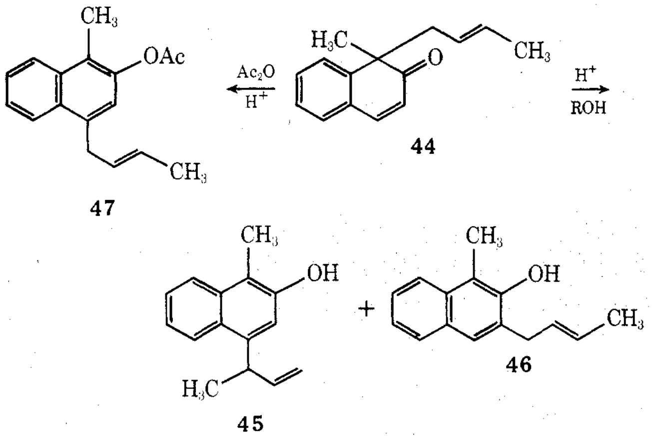
[37] U. Widmer, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta,* **56,** 1895 (1973).

[38] (a) B. Miller and M. R. Saidi, *Tetrahedron Lett.*, 4391 (1972); (b) J. Borgulya, R. Madeja, P. Fahrni, H.-J. Hansen, H. Schmid, and R. Barner, *Helv. Chim. Acta,* **56,** 14 (1973).

in chlorobenzene,[38b] gives solely phenol **43**. Studies with labeled allyl groups demonstrate that migration occurs with inversion of the allyl group. Rearrangement of **44** in either acetic acid or aqueous acid solutions similarly gives the [3,4] migration product, **45**, but the [1,5] migration product, **46**, is formed in about equal yield.[38a] Remarkably, when the rearrangement is carried out in acetic anhydride, neither [1,5] nor [3,4] migration is observed. Instead, the only product is **47**, resulting from apparent [1,4] migration.[26] Rearrangement of **42** shows no such effect of the medium. Reaction in acetic anhydride gives only **43**.

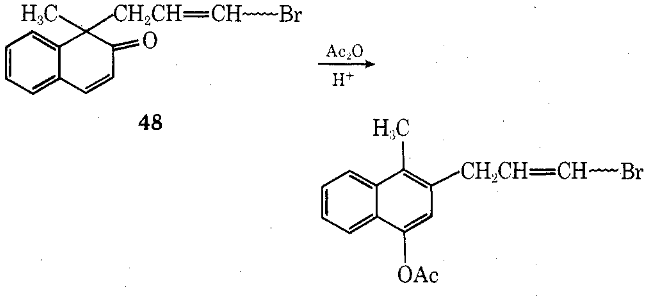


42, X = H, D **43**, X = H, D



47 **44** **45** **46**

The bromoallyl dienone **48** does not rearrange in acetic acid solution. In acetic anhydride it rearranges slowly via a [1,2] migration.[26]

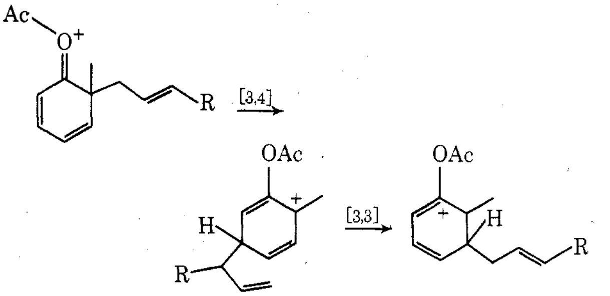


48

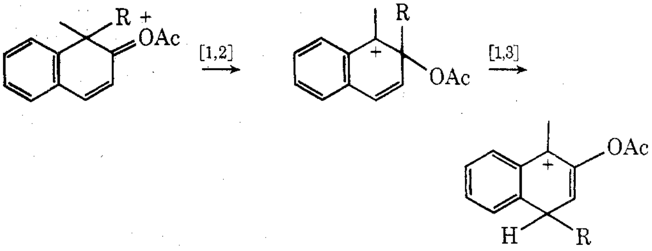
How Many Independent Reactions?

Acid-catalyzed rearrangements of cyclohexadienones can thus result in [1,2], [1,3], [1,4], [1,5], [3,3], [3,4], and [3,5] migrations of carbon–carbon bonds.[39] Are these all independent types of rearrangements, or do some of them result from combinations of the others?

[1,2] migrations of alkyl or benzyl groups are clearly fundamental, independent processes. [1,2] migrations of allyl groups could be considered to result from initial [3,4] migration, followed by a [3,3] shift (eq 1). This mechanism would require, however, that [3,3] shifts in the intermediate carbonium ions proceed about as fast as loss of protons. Except for exceptionally crowded systems,[40–42] there is no evidence that allylic migrations in carbonium ions can compete with aromatization. However, this question has not been studied in very weakly basic media (trifluoroacetic anhydride or acetic anhydride–sulfuric acid), which give the highest percentages of [1,2] and [3,4] migrations of allyl groups. While it seems most probable, therefore, that [1,2] allyl migrations are independent processes, definitive proof is not yet available.



(1)



Evidence outlined above supports the independent existence of [1,3] sigmatropic shifts of benzyl groups. [1,4] migrations of crotyl or benzyl groups in β-naphthalenones may either be written as independent processes or as combination of [1,2] and [1,3] migrations. No evidence to distinguish between these possibilities is now available.

[1,5] migrations of benzyl groups, as has been discussed above, clearly occur as independent processes. The independent existence of [1,5] shifts of allyl groups, however, is more difficult to establish. The possibility cannot be ruled out that the apparent [1,5] shift in the rearrangement of **38**, for instance, occurs via a [1,2] crotyl shift to the carbonyl carbon and then to C-2. The arguments which eliminate this mechanism for [1,5] migrations of benzyl groups are not applicable here, since steric repulsions between the migrating group and the *tert*-butyl group in **38** may well overcome the normal preference for migration to C-5.

[3,3] migrations in ortho dienones can be postulated to result from [1,2] migration to the carbonyl carbon, followed by either [3,4] migration to C-4 (eq 2) or [2,3] migration to oxygen. [3,3] rearrangements in para dienones could similarly proceed by sequential [3,4] and [1,2] migrations. However, the discussion of benzyl migrations has demonstrated the extreme dif-

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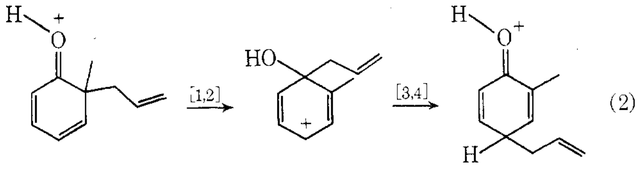
(39) For examples of acid-catalyzed [5,5] shifts in cyclohexadienones, see K. Fries, R. Boeker, and F. Wallbaum, *Justus Liebigs Ann. Chem.*, **509**, 73 (1934); B. Miller, *J. Am. Chem. Soc.*, **86**, 1137 (1964).

(40) B. Miller and K.-H. Lai, *Tetrahedron Lett.*, 3575 (1971); *Tetrahedron*, **28**, 3472 (1972).

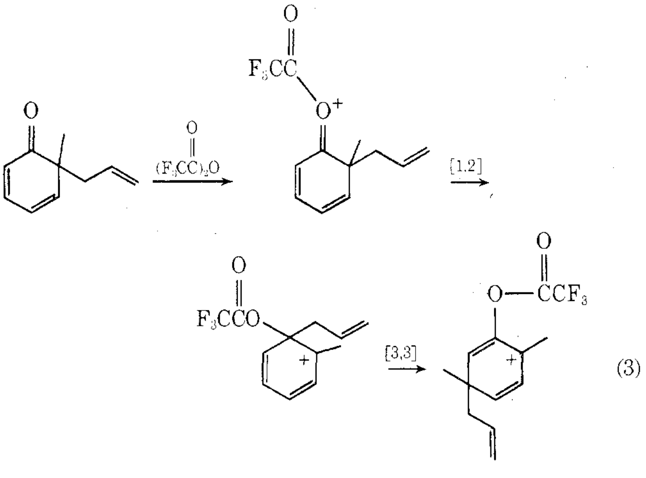
(41) B. Miller and K.-H. Lai, *J. Org. Chem.*, **37**, 2505 (1972).

(42) (a) B. Miller and H. Margulies, *J. Am. Chem. Soc.*, **87**, 5106; (b) B. Miller and K.-H. Lai, *Chem. Comm.*, 1072 (1970).

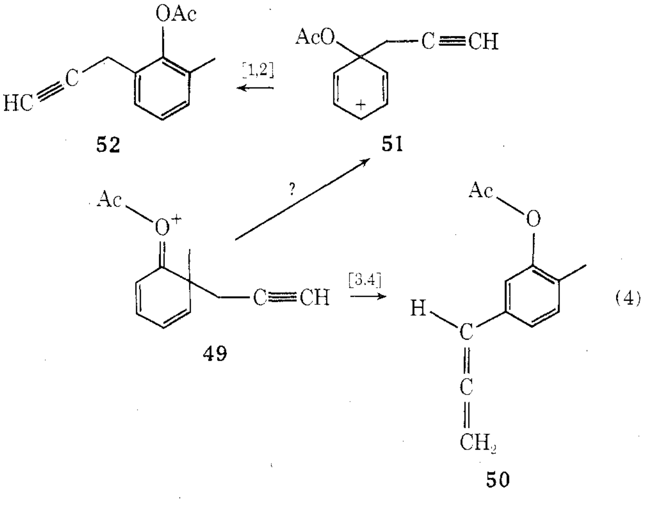


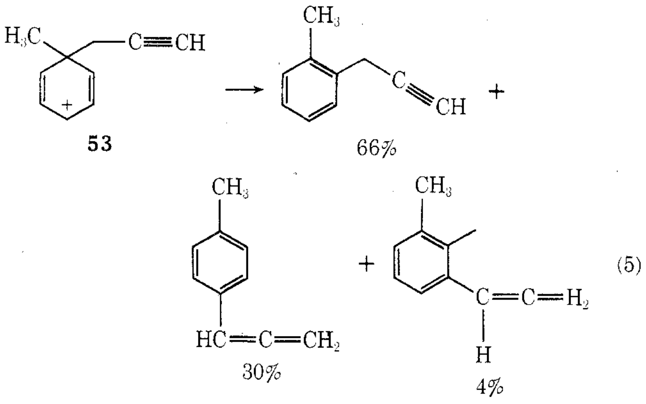
ficulties arising from assuming exclusive migration to a carbonyl carbon rather than C-5. The two-step mechanism must therefore be rejected, and acid-catalyzed [3,3] shifts of allyl groups must be accepted as primary processes.

All [3,4] shifts can be written as proceeding by initial [1,2] shifts to the carbonyl carbon, followed by [3,3] shifts to C-3 (eq 3). The high proportion of migration to the carbonyl carbon (about equal to migration to C-5)[29] may be reasonable for reactions in trifluoroacetic anhydride, since the enol trifluoroacetate may not be much more stable than the hydroxy olefin.

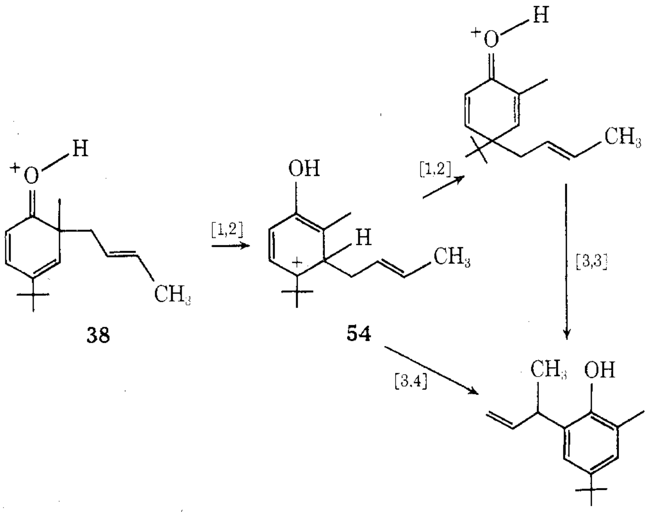


A strong argument can nonetheless be made for the independent existence of [3,4] migrations, at least of propargyl groups. Rearrangement of dienone **49** in acetic anhydride gives the [3,4] migration product **50** in 61% yield, and the [1,2] migration product in 25% yield.[37] If carbonium ion **51** were actually a major intermediate in this reaction, formation of **52** by a second [1,2] shift would be expected to occur in high yield, since it has been shown that migration of the propargyl group in carbonium ion **53** proceeds predominantly by [1,2] and [3,4] paths, with only a few percent of [3,3] migration.[43] Since no more than a few percent of **52** could have been formed from **49**,[37] it can reasonably be concluded that formation of **50** proceeds by an independent [3,4] migration.





The apparent [3,5] shift in the rearrangement of **38** may proceed either by a sequence of [1,2], [1,2], and [3,3] shifts or by a [1,2] followed by a [3,4] shift. A second migration of the crotyl group in preference to aromatization of carbonium ion **54** is feasible, since aromatization would be slowed by the necessity of forcing the *tert*-butyl and crotyl groups into the same plane.[40–42]



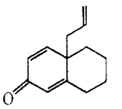
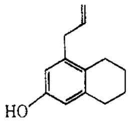
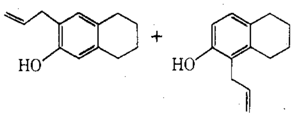
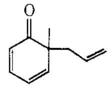
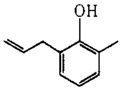
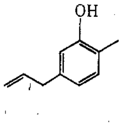
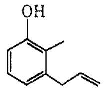
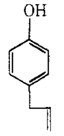
In summary, [1,2] migrations of alkyl groups, [3,3] migrations of allyl groups, and [1,5] and [1,3] migrations of benzyl groups proceed as primary, independent processes. [1,2] and [3,4] migrations of allyl groups may be intertwined to some extent. However, they form a class independent of the [3,3] migrations. Convincing evidence for the independent existence of [1,4] migrations of benzyl or allyl groups or [1,5] and [3,5] migrations of allyl groups does not yet exist.

"Thermal Type" and "Carbonium Ion Type" Migrations

Some time ago, I suggested that migrations of carbon–carbon bonds in the acid-catalyzed rearrangements of cyclohexadienones may profitably be divided into two classes: those which resemble migrations in the thermal rearrangements of cyclohexadienones, and those which resemble migrations in the rearrangements of cyclohexadienyl carbonium ions.[35,44]

[43] H. Heimgartner, J. Zsindely, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 1113 (1972).

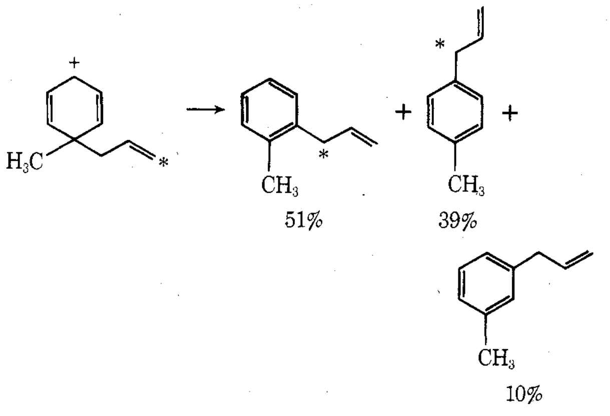
Table I
Effects of Catalysts on Products of Allyl Migrations[29]

Dienone	Catalyst–solvent	Products [migration order]			
					
		[1, 2]			[3, 3]
	$(F_3CCO)_2O$	37%			58%
	H_2SO_4–$(CH_3CO)_2O$	20%			79%
	HCl–MeOH	2.5%			96%
	CF_3CO_2H	<1%			90%
	HCl–C_6H_5	<1%			90%
					
		[1, 5]	[3, 4]	[1, 2]	[3, 3]
	$(F_3CCO)_2O$–hexane	6%[a]	23%	29%	37%
	F_3CCOH–hexane	0%	0%	0%	100%

[a] May result from [1,2] shift to carbonyl carbon.

The thermal rearrangements of cyclohexadienones can be summarized quickly: [3,3] migrations to carbon are the preferred reactions, when feasible, with [3,3] migration to oxygen the second choice. When neither of these processes is possible, [1,5] migration occurs. Acid-catalyzed rearrangements follow a similar pattern, although with an enhanced preference for [3,3] migration to carbon rather than oxygen. This preference is presumably due to the fact that migration to oxygen gives a product in which the positive charge is localized on oxygen, while migration to carbon gives a product in which the charge may be delocalized onto the ring.

The recent elegant work of Schmid and his school has greatly expanded our knowledge of the modes of rearrangements of cyclohexadienyl carbonium ions. The results of their work are summarized in eq 5 and 6.[45] It can be seen that the predominant reactions are [1,2] and [3,4] migrations, with [3,3] migrations of allyl or propargyl groups relatively minor reactions in each case.



(6)

We may thus classify [3,3] and [1,5] shifts in acid-catalyzed rearrangements of cyclohexadienones as "thermal type rearrangements", and [1,2] and [3,4] shifts as "carbonium ion type rearrangements".[46]

Is there anything to be gained, other than points for neatness, from this sort of classification? To demonstrate the virtues of this analysis, let us consider the reaction of a cyclohexadienone with a proton, with acetic anhydride, and with trifluoroacetic anhydride. Protonation of the carbonyl will, of course, place a much larger charge on the ring than exists in a neutral molecule. Since the acetyl group is more electron withdrawing than a proton, the charge on the ring will be greater in the acetylated than in the protonated ketone, and greater still after trifluoroacetylation. We may, therefore, predict that the reactions of cyclohexadienones will increasingly resemble those of cyclohexadienyl carbonium ions as increasingly electron-withdrawing reagents are used.

Schmid and his coworkers[29] have investigated the reactions of cyclohexadienones with these three reagents. Their work is summarized in Table I.

The results of these studies can be briefly summarized: as the structure of the cyclohexadienone ring approaches that of a carbonium ion, the proportion of "carbonium ion type" products increases and that of "thermal type" products decreases. This is an intellectually pleasing result, and certainly represents a major contribution to our understanding of these rearrangements.

n vs. π Protonation?

Unanswered questions remain about product distributions in the acid-catalyzed rearrangements of cyclohexadienones. In the rearrangements of ortho dienones, for instance, why do benzyl groups undergo exclusively [1,5] (thermal type) shifts, when possible, while methyl groups, under the same reaction conditions, undergo only [1,2] (carbonium ion type) shifts?

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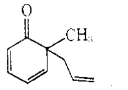
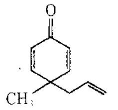
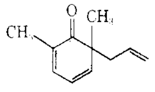
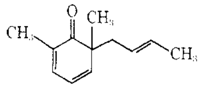
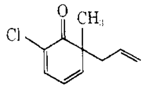
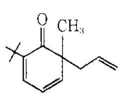
(44) B. Miller, *J. Am. Chem. Soc.*, **92,** 432 (1970).

(45) H. J. Hansen, B. Sutter, and H. Schmid, *Helv. Chim. Acta*, **51,** 828 (1968).

(46) Schmid and his coworkers use the terms "charge-induced" and "charge-controlled" reactions[29] to refer to the reactions I refer to as "thermal type" and "carbonium ion type" rearrangements. These terms seem unfortunately vague—are not "charge controlled" reactions "charge induced"?

Table II

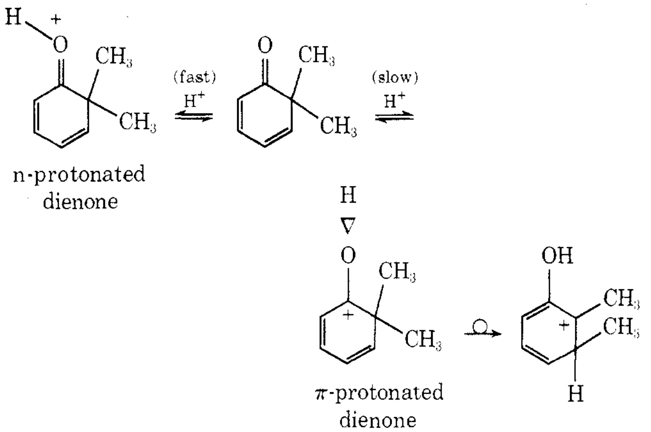
Dienone	Catalyst (solvent)	% yield of Products [3, 3]	[1, 2]	[3, 4]	Ref
 7	BCl_3 (C_6H_5Cl)	100	0	0	38a
	F_3CCO_2H (hexane)	100	0	0	29
	BCl_3 (C_6H_5Cl)	95	~5		38a
	H_2SO_4 (pentane	95	~5		38a
 32a	BCl_3 (C_6H_5Cl)	70	28[a]		38a
	HCl (C_6H_5Cl)	95	5[a]		38a
	BCl_3 + HCl (C_6H_5Cl)	75	25[a]		38a
 32b	BCl_3(C_6H_5Cl)	68	20		38a
	HCl(MeOH)	100	0		10
	H_2SO_4(HOAc)	100	0		10
 55	BCl_3 (C_6H_5Cl)	84	13	3	38a
	HCl (C_6H_5Cl)	90	<0.5	<0.5	38a
 56	BCl_3 (C_6H_5Cl)	86	7	3	38a
	HCl (C_6H_5Cl)	95	0.5	0.5	38a
	BCl_3 + HCl (C_6H_5Cl)	96	1		38a

[a] May arise from [1,2] or [3,4] migrations.

Also, why do crotyl groups give higher proportions of thermal type migrations than allyl groups? To explain this, it has been suggested that the migrating group bears a larger positive charge in the transition state for thermal type than for carbonium ion type migrations.[10,29] This is a purely post hoc argument. There seems no obvious basis on which this result would have been predicted, or, indeed, on which it can be rationalized.

Several years ago, I suggested that carbonium ion and thermal type migrations might proceed via different types of intermediates. Thermal type migrations were postulated to proceed after the normal protonation of the nonbonded (n) electrons of the oxygen atom. Since n protonation causes only a mild perturbation of the electron distribution in the cyclohexadienone, good migrating groups, such as allyl and benzyl, would undergo their normal thermally allowed migrations, although at lower temperatures than those necessary for the uncatalyzed reactions. On the other hand, very poor migrating groups, such as methyl groups, would find the activation provided by n protonation insufficient to induce rearrangement. Instead, they would await an occasional protonation of the bonding π electrons of the carbon–oxygen double bond. Since such π protonation would give rise to a cyclohexadienyl carbonium ion, carbonium ion type rearrangements—e.g., [1,2] migrations of a methyl group—would occur.[20,35]

In general, the slower the rearrangement of a dienone, the more likely that at least some of the migration might occur via the π-pronated form, and the more likely the formation of carbonium ion type rearrangement products.[47] Migrations of allyl groups should therefore be more likely to proceed by [1,2] shifts than the more rapid migrations of crotyl groups.



The n vs. π protonation hypothesis suggests that bulky substituents near the n electrons should inhibit bonding to those electrons. Bonding to the π electrons would therefore be relatively more favorable. Furthermore, when such substituents are present, increasing the size of the catalyst should favor reaction with the π electrons, and formation of carbonium ion type products. The data in Table II appear to accord with this analysis.

Interpretation of these data in terms of the n-vs. π-"protonation" hypothesis appears straightforward. In the absence of a substituent at C-2, n protonation or trichloroboronation occurs, and is followed by the

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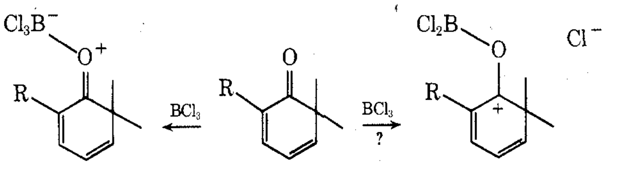
(47) Exceptions to this rule would be rearrangements which are slow because of the presence of electron-withdrawing substituents on the ring, which would inhibit π protonation more than n protonation.

thermal type [3,3] migration. The presence of a methyl group at C-2 has little effect on protonation of the n electrons, but is much more effective in inhibiting bond formation between these electrons and the bulky boron trichloride. Reaction of boron trichloride with the π electrons, and subsequent [1,2] migration, are therefore relatively favored. An electronegative chlorine atom at C-2 inhibits formation of the π-protonated dienone, in which the charge would be largely located on the ring. The yields of carbonium ion products from rearrangement of **55** are thus lower than those obtained from **32a.** The fact that replacement of a hydrogen at C-2 by a chlorine increases the yields of [1,2] and [3,4] migration products, however, demonstrates that the effect of the methyl group at C-2 in **32a** must be steric, rather than electronic, in origin.

The data in Table II may be explained in other ways than by the n- vs. π-protonation hypothesis. It might be postulated, for instance, that 2,6-disubstituted cyclohexadienones react with boron trichloride to give a trivalent boron derivative, **57,** rather than a normal tetravalent addend. However, the n- vs. π-protonation hypothesis does provide a convenient interpretation which does not demand other, ad hoc, hypotheses.



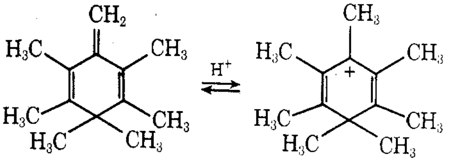
R = H

57, R = CH_3

The energy differences between n- and π-bonded forms of cyclohexadienones would depend on the electron-attracting abilities of the ligand to oxygen. An n-trifluoroacetyl ketone, for instance, would probably convert with little difficulty to the π-trifluoroacetyl rotamer. The data of Table I might therefore be rationalized by assuming all carbonium type rearrangements to proceed through π-bonded intermediates. There is no need to carry the argument that far, however. The n- vs. π-protonation hypothesis simply suggests that the charge on the ring may be increased either by employing more electrophilic catalysts, or by reacting the catalysts with the π electrons of a carbonyl. Either process should lead to an increase in the yields of carbonium ion type reaction products.

Schmid and his group have made it plain that they do not admire the n- vs. π-protonation hypothesis.[29] They quote MO calculations, which indicate π-protonated formaldehyde to be 22[48a] or 26[48b] kcal/mol higher in energy than n-protonated formaldehyde, to suggest that π protonation of ketones will be too high energy a process to compete with n protonation. The same calculations, however, indicate that π-protonated acetaldehyde is only 14 kcal/mol less stable than the trans-n-protonated form (which most closely resembles a protonated ketone). Allylic resonance in a protonated unsaturated ketone should further decrease the relative energy of its π-protonated form.

Such calculations, however suggestive, refer only to isolated molecules. As a model for a π-protonated cyclohexadienone in solution, we may start with carbonium ion **59,** the conjugate acid of the remarkably basic hydrocarbon **58.**[49] A π-protonated cyclohexadienone could, in principle, be obtained from **59** by substitution of a *single bonded* hydroxy group for a methyl group at C-1 in **59.** Carbonium ion **59** should be 3–4 p*K* units more stable than the corresponding ion with a hydrogen atom at C-1.[50] Substitution of a hydroxy group for a hydrogen, in turn, should destabilize the ion by a factor of ca. 10^6, provided only inductive effects are considered.[51] Applying these corrections to the reported[52] pK_a of **59,** and comparing it with that of the n-protonated form of **60,**[53] we can conclude that the π-protonated form of dienone **60** should be only ca. 6–8 kcal/mol less stable than the n-protonated form.



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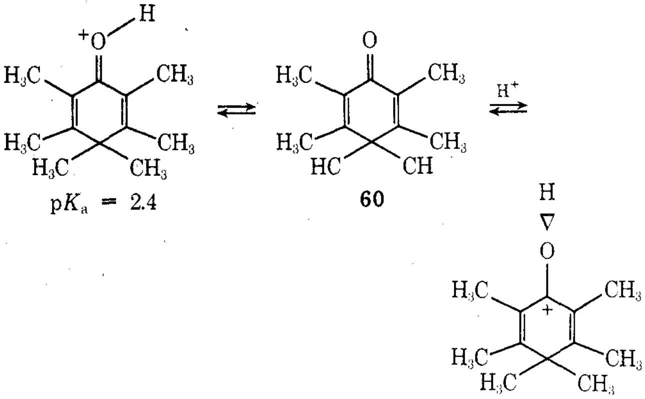
59

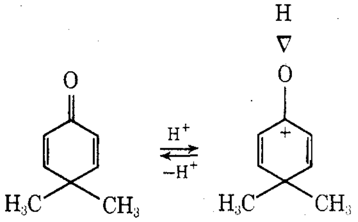
A polysubstituted dienone such as **60** offers a particularly favorable situation for π protonation. The π-protonated form of a "bare" ketone, such as **62,**



pK_a = 2.4

60

61, pK_a ≃ −8



62

pK_a ≃ −15

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(48) (a) K. F. Purcell and J. M. Collins, *J. Am. Chem. Soc.*, **92,** 465 (1970); (b) K. F. Purcell and T. G. M. Dolph, *ibid.*, **94,** 2693 (1972).

(49) W. von E. Doering, M. Saunders, H. G. Boynton, H. W. Earhart, E. F. Wadley, W. R. Edwards, and G. Laber, *Tetrahedron*, **4,** 178 (1958); see also, V. G. Shubin et al., *Zh. Org. Khim.*, **6,** 2072 (1970).

(50) N. C. Deno and P. C. Scholl, *J. Am. Chem. Soc.*, **93,** 2702 (1971).

(51) A β-hydroxy group (showing essentially no anchimeric effects) slows down solvolysis of tertiary halides by a factor of 150 [S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70,** 828 (1948)]. Application of the Taft–Ingold equation, using a ρ^* value of −3.3 for solvolysis of tertiary halides and assuming that ρ^* is 2.8 times as large for an α-hydroxy as for a β-hydroxy group [see chapter by R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956] gives the value of 10^6 for the inductive effect of an α-hydroxy group in destabilizing a carbonium ion.

(52) H. Juura and U. Haldna, *Reakts. Sposobnost. Org. Soedin.*, **3,** 162 (1966); *Chem. Abstr.*, **66,** 119381c (1967).

(53) V. G. Shubin, V. P. Chzhu, I. K. Korobeinicheva, A. I. Rezvukhin, and V. A. Koptyug, *Bull. Acad. Sci. USSR*, 1643 (1970).

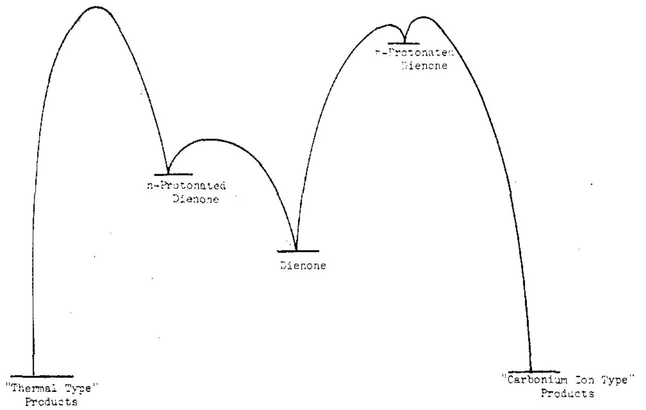


Figure 1. Schematic representation of rearrangements via n- and π-protonated cyclohexadienones.

should be ca. 6–10 kcal/mol less stable, relative to the n-protonated form, than ion **61**.[54]

The differences in energy between n- and π-protonated cyclohexadienones would thus certainly be appreciable. They should be compensated for, at least in part, by the very low energies required for alkyl shifts in carbonium ions.[55] A schematic representation of possible energy relationships for rearrangements via competing n and π protonation is shown in Figure 1. Even the maximum differences in energy between n- and π-protonated cyclohexadienones do not seem inconsistent with such a scheme, particularly for slow rearrangements such as those of methyl groups.

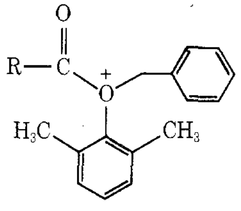
The n- vs. π-protonation hypothesis thus offers an interesting approach to rationalizing most of the observed rearrangements of cyclohexadienones. It may even be correct. We can look forward to future work in this area, particularly in regard to the question of whether a π-protonated dienone can actually exist as a discrete intermediate, rather than a transition state between n-protonated forms.

[1,3] and [1,4] Migrations

The occurrence of [1,3] and [1,4] migrations presents problems different from those offered by other types of rearrangements. Since the exceptionally strained geometries required for antarafacial [1,3] sigmatropic shifts permit only very poor orbital overlap in the transition states, very high activation energies are observed for such reactions. Acid-catalyzed [1,3] and [1,4] migrations, which proceed relatively rapidly at room temperature, therefore seem unlikely to proceed by antarafacial paths.

Recent discussions of the conditions under which formally forbidden suprafacial [1,3] shifts may occur may be summarized by the statement that the activation energies will be lowest when a good electron donor is migrating along a good electron acceptor.[56] This analysis appears to apply neatly to rearrangements of cyclohexadienones. Protonated dienone rings are clearly excellent electron acceptors. The 4-methylbenzyl and crotyl groups are better electron donors than benzyl and allyl groups, and appropriately give higher proportions of [1,3] migration products.

The electron-accepting ability of the dienone rings should increase if acylating agents were substituted for protic acids as catalysts. This indeed appears to be the case in the rearrangement of naphthalenone **44,** in which the suprafacially forbidden [1,4] crotyl migration occurs in acetic anhydride but not in acetic acid. However, substitution of acetic anhydride or trifluoroacetic anhydride for acetic acid as the solvent in rearrangement of **16b** results in no significant change in the ratio of [1,2] to [1,3] rearrangement products, other than to prevent formation of ether **19b,**[34] presumably because the charge in the initial rearrangement product, **63,** would be located on a



63

particularly electronegative atom. One conceivable explanation for the lack of difference between protic acids and acylating agents in the rearrangement of **16b** is that rearrangement in protic acids occurs from a π-protonated state, which closely resembles the acylated ketones.

Conclusion

Rearrangements of cyclohexadienones give rise to a bewildering array of migrations. Some progress has been made toward understanding the factors which determine which rearrangements will occur in a given system. However, these reactions still obviously form a fertile field for theoretical and experimental investigations.

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(54) These estimates assume that there is *no* orbital overlap between the n electrons on oxygen and the p orbital at C-1. Although the geometry for overlap is not optimal, some bonding might be expected. The actual differences in energy between n- and π-protonated cyclohexadienones might therefore be smaller than suggested by these estimates.

(55) G. A. Olah and J. Lukas, *J. Am. Chem. Soc.*, **89,** 4739 (1967).

(56) N. D. Epiotis, *J. Am. Chem. Soc.*, **95,** 1206 (1973); M. J. S. Dewar and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1,* 1839 (1974).