The Curtin–Hammett Principle

A Qualitative Understanding

Suchandra Chakraborty and Chandan Saha

This article qualitatively discusses the Curtin–Hammett principle without mathematical treatment of the kinetic model. We show how the practical application of this principle can be extended to tautomers of several compounds and to explain the diazotization of aniline. The concept of 'kinetic quenching' is also discussed as a system where the Curtin–Hammett principle is inapplicable.

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1. Introduction

The relationship between conformation and chemical reactivity was first highlighted by D H R Barton in 1950. This classical work led to the conceptualization of the Curtin–Hammett principle and the Winstein–Holness equation which provided the first quantitative relationship between conformations and their chemical reactivity. The Curtin–Hammett principle was suggested in the early 1950's to alert chemists to the possibility of miscalculating the product distribution by using only the equilibrium distribution of conformations of the ground states. In fact, the original statement of the principle gave the idea that the product composition from the two conformations which are in rapid equilibrium is not solely dependent on the relative population of the conformational isomers of the substrate; it is controlled by the difference in standard free energies of the respective transition states.

There are reviews [1, 2] that deal with the Curtin–Hammett principle and the kinetic aspects of this principle, the mathematical derivation of which is known as Winstein–Holness equation. All these papers resort to rigorous mathematical treatment to explain the principle which makes it difficult for undergraduate students to understand. Here, we intend to provide a qualitative understanding with concise description of the theory and its

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Organic chemistry, qualitative physical interpretation, history, philosophy, applications in chemistry, kinetic quenching.

applications along with some historical details without mathematical treatment. History and philosophy of science, currently considered as important classroom tools, may help in the understanding of both scientific knowledge and its progress.

From the literature [1, 3 and 4], we have chosen two definitions of the Curtin–Hammett principle, and these are as follows:

1. The relative amounts of product formed from two critical conformations are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion [1].

2. In a chemical reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and provided these two isomers are rapidly interconvertible relative to the rate of product formation, whereas the products do not undergo interconversion) the product composition is not in direct proportion to the relative concentrations of the conformational isomers in the substrate; it is controlled only by the difference in standard Gibbs energies of the respective transition states [3, 4].

A closer scrutiny of these two descriptions reveals that the Curtin–Hammett principle is related to conformational equilibrium of a substance, and reactivity of the conformations guides the product ratio. The years 1950–1955 witnessed a rather spectacular series of major breakthroughs which culminated in a set of fundamental concepts and principles on conformational analysis. D H R Barton has been acknowledged and credited for his 1950 pioneering publication in *Experientia* [5], which was based on examination and understanding of the effects of conformation, and stereochemistry on chemical reactivity. In the meantime, after studying the pinacolic deamination of aminoalcohols through conformational analysis, Pollak and Curtin put forward the fundamental concepts [6,7] of what was years later referred to as the Curtin–Hammett principle. How the principle got named is portrayed in *Box* 1 [1].

Box 1. Naming of the C–H Principle

Curtin, in his often cited 1954 review 'Stereochemical control of organic reactions' in the *Record of Chemical Progress*, has emphasized that the underlying concepts were "pointed out by Professor L P Hammett in 1950".

Hammett, on his part, has rendered complete credit to Curtin: "Because Curtin is very generous in attributing credit, this is sometimes referred to as the Curtin–Hammett principle [rather than] the Curtin principle."

In this context, it is pertinent to mention that the basic concept of the Curtin–Hammett principle was put forward by Hammett in 1950. However, the principle was properly recognized by Curtin in 1954 and supported by the mathematical derivation of Winstein–Holness equation in 1955. The introductory impulse behind the development of this Winstein–Holness equation [1] was a statement of Barton[1].

[1] The quantitative aspects of this subject (conformational analysis) have, however, been scarcely touched and it is clear that much useful work can be done by physical organic chemists in this direction.

D H R Barton, 1955

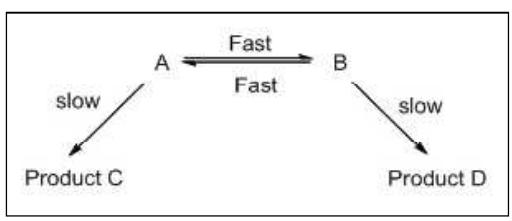
It is worthwhile to note that Holness was a PhD student of Barton and his tenure overlapped with that of Winstein during his postdoctoral work at Holness' laboratory. This mathematical treatment of Winstein–Holness equation is beyond the scope of our discussion.

2. The Curtin–Hammett Principle

Let us consider the following equilibrium (*Scheme* 1) where A and B are two conformations of a reactant and C and D are two products from A and B, respectively. To apply the Curtin–Hammett principle to this equilibration, the essential postulate is that the energy barrier for the interconversion of A and B is much lower than the energies of activation of the two reactions. Under such circumstances, the question is which will be the product: C or D? This actually depends on the free energies of activation of the two reactions. There are four possible situations:

Case I. More stable conformation leads to the major or exclusive product provided the rate of the reaction of more stable conformation is higher than that of the less stable one.

Case II. Less stable conformation leads to the major product provided the rate of the reaction of less stable conformation is higher than that of the more stable one.



Scheme 1. Basic scheme of the Curtin–Hammett principle.

Case III. More stable conformation can lead to the major product even when it is assumed that the rates of the reactions of two conformations are comparable.

Case IV. When the stability of two participating conformations is equal, i.e., these are equally populated, then that conformation leads to the major product which is associated with lower free energy of activation.

Now we look at each case in greater detail.

2.1 *Case* I

In *Figure* 1, which shows the corresponding energy profile diagram, the free energy of activation of the reaction A to C is lower than that of B to D. Under such circumstances, the percentage population of A will be higher and at the same time A will react at a faster rate. Accordingly, as fast as A is consumed, equilibrium will shift towards A, and consequently C is the major or the exclusive product.

An example [8] of this situation of Curtin–Hammett principle is the base-induced dehydrohalogenation of 2-bromobutane (*Scheme* 2). Here also, both the isomers are formed by *anti*-elimination processes, but these processes involve stereochemically distinct diastereotopic hydrogens and conformational analysis indicates

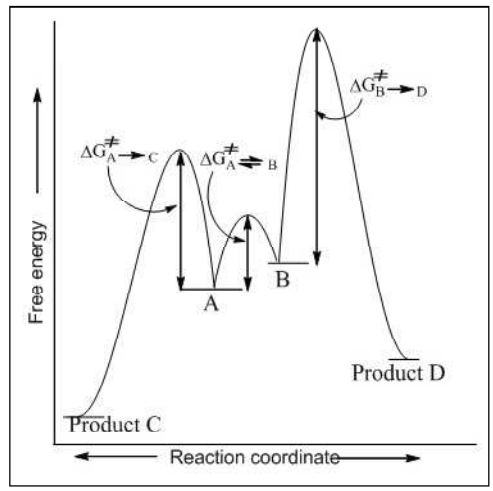
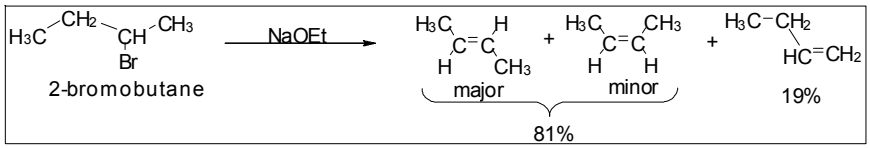


Figure 1. Free energy profile diagram for Case I.



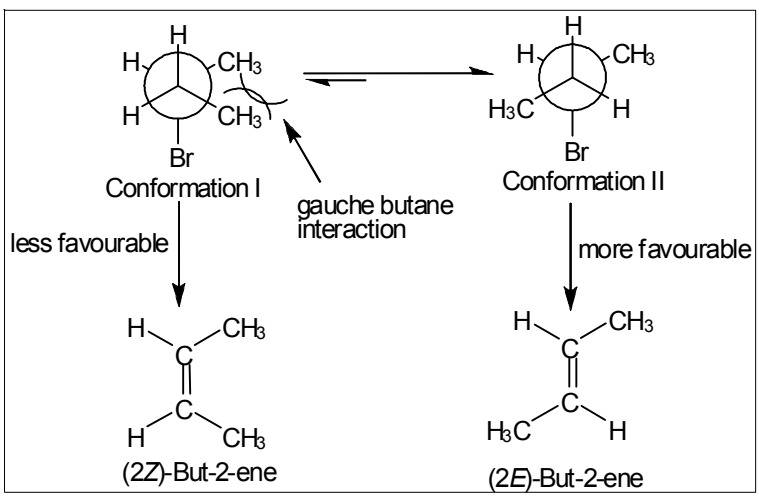
Scheme 2. Dehydrohalogenation of 2-bromobutane.

the preferential formation of *E*-alkene (*Scheme* 3). In the case of conformation I, due to the gauche butane interaction between two methyl groups, a relatively smaller proportion of the molecules will adopt the right conformation for elimination and consequently slowing the process down. In addition, the transition state is expected to be associated with the higher free energy of activation through an interaction between the methyl groups. But in the case of conformation II, there is no such gauche butane interaction[2]; consequently, a relatively larger proportion of the molecules will adopt the right conformation for elimination and thus the reaction rate is expected to be higher. Again, here the transition state is expected to be associated with a lower free energy of activation than that in the formation of the *cis*-isomer.

[2] The term 'gauche' refers to conformational isomers (conformers) where two vicinal ($-CH_3$ in this case) groups are separated by a 60° torsion angle.

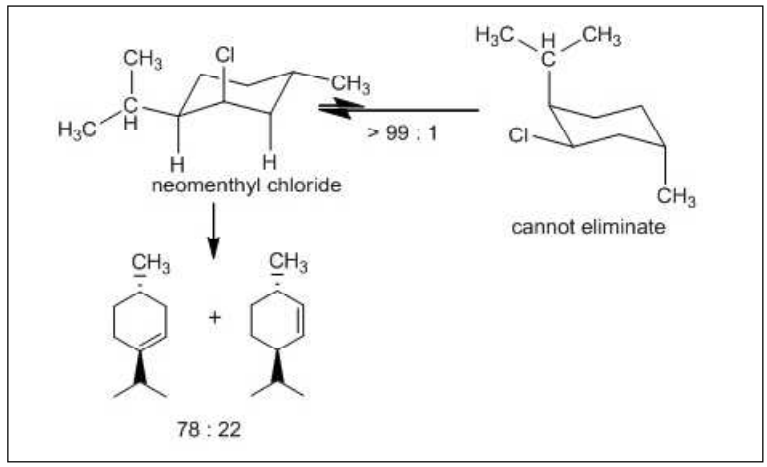
Another example is the base-induced elimination [9] of neomenthyl chloride (*Scheme* 4). Here, the conformation that is highest in concentration is the one that participates in the elimination reaction only due to its proper conformational orientation to achieve possible products; the ratio of product composition is determined by simple Saytzeff's rule[3]. Obviously, in both the

[3] Saytzeff's rule, also called Zaitsev's rule, is an empirical rule which states that in an elimination reaction, the alkene formed in greatest amount is the one that corresponds to the removal of the H-atom from the β-carbon having fewest hydrogen substituents.



Scheme 3. Conformational analyses to obtain two isomeric 2-butene.

Scheme 4. Elimination reaction of neomenthyl chloride under alkaline condition.



cases (*Schemes* 2 and 4) the more stable conformer leads to the major or exclusive product.

2.2 *Case* II

In *Figure* 2, the free energy of activation of the reaction B to D is lower than that of A to C. Undoubtedly under such a situation the percentage population of A will be higher but B will react at a faster rate. As a result, as soon as B is consumed, it is replenished from A as the energy barrier for the interconversion of A to B is low enough. Consequently, D becomes the major product.

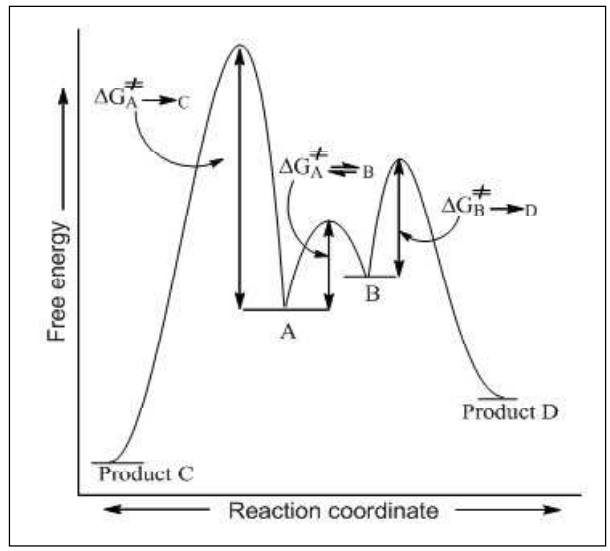
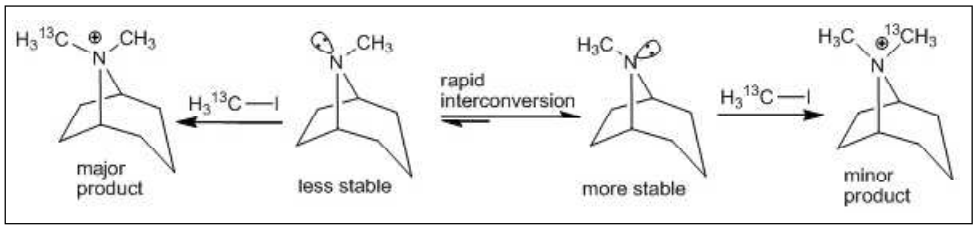


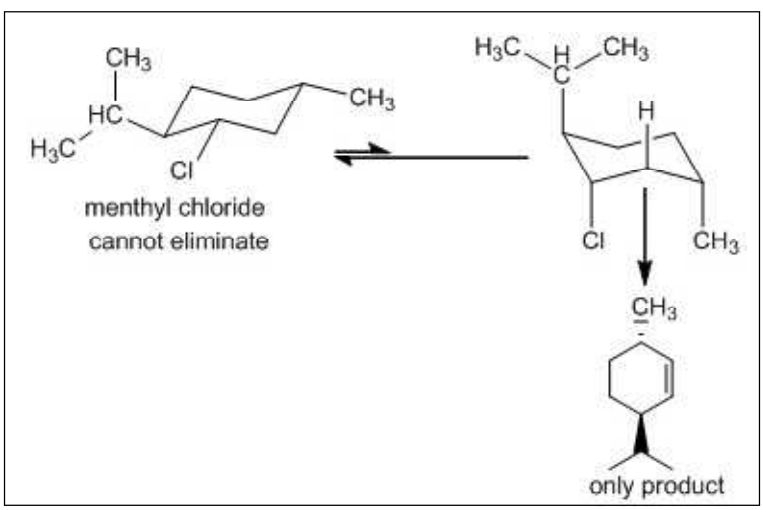
Figure 2. Free energy profile diagram for Case II.



Scheme 5. Methylation of tropane.

The alkylation of tropane [10] with methyl iodide (*Scheme* 5) is a classic example of a Curtin–Hammett scenario in which a major product can arise from a less stable conformation (as here Me group occupies an axial position of six-membered piperidine moiety). The less stable conformer reacts via a more stable transition state to form the major product. Therefore, the ground state conformational distribution does not reflect the product distribution.

Another example [9] of such a situation is the base-promoted elimination on menthyl chloride (*Scheme* 6). Here, very little of the productive conformation exists in the solution, but it is the only reactive conformation due to the 'anti-periplanar' arrangement of the leaving group and hydrogen that facilitates the reaction to the only corresponding product. Thus, from the Curtin–Hammett principle, we can say that the ground state conformation need not be the only decisive factor in determining the product of a reaction.



Scheme 6. Elimination of menthyl chloride under alkaline condition.

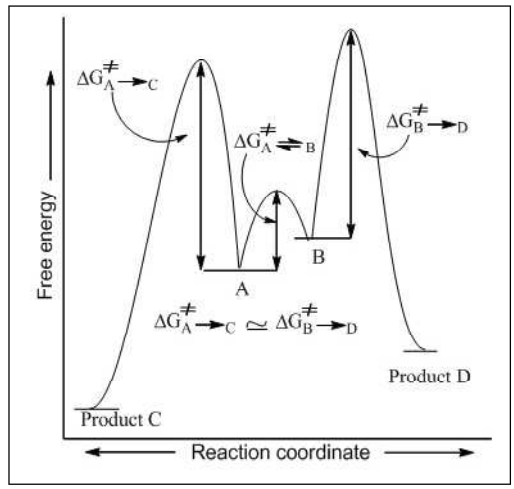
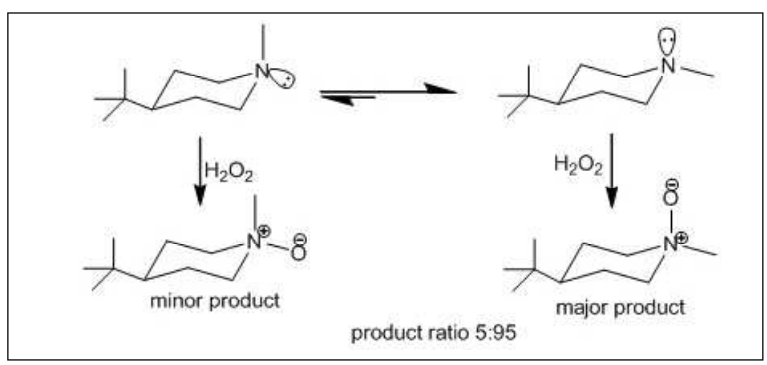


Figure 3. Free energy profile diagram for Case III.

2.3 *Case* III

In *Figure* 3, the free energy of activation of the reaction A to C is comparable to that of B to D. Consequently, the percentage population of A is higher. Since A and B react at almost the same rate, the equilibrium of the reactants remains undisturbed. Accordingly, it is the equilibrium distribution of the two conformations which determines the product ratio.

An example of this scenario is the oxidation of piperidines [1]. In the case of *N*-methylpiperidine (*Scheme* 7), inversion at nitrogen between diastereoisomeric conformers is much faster than the rate of amine oxidation. The conformation which places the methyl group in the equatorial position is more stable (energy difference 3.16 kcal/mole) than that of the axial conformer. The



Scheme 7. Oxidation of 4-*t*-butyl-*N*-methylpiperidine.

product ratio of 95:5 indicates that the more stable conformer leads to the major product, if it is assumed that the rates of the reactions of two conformers are comparable as the electrophile is less bulkier.

2.4 *Case* IV

In *Figure* 4, A and B are of comparable stability and thus they are equally populated. The free energy of activation of the reaction A to C is higher than that of B to D. Therefore, D is the major product because, as soon as B is consumed, it is replenished from A.

This situation can be exemplified as, in *trans*-2-halocyclohexanol, the diequatorial conformer is stabilized through intramolecular H-bonding and the diaxial conformer has the advantage of the absence of electrostatic repulsion between the two dipoles. A compromise is reached and the two conformers are almost equally populated [11]. When *trans*-2-halocyclohexanol is treated with alkali [9], only the *trans*-diaxial conformer leads to the formation of epoxide due to the proper conformational arrangement of the participating groups (*Scheme* 8).

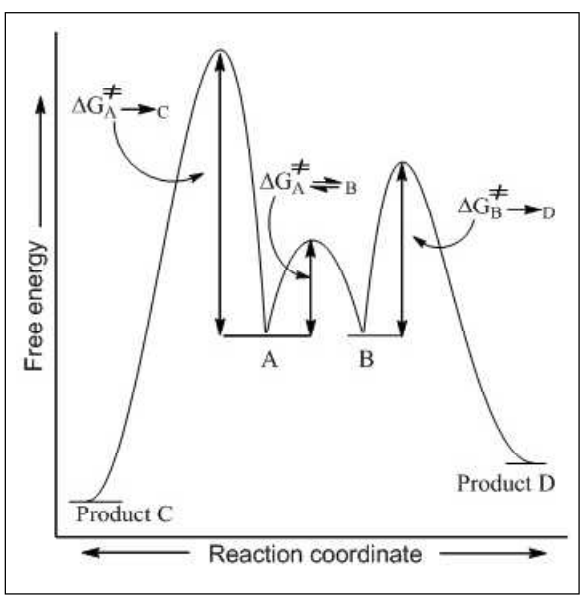
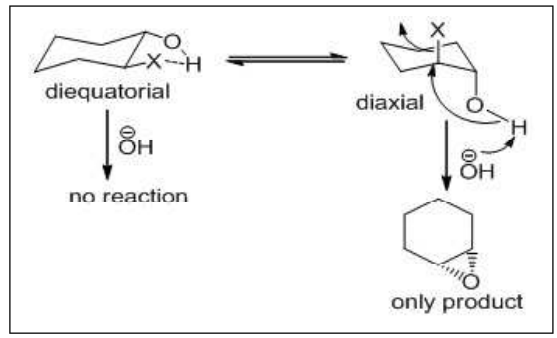


Figure 4. Free energy profile diagram for Case IV.



Scheme 8. Reaction of *trans*-2-halocyclohexanol under alkaline condition.

3. Curtin–Hammett Principle: Retrospective Application

The Curtin–Hammett principle had not been spelt out in the early days (before 1950) because of lack of proper knowledge on conformations and reactivity. A point to be noted is that the actual statement of the Curtin–Hammett principle deals with conformations only. In this section, we put forward our understanding of the principle and apply it to past instances. We show that the principle is not confined to conformations only, but in a true sense has a wide applicability.

3.1 *Acetoacetic Ester*, 1862

In 1862, Geuther [12] first noticed acetoacetic ester (EAA) and prepared it by the action of metallic sodium on ethyl acetate. He proposed a formula (*Figure* 5). In 1865, Frankland and Duppa, independently of Geuther, also prepared acetoacetic ester by the action of metallic sodium on ethyl acetate, but suggested another formula (*Figure* 6).

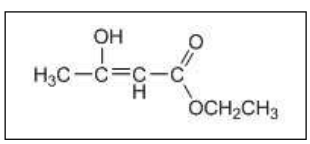


Figure 5. β-hydroxycrotonic ester.

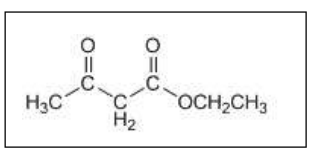
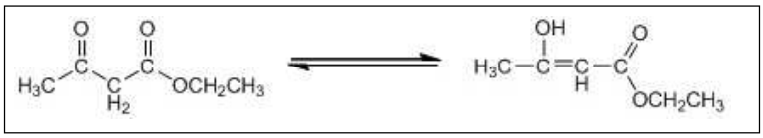


Figure 6. β-ketobutyric ester.

These two formulae immediately gave rise to two schools of thought, one upholding the Geuther formula, and the other the Frankland–Duppa formula, each bringing forward evidences [12] to prove its own claim. Thus, a remarkable situation originated where it was possible to show that a given compound had two different formulae, each of which was grounded on a number of specific reactions. The controversy continued till 1910, when



Scheme 9. Two tautomeric forms of ethyl acetoacetate (EAA).

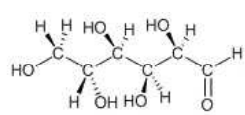
chemists reconciled to the idea that both the formulae were correct, and that the two compounds existed together in equilibrium (*Scheme* 9).

This is a case of dynamic isomerism, and the name tautomerism was given to this phenomenon by Laar (1885). These two forms are known as tautomers. When a reagent, which reacts with ketones, is added to EAA, the keto-form is removed. Consequently, to restore the equilibrium, the hydroxy-form of EAA changes into its keto-form. Similarly, when a reagent, which reacts with alkenes or with hydroxy compounds, is added in sufficient quantity to EAA**,** it reacts completely as the hydroxy form. But how this phenomenon (the consumption of one form leading to the spontaneous regeneration of another) is kinetically possible was not known at that time. Obviously, this was not satisfactorily explained until the formulation of the Curtin–Hammett principle.

3.2 *Glucose*, 1891

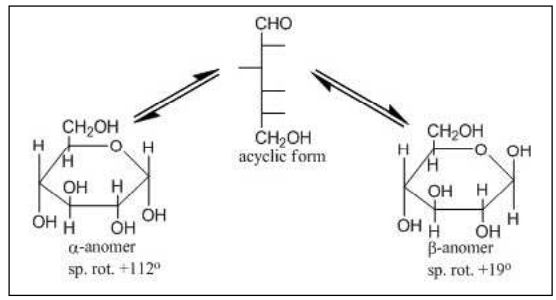
In 1891 [13], after Fischer's announcement of the straight chain relative configuration of (+)-glucose, two of his prized pupils – Heidi and Heinz – found two forms of pure (+)-glucose, with an almost same melting point, but completely different values of specific optical rotation (+112° and +19°). Till then, (+)-glucose was represented by the usual convention in Fischer projection. However, in reality, (+)-glucose has an infinite number of molecular conformations in linear zigzag form[4]. Heidi noted that the optical specific rotation of one form of (+)-glucose decreased from +112° to +52° on dissolving in water, and Heinz observed that the value for the other form of (+)-glucose increased from +19° to +52° under the same conditions. This simple physical observation was explained by the young researchers using the equilibrium shown in *Scheme* 10.

[4] If one observes the molecular model of (+)-glucose ($C_6H_{12}O_6$), a linear, zigzag conformation seems attractive:



By rotation around the various carbon–carbon bonds present, the configuration of the molecule does not change but leads to an infinite number of other conformations.

Scheme 10. Ring-chain tautomeric forms of (+)-glucose.



This phenomenon is known as mutarotation – an outcome of ring-chain tautomerism. As mentioned before, two new cyclic forms were suggested by Heidi and Heinz – indeed that glucose may have a cyclic form had already been suggested by von Bayer in 1870. Fischer, somewhat surprisingly, never completely accepted this concept.

[5] Anomers are diastereoisomers of cyclic forms of sugars.

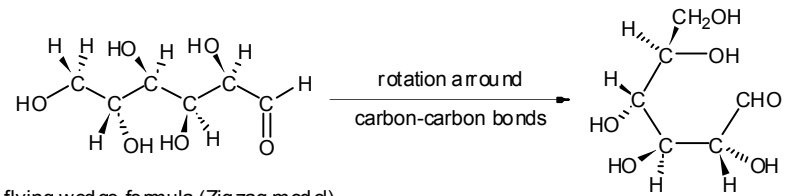
One may infer from the values of specific rotations of the two anomers[5], that in an aqueous solution, glucose exists in rapid equilibrium with its open chain and cyclic form, the linear form in virtually negligible amounts although it gets replenished as fast as it is consumed (*Box* 2). Moreover, due to the aldehyde group in its open chain form, glucose displays various reactions such as osazone formation, nitric acid oxidation; and the cyclic form causes reactions such as Br_2–water oxidation, acetal formation, etc. All these explanations are in accordance with the concept of Curtin–Hammett principle which are ingrained in the very discovery of Heidi and Heinz.

3.3 1-*Phenyl*-1*H*-1,2,4-*Triazole*-3,5-*Diol*, 1907

In 1907, Solomon F Acree published a paper [14] on his work on the diazomethane treatment on two tautomers of 1-phenyl-1-H-1,2,4-triazole-3,5-diol (*Scheme* 11). He found that the less stable enol form gives the major product unlike the keto (amide) form which is more stable. He concluded that "such reactions … do not give us decisive evidence in regard to the relative amounts of the enol and keto forms in any given amide group" [14]. Retrospectively, it is clear that his work largely outlined the concepts of the Curtin–Hammett principle and the Winstein–Holness equation.

Box 2. Diastereoisomeric Forms of Glucose

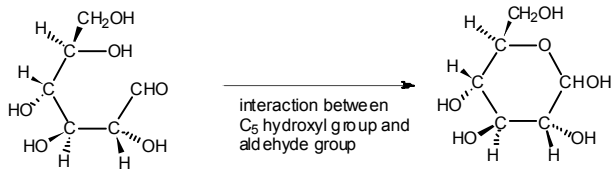
Close scrutiny of the zigzag model of the glucose molecule reveals that in atleast one of its conformations, the hydroxyl group on C_5 is adjacent to the carbonyl group.



flying wedge formula (Zigzag model)
acyclic form (I)

C_5 hydroxyl group is closer to aldehyde group

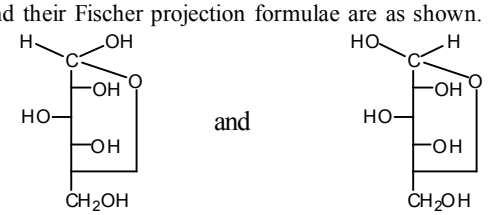
Consequently it is not surprising that the hydroxyl group of C5 interacts with the aldehyde group to form a hemiacetal.



C_5 hydroxyl group is closer to aldehyde group
acyclic form (I)

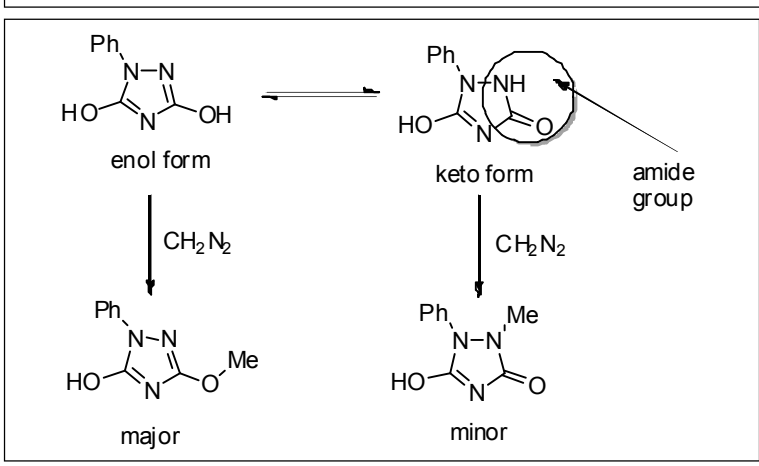
cyclic form

This new cyclic form structure contains a stereogenic centre at C_1 and thus it can exist in two diastereoisomeric forms and their Fischer projection formulae are as shown.



cyclic form (II)

cyclic form (III)



Scheme 11. Diazomethane treatment on two tautomers of 1-phenyl-1-H-1,2,4-triazole-3,5-diol.

3.4 *Diazotization of Aromatic Amines*

A common question to the students in their practical classes is: how can the diazotisation of an aromatic amine, say aniline, proceed under acidic condition while it remains in the protonated state? This can be explained by considering the Curtin–Hammett principle (*Scheme* 12). Here, when the aromatic amine is dissolved in aqueous acid medium, most of it gets converted to the corresponding amine hydrochloride. Yet the lower concentration of free amine leads to the corresponding diazonium salt as activation energy for the diazotization of free aromatic amine is lower. Thus the reaction goes to completion.

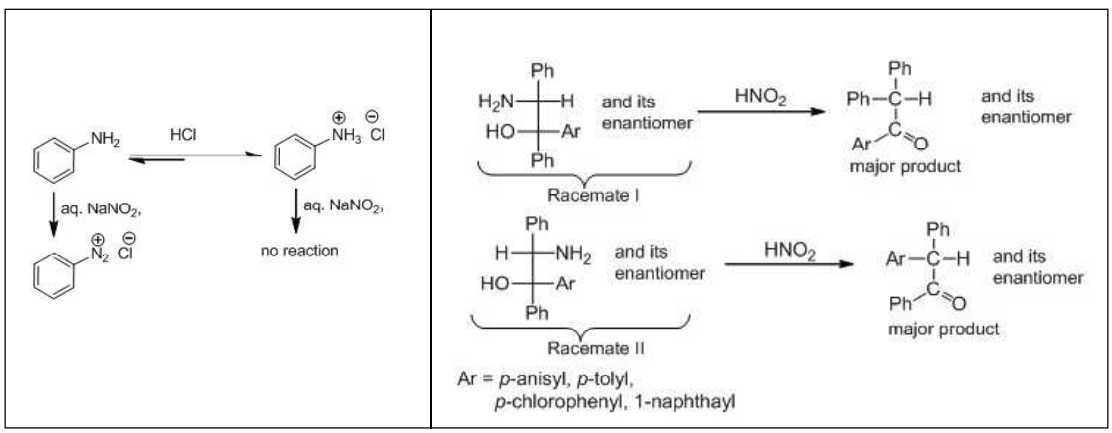
4. Development of the Curtin–Hammett Principle

In 1950, Curtin and Pollak were studying the rearrangements of aminoalcohols by treatment with nitrous acid [6,7]; from the nature of the products, they successfully established the configuration of diastereoisomeric aminoalcohols. Their observations are shown in *Scheme* 13. In this regard, Hammett and Curtin made the statements given in *Box* 3 [1].

Scheme 12 (left). Diazotization of aniline.

Scheme 13 (right). Curtin and Pollak's work on aminoalcohol rearrangement.

A closer look at their work shows that in one diastereoisomer the phenyl group migrates in preference to the aryl group, whereas, in another diastereoisomer the aryl group migrates in preference to the phenyl group. Thus the product formed from two diastereoisomers not only depends on the relative populations of their



Box 3.

At that time ('over 25 years ago') the idea was prevalent among chemists that one could determine the configuration of a reactant from the structure of a reaction product. At that time Curtin was on the staff at Columbia, and was puzzled about this idea. In a rather casual conversation I pointed out that, in terms of transition-state theory, the idea was fallacious and that the structure of the product from a rapidly interconverting set of conformers was determined solely by the structure of the transition state.

Louis Plack Hammett (1980)

I can't, in all honesty, recall any details of our conversation (with Hammett) and, in fact, it may have been Peter Pollak who first presented Louis (Hammett) with the problem... When Peter Pollak (one of my earliest graduate students) was carrying out his work on the effect of configuration on the course of reaction of diastereoisomeric amino alcohols with nitrous acid, we had attempted at length and unsuccessfully to find some basic relationship between the relative rates of formation of the two rearrangement products on the one hand and the conformational equilibria on the other. Thinking that there might be a complex underlying theory, we talked at some length to Ralph Halford about the possibility of some statistical mechanical approach which might be fruitful but were still not happy with anything that any of us had thought of.

David Y Curtin (1980)

conformations but also on the transition state energies. This was recognized by Pollak and Curtin from their studies in 1954. Although this work was not related, at least wholly, with the Curtin–Hammett principle, it was this study which ultimately led to the development of Curtin–Hammett principle (*Box* 4). There

Box 4. Excerpts from Curtin and Pollak's Original Paper [6]

To explain the preferential migration of Ph group for the Racemate I (V in the figures), they stated: "The geometry of the reacting molecule can influence the reaction in one or more of several possible ways. Molecules with the general formula V have three staggered configurations which are presumed initially to be in equilibrium with one another. Should Va have a sufficiently lower free energy to be present in appreciably greater concentration than Vb, a larger fraction of rearranging molecules would have the correct configuration for the replacement of nitrogen by phenyl rather than by aryl." See *Figure* A.

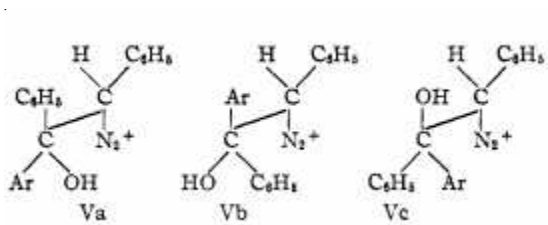


Figure A.

Box 4. Continued...

Box 4 Continued...

"Furthermore, if the diazonium ion V loses nitrogen with simultaneous migration of phenyl, the transition state has the configuration VIa while migration of aryl leads to transition state VIb. It seems possible that VIa may be of sufficiently lower energy than VIb to influence the relative rates of the two migrations." See *Figure* B.

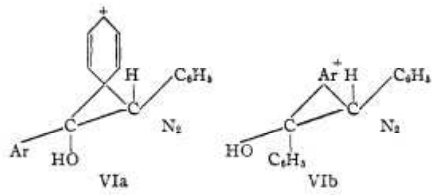


Figure B.

is another very interesting literature [9] with a precedence of this observation as stated by Eliel in *Box* 5.

With the help of this concept we can explain the actual observation of Pollak and Curtin (*Scheme* 14).

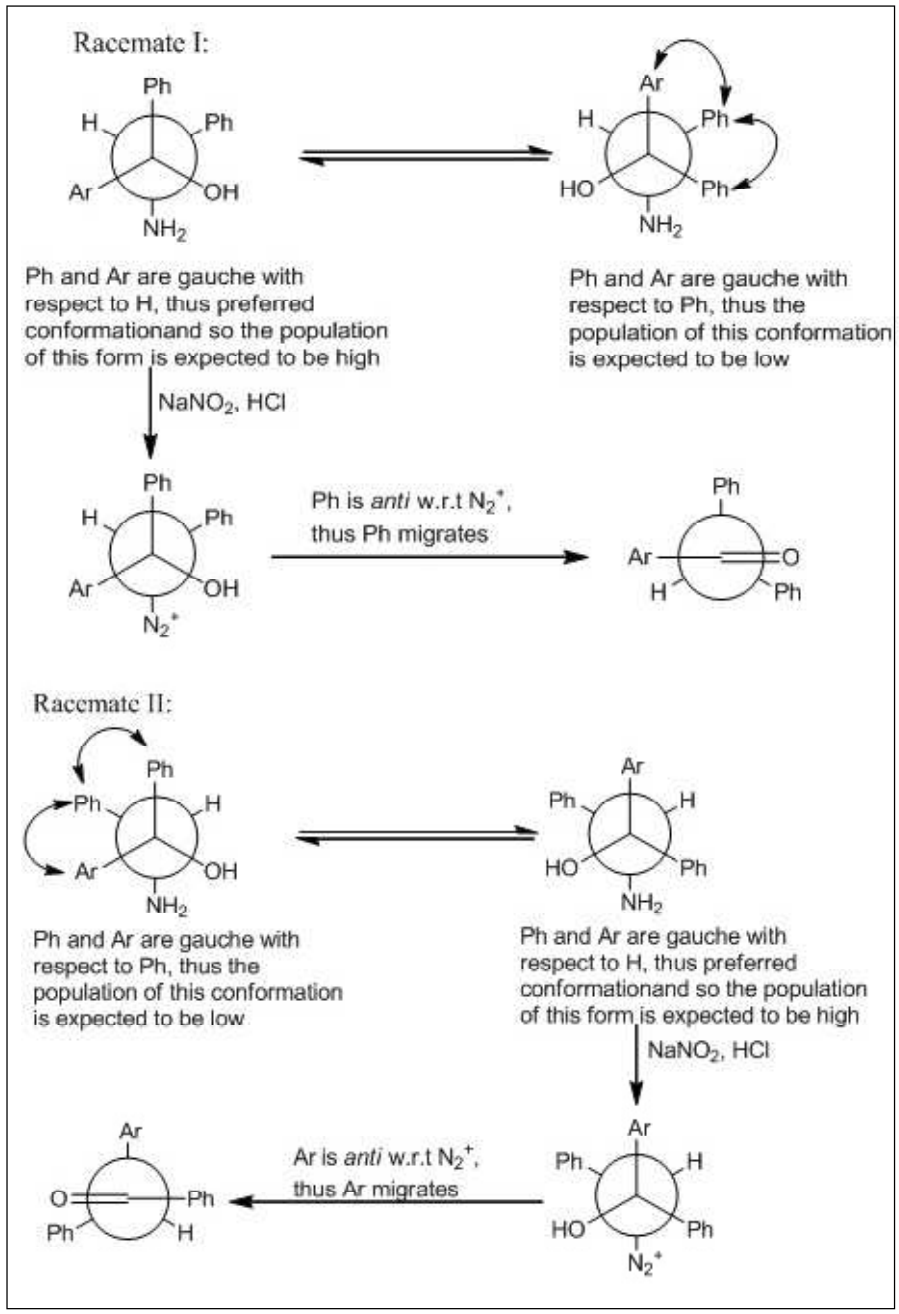
5. The Concept of Kinetic Quenching

The studies of Curtin–Pollak on pinacolic deamination dictate that this article cannot be rounded off without referring to the situation where the Curtin–Hammett principle is not applicable, i.e., where the rates of reactions are faster than the rate of interconversion of two conformations (*Scheme* 15).

Box 5.

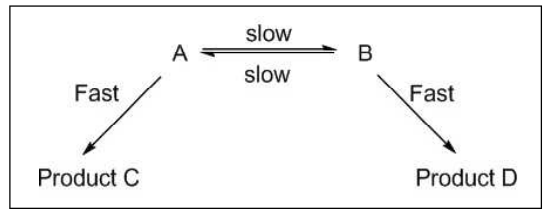
The explanation given for preferential migration….would seem to be contrary to the Curtin–Hammett principle, in as much as this explanation was based on ground-state conformations. It must be pointed out, therefore, that the principle cannot be expected to apply to this case. The essential step in the deamination (amine-nitrous acid) reaction is the loss of nitrogen from the diazonium salt intermediate. All evidence points to the fact that this step has a very low activation energy and that the assumption embodied in the Curtin–Hammett principle, namely, that the activation energy of the processes studied is large compared with the barrier to the internal rotation, can thus not be made in this case. If one makes the extreme opposite assumption, namely that the activation energy in the deamination is very small compared with the barrier height, then conclusion would follow that the ratio of the products is equal to ratio of the population of the starting states.

L E Eliel (1994)



Scheme 14. Rearrangement of aminoalcohols.

Scheme 15. Basic scheme of kinetic quenching.



Here, A and B are two conformations of a reactant and C and D are two products from A and B, respectively. However, A and B cannot equilibriate during the course of the reaction and the product composition is simply dependent on the population of reactants. This is actually known [15] as 'kinetic quenching', as A and B are quenched by the reaction in their equilibrium concentrations (*Figure* 7). Here, when B is consumed at a faster rate, it is not replenished from A as the energy barrier for the interconversion of A to B is high enough in comparison to the reaction rates. As a result, A and B will react accordingly to yield the product C and D, respectively. Since the percentage population of A is higher than that of B, C will be the major product.

Protonation of a tertiary amine with trifluoroacetic acid may be considered to be an example of kinetic quenching [16] (*Scheme* 16). In the case of 1,3,5-trimethylpiperidine shown, the inversion at nitrogen between diastereoisomeric conformers is much slower

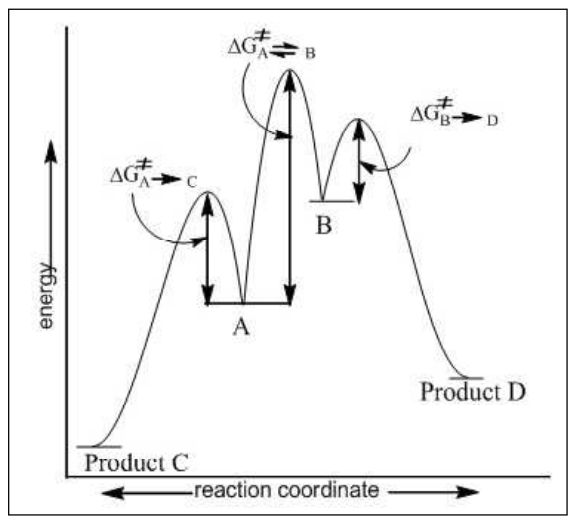
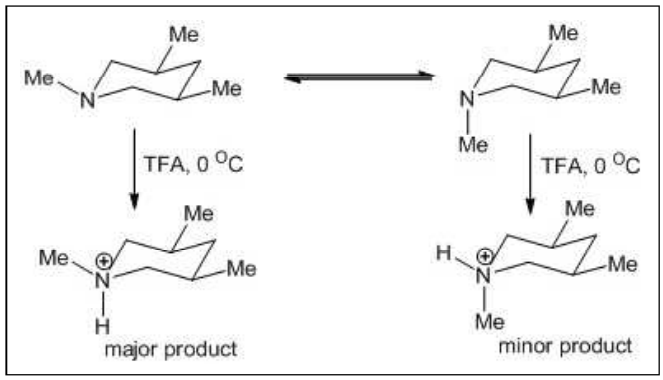


Figure 7. Free energy profile diagram for kinetic quenching.



Scheme 16. Kinetic quenching: protonation of a tertiary amine with TFA.

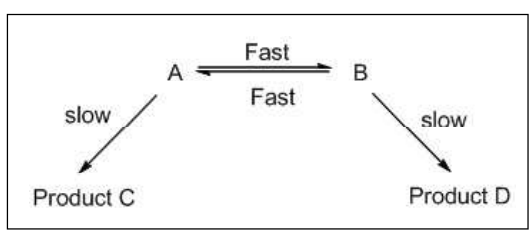
than the rate of protonation on nitrogen. The conformation which places the methyl group in the equatorial position is more stable than the axial conformer. The product ratio indicates that it is the more stable conformer which determines the major product (>15:1).

However, here the results may be complicated to some extent because of the possibility of interconversion of products.

Our above discourse indicates that though Curtin was unable to explain all the observations of his experiment in the initial stage, yet he was able to develop a basic principle in 1950 and the principle was biased almost towards the conformational equilibrium. However, if we analyse historical anecdotes along with the phenomena in present day science, we find that the Curtin–Hammett principle has a wide applicability.

So, the Curtin–Hammett principle can be reframed thus (*Scheme* 17):

In a chemical reaction, which yields one product from one form of a substrate and a different product from another form of the same



Scheme 17. Reframed scheme for Curtin–Hammett principle.

substrate, the product composition (one of the forms may not even undergo any reaction) is not solely dependent on the relative populations of the forms, but is controlled by the difference in free energies of activation for the two reactions provided that:

- The two forms of the substrate are a) a conformation, or b) a tautomer, or c) an acid or a basic form and its conjugate base or acid, respectively, under acid-base equilibria.
- These forms have equal or different stability.
- The products are not interconvertible.
- The two forms are rapidly interconvertible relative to the rates of products formation.

The major product will be obtained from that form (population of which may be higher or lower or equal) which is associated with the lower free energy activation for the corresponding reaction. In addition, if the rates of reactions from two forms are comparable, then only populations of two forms will determine the product ratio.

6. Conclusion

This article thus corroborates the profoundly thought-provoking and near-proverbial observation [17] that:

'The way in which a scientist remembers and publishes his arguments of his research work may not necessarily be the order in which the idea originally occurred to him. Scientists are notoriously forgetful about the origin of their most interesting conjectures...'

Suggested Reading

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