Kinetic Protonation of Enols, Enolates, and Analogues. The Stereochemistry of Ketonization

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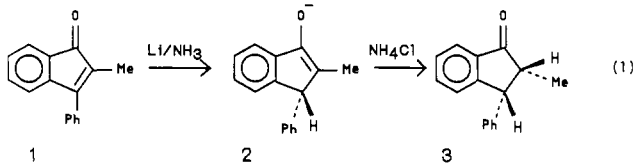
Our research on kinetic protonation began in 1954. It was clear that a very large number of organic reactions proceed via unstable enolic intermediates, and there was suggestive evidence that many of these reactions led to the less stable of two possible stereoisomeric products. Knowledge of what was controlling the stereochemistry of ketonization under kinetic conditions promised to afford insight into the stereochemistry of this large number of organic reactions.

We reported a large number of examples in the 1955–1960 period.[1-10] However, it was apparent that the problem was of more general interest and our studies continued[11,12] over the years. Furthermore, in the past decade the subject has assumed an ever increasing importance in controlling stereochemistry in natural product and general synthetic organic chemistry.

The Hypothesis. In a very early report[1] the author suggested that the transition state for ketonization of enols comes early along the reaction coordinate and is close to sp^2 hybridized, with the consequence that steric hindrance to approach of the proton donor is a major factor in controlling from which face a proton is delivered to the α-carbon. The effect is enhanced with large proton donors.

Thus, in a generalized molecular situation, as depicted in Figure 1 ketonization occurs by delivery of a proton to one of the two lobes of the α-carbon p orbital. If the upper face of the molecule is less hindered sterically, one would anticipate protonation from above, while if the lower face is the less hindered, the approach from the bottom would be expected.

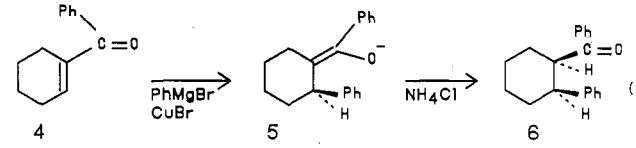
Some Examples of Kinetic Ketonization. In one example, the Barton reduction[13] of 2-methyl-3-phenylindenone (1), enolate **2** and the corresponding enol are the penultimate intermediates.[2] Ketonization occurs stereoselectively[14] to give the less stable cis product **3** under kinetic conditions. It was noted that, in the ketonization process, the α-carbon is protonated from the less hindered side, namely, trans to the β-phenyl group. Note eq 1.



1 2 3 (1)

Howard E. Zimmerman, a native of Connecticut, received his B.S. and Ph.D. degrees from Yale in 1950 and 1953. He served in the U.S. Armored Corps in Europe during World War II. After a N.R.C. Postdoctoral Fellowship at Harvard spent with R. B. Woodward, he served on the Northwestern faculty from 1954 to 1960 when he moved to the University of Wisconsin. He has held the Arthur C. Cope chair there since 1975. He is a member of the National Academy of Sciences and cites as his best accomplishment the fact that 71 of his research students are in academia. His research interests include the synthesis of unusual organic molecules, reaction mechanisms, mechanistic and exploratory organic photochemistry, and theoretical organic chemistry such as the Möbius–Hückel differentiation of transition states.

In the author's first publication on the subject of ketonization, the conjugate addition of phenylmagnesium bromide to benzoylcyclohexene (**4**) was found to afford the less stable, cis stereoisomer of 1-benzoyl-2-phenylcyclohexane (**6**).[1] Here, too, formation of the less stable of two potential stereoisomeric products was attributed to kinetic protonation from the less hindered side of the enol or enolate in an essentially sp^2-hybridized transition state. Independent of whether a 2-phenyl axial or equatorial conformer is being protonated, the less hindered approach leads to cis product **6**. Refer to eq 2.



4 5 6 (2)

A third reaction proceeding via a transient enolic intermediate is the debromination of α-bromo ketones with zinc and proton donors or dilute HI in acetone. Thus, each of the two stereoisomers of 1-acetyl-1-bromo-4-phenylcyclohexane (**7a** and **7b**) leads to the same distribution of debrominated stereoisomers on treatment with zinc and various proton donors.[11] The reaction proceeds via the enol **8**, which undergoes kinetic protonation preferentially to afford the less stable, cis product **9a**. The regioselectivities range from 61% to 79%, depending on the steric demands of the proton donor (Scheme I). Of the transition states available to enol **8**, it can be seen that exo protonation, leading

(1) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549–557.
(2) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168–1173.
(3) Zimmerman, H. E.; Giallombardo, H. J. *J. Am. Chem. Soc.* **1956**, *78*, 6259–6263.
(4) Zimmerman, H. E. *J. Am. Chem. Soc.* **1957**, *79*, 6554–6558.
(5) Zimmerman, H. E.; Nevins, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559–6561.
(6) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1958**, *80*, 2893–2896.
(7) Zimmerman, H. E.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1958**, *80*, 3060–3064.
(8) Zimmerman, H. E.; Chang, W.-H. *J. Am. Chem. Soc.* **1959**, *81*, 3634–3643.
(9) Zimmerman, H. E.; Mais, A. *J. Am. Chem. Soc.* **1959**, *81*, 3644–3651.
(10) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1959**, *81*, 4305–4308.
(11) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091–6096.
(12) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *48*, 1637–1646.
(13) Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3045–3051.
(14) Stereoselectivity and stereospecificity are defined following the usage put forth in ref 15a and as used in accordance with ref 15b. Thus, a reaction is stereoselective, or partially so, if each of two reactant stereoisomers leads preferentially to the same product isomer, while in a stereospecific reaction each reactant isomer preferentially affords a corresponding product isomer.
(15) (a) Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108–116, footnote 16. (b) Eliel, E. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962.

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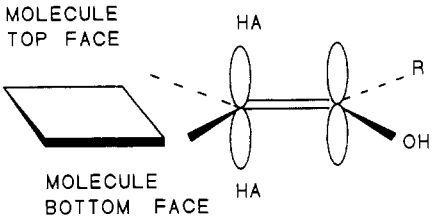
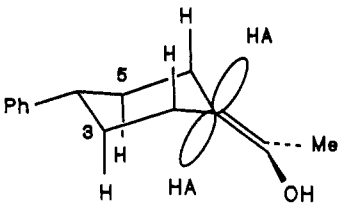


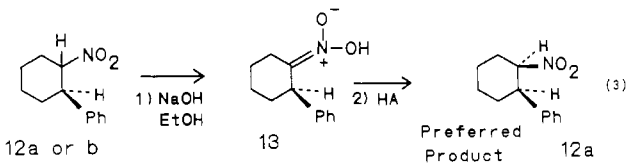
Figure 1. A generalized picture showing two approaches of a proton donor.

to cis product, avoids steric interactions between the proton donor and the axial hydrogens at C-3 and C-5.



Transition States from 8

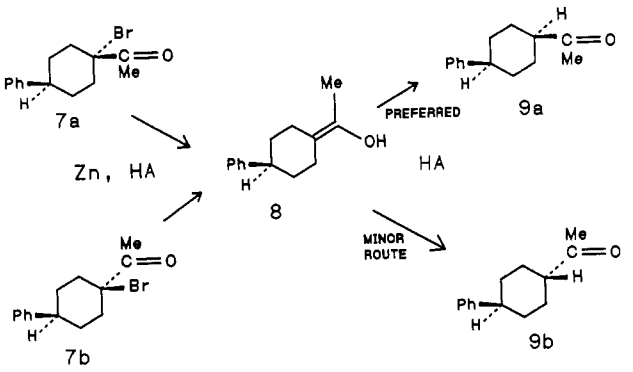
The same publication[11] reported still another example of kinetic protonation, namely, that of the aci-nitro isomer **11** of 1-nitro-4-phenylcyclohexane (**10**). For example, with collidinium bromide as the proton donor, 61% of the cis isomer of 1-nitro-4-phenylcyclohexane was observed. Here deprotonation–kinetic protonation is the fourth reaction affording an unstable enolic intermediate (Scheme II). Deprotonation–kinetic protonation in the case of 1-nitro-2-phenylcyclohexane (**12**) provided still greater (ca. 90%) stereoselectivity[5] favoring cis product and represents another example of kinetic protonation to give the less stable stereoisomer. This is outlined in eq 3.



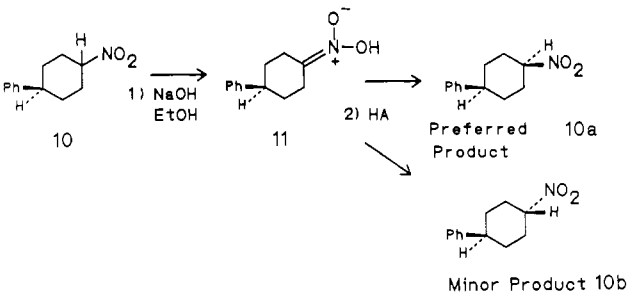
Enol vs. Enolate Protonation. Thus far we have discussed kinetic protonation without specifying whether the protonation process is that of the neutral enol or, instead, its conjugate base. It has been shown in our earlier studies[16] on the tautomerization of the conjugated enol **15** of cholest-4-en-3-one (**14**) that over a broad pH range (2–8) it is the enolate anion **16** which is protonated during ketonization. Only at very low pH is the enol itself protonated. Furthermore, the enolate is protonated kinetically at the center of the conjugated system (i.e., at C-4) while the enol is protonated at the end (i.e., at C-6). One concludes that the enolate is so much more reactive than the enol that enol–enolate equilibration provides sufficient enolate to favor C-4 protonation under most conditions. At times, literature

(16) (a) Zimmerman, H. E. In *Molecular Rearrangements*; DeMayo, P., Ed.; Interscience: New York, 1963; Chapter 6, pp 345–406. (b) Paufler, R. M. Ph.D. Thesis, Northwestern University, 1960. (c) Note also the studies of Ringold et al.: Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1965**, *87*, 3228–3236 and references cited therein. (d) For a broader survey of ketonization mechanisms including those operating under nonkinetic conditions, see: House, H. O. *Modern Synthetic Reactions*, 2nd. ed.; W.K. Benjamin: Menlo Park, CA, 1972; pp 503–509. (e) Similarly, see ref 25 for further discussion.

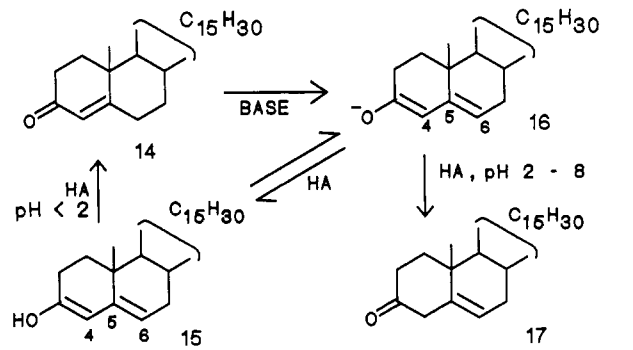
Scheme I.
Stereoselective Protonation of 4-Phenyl-1-acetylcyclohexane Enol



Scheme II.
Kinetic Protonation of 4-Phenylnitrocyclohexane Conjugate Base



Scheme III.
Selective Protonation of Enolates Relative to Enols, and Kinetic α-Protonation to Effect Deconjugation

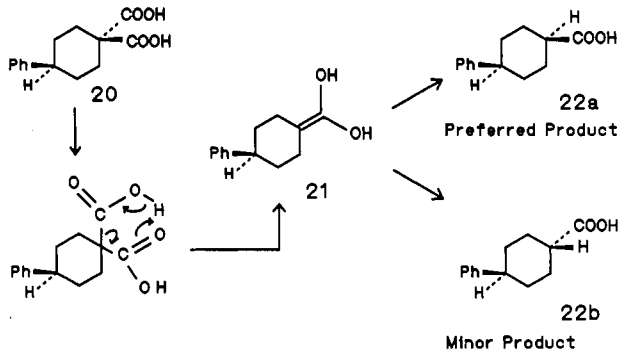


discussions have questioned whether oxygen protonation should not be more rapid than carbon protonation in ketonization. Doubtlessly it is. However, this is not relevant to product formation, since oxygen protonation is reversible while under kinetic conditions carbon protonation is not. Scheme III describes this chemistry. While this example of a conjugated ketone may not be totally general, it does reveal a preference for ketonization in protic media via the enolate when possible and under the relatively neutral conditions used for kinetic protonation.

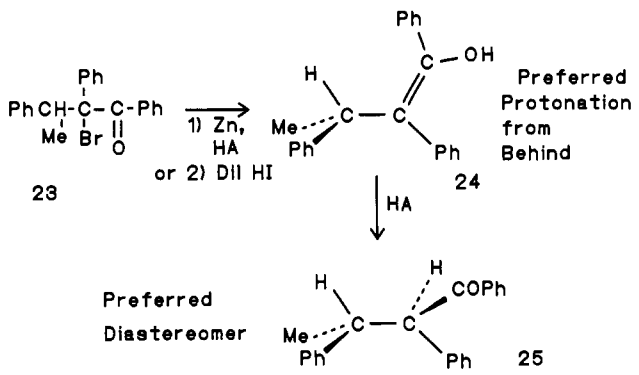
One exception where protonation of the neutral enol is likely is the debromination of α-bromo ketones with dilute HI in acetone. This is the approximate microscopic reverse of the acid-catalyzed bromination of ketones which proceeds via the enol.

A parallel situation was shown[5] to exist in the conversion of the aci-nitro isomer 11 of 2-phenyl-1-nitrocyclohexane (**12**) to its nitro tautomer. Here the conjugate base is protonated with facility while the aci-nitro

Scheme IV.
The Stereochemistry of Decarboxylation of 4-Phenylcyclohexane-1,1-dicarboxylic Acid



Scheme V.
Stereochemistry of Ketonization of 2,3-Diphenylbutyrophenone



compound itself is relatively unreactive. In summary, we may conclude that the most facile pathway for ketonization of unstable enols and their analogues is by initial ionization followed by carbon protonation of the conjugate base.

Further Examples of Kinetic Protonation. Thus far we have considered generation of the unstable enolic tautomers by conjugate addition to enones, by debromination of α-bromo ketones, by Barton reduction of enones, and by deprotonation–protonation. Still another reaction leading to enolic intermediates is the decarboxylation of substituted malonic acids. For example, the thermal decarboxylations of 2-phenylcyclohexane-1,1-dicarboxylic acid (**18**)[6] and 4-phenylcyclohexane-1,1-dicarboxylic acid (**20**)[3] led preferentially to the cis monoacid products (i.e., **19a** and **22a**, respectively). Again there is a transient enolic intermediate whose protonation determines the reaction stereochemistry. The example of 4-phenylcyclohexane-1,1-dicarboxylic acid decarboxylation is outlined in Scheme IV.

A more difficult problem is posed when the enolic carbon is adjacent to an asymmetric center of an acyclic enol. This problem was investigated[8] both experimentally and theoretically. One example studied was that of the enol of 2,3-diphenylbutyrophenone (**25**). The enol (**24**) was generated from the corresponding α-bromo ketone by debromination either with dilute HI in acetone or with zinc and various proton donors. Ketonization led preferentially to the erythro diastereomer as shown in Scheme V.

The theoretical approach utilized an algebraic solution of the minimization of van der Waals energy of repulsion between pairs of groups as a function of

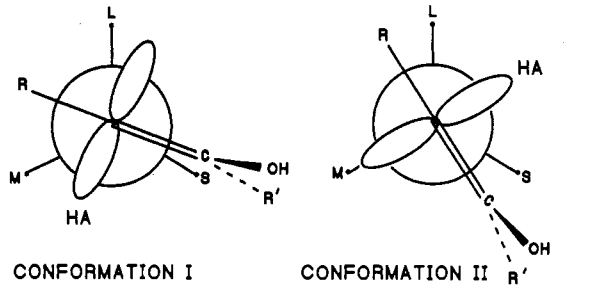
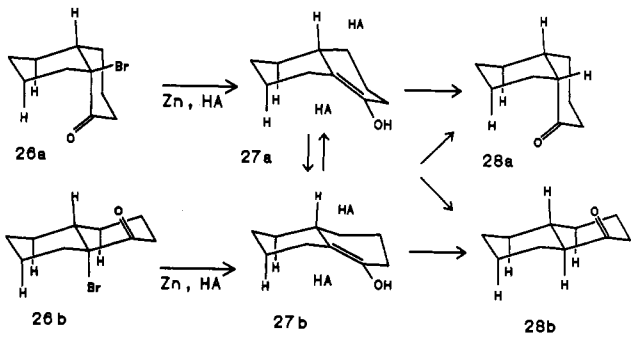


Figure 2. The preferred conformations of acyclic enols. In conformer I R is larger than hydrogen; in conformer II, the α-group is small, as hydrogen.

Scheme VI.
Ketonization of the $\Delta^{1,9}$ Enol of 1-Decalone



conformation and hence amounted to an analytic molecular mechanics treatment. It was ascertained that, where the substituent R in Figure 2 is appreciably large, the preferred conformation (i.e., conformer I) has the enolic double bond close to the small group on the adjacent chiral center as depicted in Figure 2. While one can anticipate that the steric effect of the proton donor will somewhat modify the preferred transition-state conformation, predictions based on this model have been remarkably good.[17] Also, this model rationalizes a modest number of cases presented in the original work[8] and also a number of subsequently described cases. Conformation II was calculated to be preferred where there was a very small group on the α-carbon such as hydrogen. An adequate series of tests of this latter suggestion is lacking.

Still another example of some interest is the kinetic protonation of the enol **27** of 1-decalone.[9] (See Scheme VI.) Here the enol was generated from the stereoisomeric α-bromo ketones (**26a, 26b**) under kinetic conditions with zinc and several proton donors. With acetic acid as a proton donor, the ketone product consisted of only 38% cis isomer **28a**, while with the bulky collidinium ion as donor 78% cis isomer **28a** resulted. Interestingly, when collidinium ion in methanol was employed, the stereoselectivity dropped to 59% cis product, suggesting that the donor was no longer collidinium ion but instead a smaller, methanol-related donor.

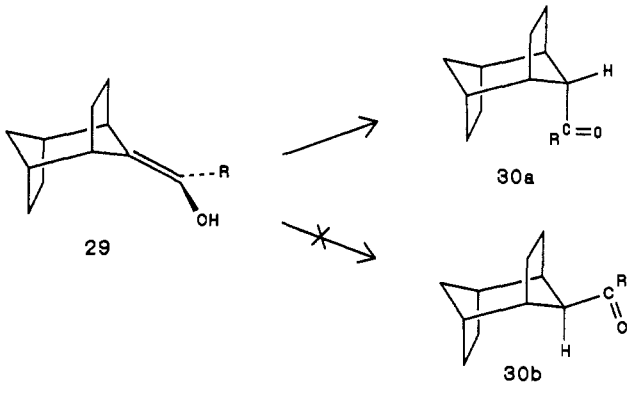
A further point is that there are several factors af-

(17) (a) More recent studies have been in agreement with this model. (b) For example, the model of Houk et al.[17c] seems to be in agreement with that discussed here. (c) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166.

(18) (a) Malhotra, S. K.; Johnson, F. *J. Am. Chem. Soc.* **1965**, *87*, 5493–5495. (b) Johnson, F.; Dix, D. T. *J. Am. Chem. Soc.* **1971**, *93*, 5931–5932.

(19) (a) Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1969**, *90*, 5933–5938. (b) Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1969**, *90*, 5939–5944.

Scheme VII.
Stereochemistry of Ketonization of the Tricyclic Enol

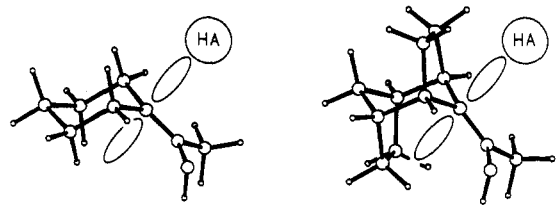


fecting the transition-state energies in this example. First, only the transition states *exo*-**27a** and *endo*-**27b** give protonation which is axial in the ring being protonated and thus satisfying the Corey requirement[20] (vide infra) for overlap. Second, only *exo*-**27a** and *exo*-**27b** minimize the steric effects we have considered. Hence, transition-state *exo*-**27a** satisfies both overlap and least hindered approach criteria, and its being favored with bulky donors is reasonable. The preference for *endo*-**27b** with small donors is also understandable to the extent that product stability is reflected to some degree in the transition state.

An example[12] of extreme stereoselectivity was encountered in the tricyclic system of enol **29** depicted in Scheme VII. Steric hindrance to endo protonation results from an ethano bridge, and only **30a** is formed. This is rather effective compared with the hindrance provided by the axial hydrogens at C-3 and C-5 of the simple exocyclic six-ring enols discussed above. Hence, it may not be surprising that a stereoselectivity of greater than 3000:1 was encountered.

Some Further Mechanistic Considerations. Several aspects remain to be discussed. For example, molecular mechanics calculations were carried out on **29** and several related enolic systems in order to assess the relative steric forces favoring exo over endo protonation. Figure 3 gives the drawings resulting from the molecular mechanics calculations[12] of the transition states for protonation of tricyclic enol **29** and also an ordinary cyclohexane exocyclic enol **31** lacking the ethano bridges. In each case, a proton donor was simulated by a spherical molecule of 3-Å van der Waals radius to approximate the size of ammonium ion. While only the preferred exo attack is drawn, it can easily be seen that the endo approach is subject to steric hindrance which is especially severe in the tricyclic case. Implicit in this treatment is the assumption that the transition state depicted has a geometry close to that of the reaction enol. The idealized model with a spherical proton donor is still another approximation. Interestingly, the energy difference in the case of the tricyclic enol is calculated to be ca. 14 kcal/mol (cf. **29**) and thus large, while that for a simpl exocyclic cyclohexane enol (**31**) is predicted to be only ca. 2.6 kcal/mol. Clearly, the precise values depend on many assumptions and are not to be used quantitatively. However, the large stereoselectivity encountered experimentally in the tricyclic example and the small selectivities found

(20) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.



31T **29T**

Figure 3. MM2–ORTEP drawings of two possible transition states for the tricyclic enol and a simple exocyclic cyclohexane enol.

in the simple cyclohexane cases are in agreement with the molecular mechanics findings.

The same publication considered the transition states for a series of different exocyclic six-ring enols. Of interest was the observation that two transition-state conformations were close in energy for the 2-phenyl-substituted enols. These were the exo protonation 2-(e)-phenyl and the endo protonation 2(a)-phenyl transition states with the former about 0.5 kcal/mol lower in energy. However, the ordering was dependent on enol hydroxyl being cis to the phenyl-bearing carbon (i.e., C-2). The 2(e)-phenyl transition state is the one we initially suggested, and the 2(a)-phenyl transition state was suggested as favored by $A^{1,3}$ strain by Johnson.[18] However, independent of which transition state is favored, both conform to the basic premise of the author, namely, that the kinetic protonation transition state is close to sp^2 hybridized and protonation occurs from the less hindered side of the molecule.

It is interesting that the 2-substituted cyclohexane exocyclic enols show higher stereoselectivity than the 4-substituted analogues. This may be an entropy effect in which a 2-phenyl group accentuates the effect of steric hindrance by eliminating some of the orientations of the proton donor as it approaches.

One other point is that the size of the proton donor is important as has been noted.[1-12] In a number of examples, some cited above, a small proton donor either gives little selectivity or actually favors formation of the more stable product.[19] Additionally, it needs to be pointed out that a variety of delocalizing groups give rise to sp^2-hybridized transition states with kinetic protonation occurring from the less hindered side of the anion. However, not all carbanions are protonated with this geometry. For example, a simple nonstabilized carbanion might be anticipated to be protonated in an sp^3-hybridized transition state and give rise to the more stable product. One example of a stabilized carbanion giving the more stable product is that of sulfone anions.[7] The stereochemistry observed thus is a function of the importance of electron delocalization by p–p overlap.

The Role of Overlap in Endocyclic Enols. Thus far we have discussed examples where steric control is the overriding factor, with the least hindered approach of the proton donor being preferred. While this type of control is most common, there is one further factor to be considered. Thus, in 1956 it was shown by Corey and Sneen[20] that, in the case of endocyclic six-ring enolate protonation, axial approach of the proton donor is preferred. The basis of this electronic effect was noted to be the requirement for continued overlap of the orbital being protonated at the enolate α-carbon. This effect has been studied and confirmed by a number of authors.[21-25] The selectivity observed in these

Table I.
Literature Examples Involving Kinetic Protonation of Enols and Enolates

type of system and reaction	result	ref
2,3-disubstituted indenone; electrochemical reduction	preferential formation of cis stereoisomer	28
6-phenyl-1-benzoylcyclohexene; Barton reduction	formation of *cis*-1-benzoyl-2-phenylcyclohexane	29
acyclic enones conjugate addition of $BuCu{\cdot}BF_3$	excess of meso diastereomer	30
hydrolysis of a bicyclo[4.2.1] 2,4,6-triene-7-ketene	formation of *endo*-carboxylic acid	31
hydrolysis of a 1,3,3-trimethylbicyclo[2.2.1] 2-ketene	formation of *endo*-carboxylic acid	32
2-methylcyclopentenone; conjugate addition of (2-methylphenyl)acetonitrile conjugate base	excess cis product	33
pilocarpine synthesis; kinetic protonation of an α-ethyl-3-substituted γ-butyrolactone enolate	cis/trans = 75:25	34
2-desoxycrustecdysone synthesis; kinetic protonation of a γ-butyrolactone enolate	conversion to cis isomer	35
enolic intermediate in a modified Nazarov cyclization	excess of cis isomer	36
synthesis of damsin; deprotonation of a cycloheptanone derivative and kinetic protonation	excess of unstable stereoisomer	37
isoserine synthesis; kinetic protonation of a lithium nitronate	erythro/threo = 66:33	38
synthesis of epidehydroaspidospermidine and relatives; kinetic protonation of an enol borate	cis product	39
hirsutic acid synthesis; LDA on ester followed by kinetic protonation	endo/exo (COOMe) = 5:1	40
conjugate addition of cuprates to acyclic enones with kinetic protonation	preferred formation of threo isomer	41
synthesis of carbapenem antibiotic from penicillins; conversion of a trans isomer to cis by kinetic protonation of a azetindinone enolate (β-lactam enolate)	excess of cis stereoisomer with Ph_3SnH as a bulky proton donor	42
conjugate addition of Grignard reagents to a 4-methoxy-1-nitronaphthalene	formation of excess *cis*-2-alkyl-1,2-dihydronaphthalenes	43
conjugate addition of methylcopper to acetylcyclohexenone	67% formation of *cis*-methyl-1-acetylcyclohexane	44
kinetic protonation of a β,γ-unsaturated γ-lactone having γ-benzyloxymethyl and α-isopropenyl groups in synthesis of terpenes	preferential formation of the cis β,γ-unsaturated ketone (62%)	45
protonation of a steroidal γ-lactone enolate at C-20	protonation from less hindered side	46
kinetic protonation of a γ-lactone enolate in the synthesis of iboga alkaloids	used to invert chiral center at 2-position to give *cis*-lactone in excess (1:4.7 to 1:9 with different proton donors)	47
kinetic protonation of a α-tolyl-γ-benzyloxymethyl γ-lactone in synthesis of sesquiterpene nuciferol	cis product in 74% yield as only observed product	48
protonation of C-20 in a γ-lactone steroid side chain	75% of one diasteromer resulting from protonation from the least hindered side	49
protonation of the α-carbon of γ-lactone enolates	protonation from the less hindered side with ratio depending on proton donor	50
Barton reduction of 4-*tert*-butyl-1-aroylcyclohexenes and Zn–HA on 1-aroyl-1-bromo-4-*tert*-butylcyclohexanes	excess cis isomer formed depending on conditions	51
2-nitrobicyclo[2.2.1]heptane protonation of conjugate base	86% endo	19

studies is consistent but small, corresponding to less than (ca.) 1 kcal/mol.

The selectivity encountered as the result of steric effects ranges from a similarly small magnitude to large selectivities of the kind observed in the case of the tricyclic enol discussed above.

There appear to be examples where overlap and steric control are both involved. One example is the conjugate addition of the conjugate bases of certain arylacetonitriles and arylthioacetonitriles to 2-substituted cyclohexenones, a reaction reported[26] to give the cis product predominately. Still another such reaction is the conjugate addition of $MeC(SeMe)_2Li$ to 2-methylcyclohexenone.[27] The kinetic preference for cis products has been interpreted as arising from protonation being more rapid than conformation equilibration.[26] Kinetic protonation axially to give the less stable cis product is favored by both electronic overlap considerations and also least hindered approach. Nevertheless, were conformational equilibration to be rapid, one might anticipate that the less hindered protonation would still be trans to the β-substituent on the basis of steric hindrance.

The Utility and Generality of Kinetic Protonation. Thus far we have considered a variety of reactions

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which proceed via enolic and similar intermediates, where the reaction stereochemistry can be understood as being determined in a kinetic protonation step. Indeed, kinetic protonation has been used in an exceptionally broad variety of synthetic organic chemistry, particularly in natural product synthesis. Often, for example, a substrate having an undesired configuration is deprotonated to afford an enolate and then reprotonated under kinetic conditions to afford the desired diastereomer. This naturally is practical only where the less hindered protonation process leads to the desired product. In Table I there is summarized a number of literature examples where our concept of least hindered approach of a proton donor has proven useful.

Concluding Remarks. Our discussion has dealt with the broad spectrum of reactions proceeding via transient enolic, or similar, intermediates which have the a priori possibility of protonating to give stereoisomers. Since there are so many such reactions, an understanding of the stereochemistry of kinetic protonation leads us to an ability to understand, and often control, reaction stereochemistry. In this Account we have made a number of approximations. One is that the protonation transition state most often is very close to sp^2 hybridized. Despite the approximations, the constancy of the stereochemical outcome is considerable. In fact, it is likely that the most remarkable feature of the subject is the surprising constancy of the observed effect, not only in a broad variety of molecular systems but also over three decades of investigation and use.

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