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HALF A CENTURY OF RESEARCH, TEACHING, SERVICE

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Abstract

This is a summary of the research of Charles L. Perrin and his coworkers in the areas of aromatic mercuration, vibronic borrowing, ipso factors in electrophilic aromatic substitution, malonic anhydrides, mechanisms of proton exchange in amides, stereoelectronic control, the so-called reverse anomeric effect, an NMR titration method for highly accurate measurement of relative acidities, secondary deuterium isotope effects on acidity, symmetry of hydrogen bonds in solution, and nucleophilic addition to a para-benzyne diradical, along with Perrin's contributions to teaching and to service.

Keywords:

hydrogen bonds
para-benzyne
NMR titration
isotope effects
stereoelectronic control
reverse anomeric effect
vibronic borrowing
electrophilic aromatic substitution
malonic anhydrides
proton exchange in amides

Apologia Pro Vita Sua

In September 2013 my department did me a great honor by organizing a symposium to celebrate my fifty years at UCSD. Among the > 200 attendees were current colleagues, many of my former students, my wife Marilyn, and my sons David and Edward and their families.

Speakers included my colleague Roger Tsien and two of his coworkers, one of whom was my son's Ph.D. student; my former colleague Jay Siegel; former Ph.D. students Tammy Dwyer, now a professor at the Univerity of San Diego, and Miles Fabian, now at NIH; a former undergraduate researcher Marcey Waters, who is now a professor at UNC Chapel Hill; a collaborator Julius Rebek at TSRI; and most gratifyingly my son David, who is a professor of chemistry at UBC Vancouver. Chair Seth Cohen announced that the Department is establishing a permanent endowment in my name to support two UCSD undergraduates to carry out summer research in organic chemistry. Already > $60K has been raised. It was a truly heartwarming experience, and I am most grateful to Haim Weizman, Yitzhak Tor, and Emmanuel Theodorakis for organizing the event plus an elegant dinner following the talks. I look forward to this special issue of JPOC, with contributions from many friends and colleagues from around the world. Special thanks go to my dear wife Marilyn for her presence and support during these fifty years and for preparing a delicious dinner for the speakers and out-of-town guests the night before the symposium.

After 50 years at UCSD I am still not retired but continue to enjoy teaching and research. One of the joys of a research career has been the opportunity for frequent travel. My first sabbatical was the 1972-3 academic year in Gothenburg, Sweden, devoted to an attempt to elucidate the mechanisms of learning and memory. Unfortunately, I did not learn enough neurobiology, and the techniques available then were too crude for significant progress. Other sabbaticals were limited to one month each in Padua, Paris, Copenhagen, Zurich, and back to Gothenburg. Besides, there have been many conferences that have taken me to interesting locations in North America, Europe, Israel, Asia, and Latin America, and Marilyn took me to her conferences in Europe and Australia.

Research

Whenever I am asked what my research is about, my response is that it is about physical organic chemistry, trying to understand molecular structure and how molecular structure determines chemical reactivity. It is all curiosity-driven basic research, with no practical applications apparent. But solving puzzles is great fun, and Mother Nature presents the most challenging ones.

UV Spectroscopy. In 1960 my first publication, "Thermochromism of Two Disulfides", was published.[1] Its genesis was an undergraduate lab course on physical optics, emphasizing the wave nature of light. Its second half consisted of an individual project. The Physics Department was kind enough to allow me to do a project in Chemistry. My adviser, P. D. Bartlett, turned me over to his postdoc, Robert Earl Davis. My task was to take the UV spectra at various temperatures of some rubber vulcanizers (**1**, **2**) that were thought to dissociate to colored free radicals. The spectrophotometer was a Beckman DU, powered by an automobile battery. It required selecting each wavelength on the monochromator, zeroing the absorbance of a blank, reading the absorbance of the sample from the galvanometer needle, and plotting the spectrum on graph paper. The results indicated that the color changes seen are not due to free radicals but to UV excitation from thermally excited vibrational states, and Bob Davis persuaded me to present the results at a national ACS meeting while I was still an undergraduate.

1 **2**

Mercuration of Benzene. My senior year of college I took Frank Westheimer's graduate course on physical organic chemistry, where he proposed an intriguing situation whereby the rate of a reaction in solution would increase as the temperature is lowered. He agreed to accept me as a graduate student to work on that project. But shortly after embarking on it, I found that the technique he proposed using was not feasible. So he set me to work instead on the kinetics of the mercuration of benzene, which led to our 1963 paper "The Rate of Mercuration of Benzene as a Function of the Activity of Water",[2] in which we defined a new acidity function. We showed that it was intimately associated with the thermodynamic activity of water, and I also published a paper on the relation between water activity and Hammett's H_0 acidity function.[3] Westheimer, who had been a postdoc with Louis Hammett, was very disappointed that our acidity function should be called the Hg_0 function, for mercury, rather than the W_0 function, for water (or for Westheimer).

Vibronic Borrowing. When my wife Marilyn came to graduate school, she asked to work with Westheimer, but he told her that he already had one physical chemist (me) and didn't want another. So she worked with Martin Gouterman on vibronic borrowing. But he moved to the University of Washington and she married me, moved to La Jolla, had two children, and served as assistant editor at the *Journal of Physical Chemistry* and then at *Molecular Pharmacology*. Completing her Harvard Ph.D. at long distances was difficult, so I familiarized myself with her project. Meanwhile, a student of George Feher, in the Dept. of Physics at UCSD, was measuring the molecular Zeeman effect on porphyrin spectra. He had some mystifying results, where absorption of a photon with positive angular momentum created an excited state with negative angular momentum, in violation of the principle of conservation of angular momentum. As a member of his Ph.D. committee I interpreted those results in terms of an

excited state with both electronic and vibrational angular momentum. Marilyn then consulted her vibronic wavefunctions, which supported this interpretation. Our manuscript was the first explanation of what became known as negative *A* terms in magnetic circular dichroism, and Marilyn made clear the connection.[4] When I presented these results at a PChem seminar, the front row was Harold Urey, Joe Mayer, and Linus Pauling, an intimidating lineup for an Assistant Professor.

Ipso and Ipso Factors. Following my thesis on electrophilic aromatic substitution, we investigated directive effects on reactivity. Reactivities at positions ortho, meta, or para to a substituent are expressed as ortho, meta, or para partial rate factors, but what about reaction at the carbon bearing the substituent? There was then no way to express that partial rate factor, so we called it an "ipso factor",[5] and we proposed to designate the position bearing the substituent the ipso position, a term that has pervaded organic chemistry.

Malonic Anhydrides. Our contribution to organic synthesis was the preparation of four-membered-ring malonic anhydrides (**3**, R,R' = H, CH_3),[6] which had been sought for 70 years. The synthesis is maddeningly easy, by ozonolysis of a ketene dimer (**4**), as carried out in my lab by an undergraduate who is the great-grandson of Svante Arrhenius. The structure proof included the Raman spectrum, with a 1947-cm^{-1} frequency that sets a record for organic carbonyl compounds.[7] However, malonic anhydrides are unstable at room temperature, decomposing to a ketene (**5**) and CO_2 (**6**) and documenting the falsity of previously claimed syntheses (a "uniqueness proof" rare in chemistry). Because malonic anhydrides might be useful for synthesizing new penicillin derivatives, the University patented the procedure.[8] I would have been content with riches within the dreams of avarice, but the peroxide byproducts from the ozonolysis discourage large-scale production. Recently we returned to the kinetics of this

decomposition, now that NMR instrumentation has become sensitive enough to permit concentrations low enough that the peroxide byproducts do not endanger the researcher or the spectrometer probe. We found that the enthalpy of activation is exceptionally low and that the entropy of activation is positive, consistent with a concerted [2+2] process that requires a more organized antarafacial transition-state structure.[9] We also found that the rates are not monotonic in the number of methyl substituents, and we rationalized this behavior with density-functional theory (DFT) calculations.
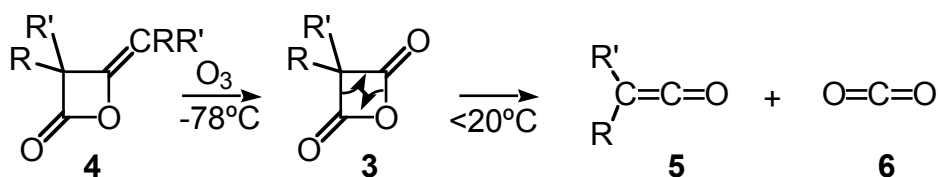
Mechanisms of Proton Exchange in Amides. In a series of papers we elucidated the mechanisms of acid-catalyzed proton exchange in amides, which can proceed either by *N*-protonation (Scheme 1, top row) or by *O*-protonation followed by deprotonation from N (Scheme 1, bottom row). This reaction is often used to probe the structure of proteins, the accessibility of NH groups to solvent, and the course of protein folding. Our NMR results revealed a discrepancy that led to the unexpected conclusion that ordinary primary amides $RCONH_2$ undergo acid-catalyzed exchange via *N*-protonation, to form the intermediate $RCONH_3^+$, but with the novel feature that its deprotonation and C–N rotation are competitive on a picosecond timescale.[10] In related studies on amidinium ions we verified the equivalent "slow" rotation about the $C–NH_3^+$ bond.[11]. We also demonstrated that amides with electron-withdrawing substituents instead exchange via the imidic acid $RC(OH)=NR'$,[12] which does not

undergo *E*/*Z* isomerization during its lifetime. A key distinction between the two mechanisms is that *N*-protonation allows both intermolecular and intramolecular H exchange, but the imidic-acid mechanism allows only intermolecular exchange.
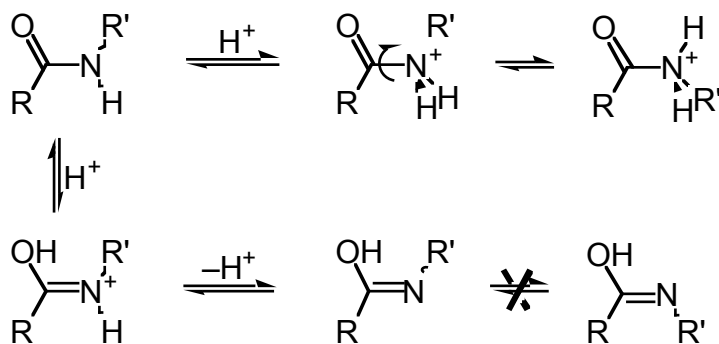
Scheme 1. Mechanisms of Proton Exchange in Amides

By studying proton exchange in *N*-methyl amides and by measuring site-to-site rate constants for proton exchange in some secondary amides we verified this dependence of mechanism on substituents, and we concluded that amides of peptide and protein backbones exchange via the imidic acid.[13] We further addressed the implications of this mechanism for questions of solvent effects and solvent accessibility,[14] and we used one of Rebek's frameworks with convergent amide groups to study the effect of intramolecular hydrogen bonding.[15] We also studied rates of proton exchange in biotin, which have implications for the mechanism of CO_2 transfer. A personal review, "Proton Exchange in Amides: Surprises from Simple Systems", summarized these studies.[16]

Base-catalyzed exchange led us to the characterization of imidate anions RCONR'⁻, their stereochemistry, and their mechanism of stereoisomerization.[17] We also reported the kinetics of amide proton exchange in micelles, which was the first study of all four combinations of acid-

and base-catalyzed reactions in anionic and cationic micelles, and we introduced absolute activity coefficients to analyze micellar effects on reactivity.[18]

The results regarding $C-NH_3^+$ rotation in $RCONH_3^+$ prompted the measurement of the rate of rotation of NH_4^+ within its solvent cage.[19] We found that this rotation is remarkably fast, even though it requires breaking NHO hydrogen bonds. This study then led to an elucidation of the nature of NH_4^+ solvation and to an estimate of the lifetime of a strong acid in water.[20]

In the course of studying these exchange reactions we developed powerful NMR methods for multisite kinetics involving magnetization transfer,[21] 1D-EXSY,[22] and quantitative 2D-NMR,[23] where we were the first to present the matrix-inversion method for evaluating rate constants from 2D-EXSY intensities. These methods have the advantage of measuring site-to-site rate constants, which often provide more mechanistic information than do the common line-broadening and coalescence techniques. An extensive review on the applications of 2D-EXSY to kinetics of chemical exchange has become a widely consulted reference for procedure and data analysis.[24] These methods enabled us to measure the primary kinetic isotope effect (KIE) for direct nitrogen-to-nitrogen proton transfer in aqueous solutions of ammonium ion,[25] the secondary KIE on dissociation of aqueous ammonium ion,[26] and the secondary KIE on amide rotation, including the first experimental observation of a contribution of the thermal excitation factor to a KIE.[27]

Stereoelectronic Control. According to Deslongchamps' hypothesis of stereoelectronic control, preferential cleavage of a tetrahedral intermediate occurs when a leaving group is antiperiplanar to two lone pairs.[28] Scheme 2 presents the prediction of stereoelectronic control for the hydrolysis of cyclic hemiorthoesters, which are created in conformation **7** ($n = 6$). In the

Scheme two lone pairs antiperiplanar to a potential leaving group are open lobes, but a single antiperiplanar lone pair is shaded. Reactions with or without two antiperiplanar lone pairs are designated with a solid or dashed arrow, respectively. Lone pairs on the OH and the exocyclic OR in **7** are antiperiplanar to the ring oxygen, which can therefore be cleaved to hydroxyester **8**. However, only one lone pair is antiperiplanar to the exocyclic OR, so it cannot be cleaved to lactone **9**. Cleavage would require ring inversion to **10**, with two lone pairs antiperiplanar to the OR. Only **8** is formed, presumably because ring inversion in a six-membered ring is too slow. This result and several similar ones were taken as evidence for stereoelectronic control. Addressing this hypothesis and the evidence for it became a challenging exercise in scientific logic.
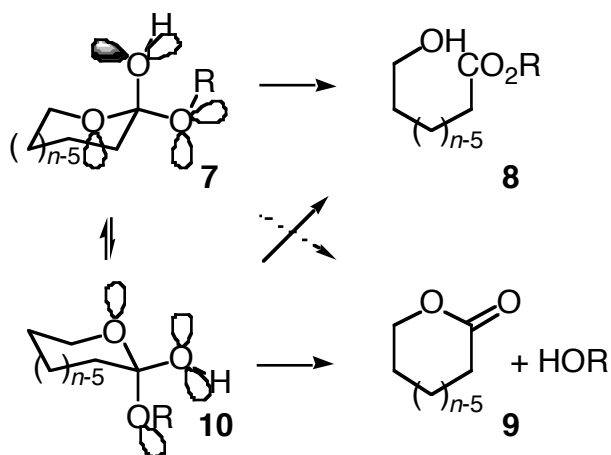
Scheme 2. Stereoelectronic control in hydrolysis of cyclic hemiorthoesters.

A serious inconsistency is that the five-membered-ring hemiorthoester (**7**, $n = 5$) also gives only **8**. Here ring inversion becomes pseudorotation, faster than any possible cleavage, and must lead to conformer **10**. Now there are two lone pairs antiperiplanar to the OR, which can cleave not only to **8** but also to **9**. Since lactone **9** is not formed, the hypothesis does not account

for the products, and such observations cannot be taken as evidence for stereoelectronic control. We therefore proposed that the general absence of lactone can be associated simply with their destabilization, relative to acyclic esters,[29] as evidenced by their faster hydrolysis.[30]

Hydrolysis of cyclic amidines, to amides or lactams, provides an unambiguous test of stereoelectronic control. The advantage is that no bias arises from product stabilities, because lactams do not share the destabilization of lactones. Scheme 3 presents the hydrolysis of cyclic amidinium ions (**11**), via addition of OH⁻ to form an intermediate, followed by deprotonation from oxygen (omitted from Scheme) and C-N cleavage with concerted protonation (or pre-protonation) at nitrogen. As in Scheme 2, two lone pairs antiperiplanar to a potential leaving group are open lobes, but a single antiperiplanar lone pair is shaded, and reactions with or without two antiperiplanar lone pairs are designated with a solid or dashed arrow, respectively.
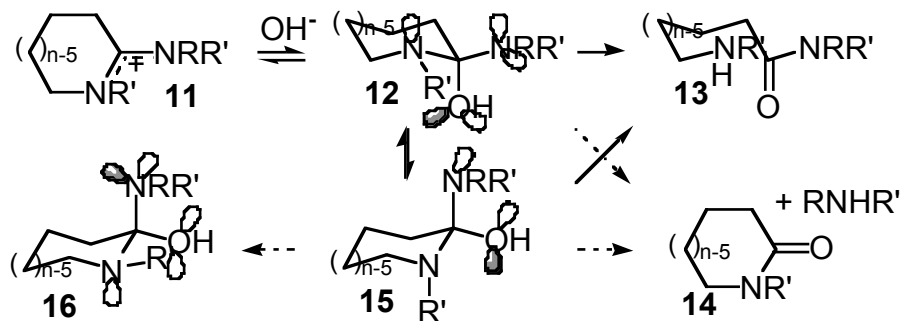
Scheme 3. Stereoelectronic Control in Hydrolysis of *n*-Membered-Ring Amidines.

The consequences of stereoelectronic control can be analyzed. Rapid rotation about the exocyclic C-N bond of the initial intermediate produces intermediate **12**, with two lone pairs antiperiplanar to the endocyclic C-N bond but only one antiperiplanar to the exocyclic bond. This should cleave the endocyclic bond and produce aminoamide **13**, but exocyclic cleavage to

lactam **14** would require a syn lone pair on N. In contrast to hemiorthoesters (Scheme 2), ring inversion, leading to conformer **15**, does not create a second lone pair antiperiplanar to the exocyclic C-N bond, so this too cannot cleave to lactam. Two antiperiplanar lone pairs are obtained only upon nitrogen inversion, leading to conformer **16**. However, this conformer is inaccessible during the lifetime of the intermediate because nitrogen inversion is too slow. Thus if stereoelectronic control is operative, the aminoamide **14** is predicted to be the kinetic product.

We therefore studied the hydrolysis of amidines (carefully chosen with leaving groups of equal basicity).[31] Consistent with stereoelectronic control, six-membered-ring aminoamide **13** ($n = 6$) is the dominant product (≥93%) from **11** ($n = 6$). In contrast, with five- and seven-membered-rings substantial amounts (>50%) of lactams **14** ($n = 5,7$) are produced, along with **13**. These results are counter to stereoelectronic control. They require the involvement of a syn lone pair. This is consistent with E2 eliminations, which in six-membered rings show a strong preference for anti, but which in five- and seven-membered rings permit syn eliminations.[32] These studies were summarized in a review, "Is There Stereoelectronic Control in Formation and Cleavage of Tetrahedral Intermediates?".[33]

Reverse Anomeric Effect. The anomeric effect is the additional stabilization observed when an electronegative group is antiperiplanar to a lone pair.[34] This is the thermodynamic counterpart of stereoelectronic control. It is responsible for the preference of an electronegative group for the axial position of a tetrahydropyran, as expressed in Scheme 4a. It is important for understanding the conformational behavior of carbohydrates and related molecules. It is generally attributed to n-σ* delocalization in the axial stereoisomer, as suggested in the Scheme. Yet it had been thought that cationic substituents show an increased preference for the equatorial position, despite an expected increase in n-σ* delocalization, as expressed in Scheme 4b. We

conclusively demonstrated that this so-called reverse anomeric effect is not operative for $X^+ =$ NH_2R^+ or for protonated imidazolyl,[35] and we assessed the contribution from steric hindrance to solvation of a protonated imidazolyl.[36] Moreover, substituted anilines provide a fine-tuning of the localization of the positive charge, so that the comparison of glucosylanilines with cyclohexylanilines allowed us to define the substituent dependences of both the anomeric effect and steric hindrance to ionic solvation.[37]
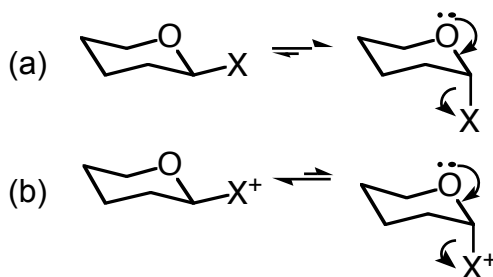
Scheme 4. (a) Anomeric and (b) Reverse Anomeric Effects

In a related study we showed that the anomeric effect decreases the barrier to ring inversion in 2,2-dimethoxytetrahydropyran.[38] In another study we found that the lower one-bond NMR coupling constant to the axial CH in tetrahydropyran and similar ethers (known as the Perlin effect) is *not* due to n-σ* delocalization.[39] This was an astounding result that invalidated an interpretation that had been accepted for 35 years! Moreover, my laboratory confirmed this conclusion experimentally, through measurements of C–C spin-coupling constants in ethers.[40]

NMR Titration. In the course of these studies we developed a powerful new NMR titration method for highly accurate measurement of relative pK_as within a set of similar acids or bases.[41] The ratio K of acidity constants is defined in Eqn 1. The observed chemical shifts of

two competing bases A and B are given by Eqns 2-3, where δ_{A° and δ_{AH^+} or δ_{B° and δ_{BH^+} are the limiting chemical shifts of the neutral and protonated forms, respectively. These equations lead to Eqn 4, relating observed chemical shifts to K. Thus from the variations of the chemical shifts during titration of a mixture of the two acids the ratio of the acidity constants can be calculated from a plot of $(\delta_b - \delta_{B^\circ})(\delta_{AH^+} - \delta_a)$ versus $(\delta_a - \delta_{A^\circ})(\delta_{BH^+} - \delta_b)$, which is a straight line with slope K and zero intercept.

$$K = \frac{K_a^{AH^+}}{K_a^{BH^+}} = \frac{[A][BH^+]}{[AH^+][B]} \tag{1}$$

$$\delta_a = \frac{\delta_{A^\circ}[A] + \delta_{AH^+}[AH^+]}{[A] + [AH^+]} \tag{2}$$

$$\delta_b = \frac{\delta_{B^\circ}[B] + \delta_{BH^+}[BH^+]}{[B] + [BH^+]} \tag{3}$$

$$(\delta_b - \delta_{B^\circ})(\delta_{AH^+} - \delta_a) = K(\delta_a - \delta_{A^\circ})(\delta_{BH^+} - \delta_b) \tag{4}$$

For example, the ΔpK between the cis and trans stereoisomers of 4-*t*-butylcyclohexylamine (**17**) was determined from the variations of the H1 chemical shifts in a single ^1H NMR titration experiment. Similarly, the ΔpK_a between the two stereoisomers of 4-*t*-butylcyclohexanecarboxylic acid (**18**) could be determined using either ^1H or ^{13}C NMR. To demonstrate the power of this method, it was applied to the four stereoisomeric 2-decalylamines (**19**), without the necessity of separation. The method is widely applicable and is effective even in solvents where a pH electrode is useless. It is especially suitable for making comparisons, because it is not subject to systematic error due to impurities. It is exquisitely accurate, capable

of measuring ΔpK_a to ±0.0004 pH units.
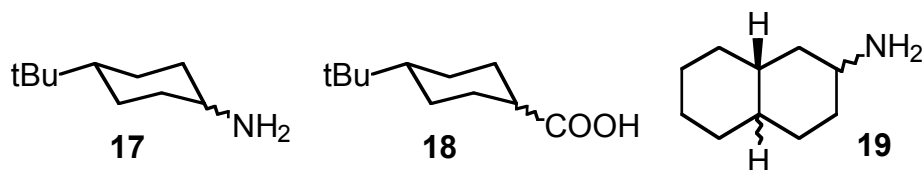
This titration method permitted us to measure relative basicities of a series of cycloalkylamines,[42] which confirmed the reduced basicity of small-ring amines and an increase for medium-sized rings. More surprisingly, large-ring amines are slightly less basic than cyclohexylamine, even though all have tetrahedral carbons and identical hybridization. We also demonstrated that the axial/equatorial preference of a dimethylamino substituent varies with solvent by > 1 kcal/mol, corresponding to an unusually large variation of hydrophilicity between stereoisomers.[43]

Secondary Deuterium Isotope Effects. We applied this NMR titration method to the measurement of secondary deuterium isotope effects (IEs) on amine basicities.[44] We verified that α-deuteration increases basicity. We demonstrated that this IE varies with the dihedral angle between the nitrogen lone pair and the C-H bond. In particular, for 1-benzyl-4-methylpiperidine-2,2,6-d_3 (**20**) we demonstrated that the stereoisomer with axial deuterium is the more basic. Notice that this method permits the measurement of the difference in basicities between two exceedingly similar isotopomers (stereoisomers that differ only in the position of an isotope). The result shows that the IE is stereoelectronic, arising from zero-point energies that depend on the orientation of the C-H or C-D bond relative to the lone pair. We have shown further that a deuterium synperiplanar to the lone pair also shows an IE, but only about half as large as an anti

deuterium, as is consistent with our DFT calculations on CH_3NH_2 and DCH_2NH_2. We took advantage of the exquisite accuracy possible with our NMR titration to provide an experimental demonstration of a predicted nonadditivity of secondary deuterium IEs on the basicities of isotopologues of trimethylamine.[45] We also measured IEs of distant deuteriums on the acidities of carboxylic acids and phenols and on the basicities of pyridines, which were modeled with DFT calculations of zero-point energies.[46] Recently we extracted the temperature dependence of the secondary deuterium IE on acidities, to demonstrate that the IE resides entirely in the enthalpy, with no detectable entropic contribution.[47] This result enabled us to exclude an inductive origin for the IE, which had been proposed 50 years ago and never before refuted.
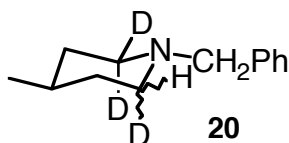
Symmetry of Hydrogen Bonds. Hydrogen bonds are one of the most widely studied aspects of molecular structure. Our interest has focused on "symmetric" hydrogen bonds **21**, where the hydrogen is centered between the two donor atoms, in a single-well potential. The contrast is with the more usual case of a double-well potential **22ab**, where the hydrogen is bonded to one of the donor atoms but may jump to the other. Centered hydrogens are quite unusual, and they are associated with extra stability. The NMR method of isotopic perturbation is a direct and definitive method for distinguishing the symmetry of hydrogen bonds. In careful studies of ^{18}O effects on ^{13}C NMR chemical shifts, we documented that the hydrogen bonds in maleate, phthalate, and similar monoanions are asymmetric (present as a mixture of two

tautomers, not as a single symmetric structure) not only in aqueous solution but also in organic solvents.[48] This result was quite unexpected, and we had difficulty to publish this, because these monoanions are the paradigms of symmetric hydrogen bonds in crystals. We attributed the asymmetry to the disorder of the local environment, which has been supported by simulations.[49] Moreover, we recently used ^{19}F NMR to show that the hydrogen bond of difluoromaleate monoanion becomes symmetric in a liquid crystal.[50] We extended these studies to 3-hydroxy-2-phenylpropenal-*d* and its metal chelates,[51] to the monoanion of (±)-di-*t*-butylsuccinic acid,[52] and to NHN hydrogen bonds in bis(dimethylamino)naphthalenes and aminofulveneimines.[53] Similarly, we demonstrated that 1,6-dioxa-6aλ^4-thiapentalene and 1,6,6aλ^4-trithiapentalene have C_{2v} symmetry in solution.[54] The scarcity of symmetric hydrogen bonds in solution led us to the conclusion that low-barrier hydrogen bonds are not especially stable and do not facilitate enzymatic reactions through any increased strength of the hydrogen bonds themselves, but through relief of strain.[55] It should be noted that although our results were initially met with skepticism, the scientific community now accepts the obvious fact that the symmetry of hydrogen bonds can depend on their environment. This led to the proposal that symmetry can be broken by solvation and the formation of "solvatomers".[56] Moreover, our inability to detect symmetric hydrogen bonds in solution led us to question the premise that symmetric or short H-bonds are unusually strong, and we therefore deplored the common custom of considering short, low-barrier H-bonds as unusually strong.[57]

$$A\cdots H\cdots B \qquad A–H\cdots B \rightleftharpoons A\cdots H–B$$
$$\textbf{21} \qquad\qquad \textbf{22a} \qquad\qquad \textbf{22b}$$
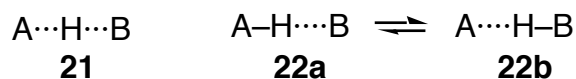
Controversies were not always avoided. I suggested that the atomic-size dependence of

Bader charges leads to ambiguities in assigning electron populations.[58] I proposed an alternative to Breslow's mechanism for buffer-catalyzed hydrolysis of RNA models.[59] We demonstrated that isotopic perturbation of resonance is real, in a series of metal complexes.[60] We measured the intramolecular KIE for hydride transfer from an NADH model to a quinolinium ion,[61] and found that it is inconsistent with the intermolecular IEs that had been claimed as evidence for a two-step mechanism.

Some other contributions are worth noting: We discovered a chain mechanism for proton exchange in amines.[62] My last hands-on experience with an NMR spectrometer led to the development of a rapid and convenient method for variable-temperature NMR without a variable-temperature probe.[63] An apparatus was designed and constructed for direct addition of reagents into an NMR sample in the NMR probe.[64] A simple formula, $\sigma_{\Delta H} = T_{avg}\sigma_{\Delta S}$, relating errors in enthalpy and entropy, can warn about miscalculations.[65]

The years have seen collaborations with quite a few researchers. Teddy Traylor and I measured the rates of methoxyl exchange of camphor and norcamphor dimethyl ketals (**23**, R = H or CH_3) in methanol-d_4,[66] as a response to H. C. Brown's rejection of nonclassical carbocations. John Faulkner and I analyzed cis/trans ratios in Claisen and Cope rearrangements in terms of conformational preferences of substituted cyclohexanes.[67] Those two former colleagues are sorely missed. Jeff Seeman and I proposed the first new development in 30 years on the Curtin-Hammett Principle, namely that linear free-energy relationships overcome the limitations on relating product ratios to conformational ratios.[68]

23
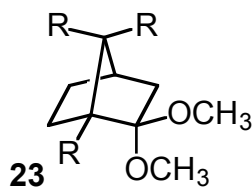
Michael Szwarc was an eminent polymer chemist who retired to the San Diego area and would visit to discuss science. As a result we published a couple of papers on the application of probability theory to polymerization.[69] Later he posed a question about the reaction of potassium anion with a peroxide: Does it react by a two-electron transfer or by two single-electron transfers? When I told him that phenylacetyl peroxide could be used to answer that question, he urged me to do the experiment. I demurred, because I don't have experience with peroxides. Couldn't he have one of his former students try it? He explained that not only was he retired but also all his students were retired! So my postdoc was assigned the project, and we showed that the electron transfer is stepwise, a conclusion that became one of Michael's last publications.[70]

Another collaboration, with Joe O'Connor, led to the discovery of a remarkable new reaction, prompted by the isolation by Bill Fenical, at the Scripps Institution of Oceanography, of some halogenated marine natural products. As a model for halogen incorporation, we showed that the enediyne cyclodeca-1,5-diyn-3-ene **24**, in the presence of lithium halide and a weak acid, can be converted to a good yield of 1-halotetrahydronaphthalene **25**. The kinetics are consistent with rate-limiting cyclization to a *p*-benzyne diradical **26** that rapidly adds halide anion, to form an aryl anion **27**, which is then protonated.[71] The reaction thus involves nucleophilic addition of halide, which is novel and quite different from the usual radical reactivity of **26**. This mechanism has some unique features, owing to the way electron pairs and single electrons must

interact.
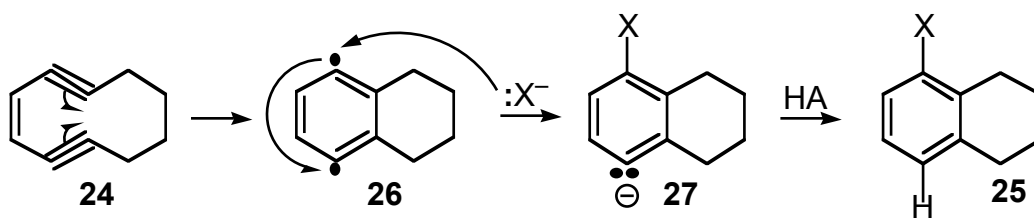
Service

I have been active in chemistry nationally and internationally. As the elected Chair of the IUPAC Commission on Physical Organic Chemistry I became a spokesperson for structural and mechanistic chemistry worldwide. We all collaborated on preparing the IUPAC Glossary of Physical Organic Chemistry, and I worked with Gerry Moss to post an electronic version of it on the worldwide web.[72] Now I am the Chair of a Task Force to revise the Glossary, which continues to provide a major service to students and researchers. In 2002 I organized ICPOC16, the highly successful 16th IUPAC Conference on Physical Organic Chemistry, held in August on the UCSD campus. Also, I was elected Vice-Chair of the Gordon Conference on Isotopes for 2004, and Chair for 2006.

Within the University I have served on many committees, but have escaped being Chair of my department. The most significant service was as Vice-Chair and then Chair of the Coordinating Council on Graduate Affairs, a UC-wide committee that has authority over graduate curricula and programs. One of our accomplishments was the approval of a new School of Pharmacy at UCSD.

Teaching

Several of my teachers have inspired me. The first was Glenn Berkheimer, at Aspinwall High School, who encouraged us to learn more than was in the textbook and who allowed us to have fun in the lab after school. In college I was fortunate to take Frank Westheimer's clearly presented Physical Organic Chemistry, and also Thermodynamics from William Moffitt, a witty Englishman whom I might have chosen for my Ph.D. had he not died tragically young. R. B. Woodward never taught a course while I was a student, but his Thursday night seminars were phenomenal, an open-ended discussion of current research puzzles that Woodward would pose and if necessary present a solution, complete with beautifully drawn structures.

Another lucid lecturer was E. M. Purcell, whose course on Electricity and Magnetism concluded with an account of the behavior of nuclear magnets in a magnetic field, the basis of NMR, for which he had won the Nobel Prize. At the same time I was taking my adviser P. D. Bartlett's course on Organic Mechanisms. With my usual lack of tact I complained that his course was not as clear as Purcell's. Whereupon Bartlett gave me one of the best pieces of advice I have ever received. He gently explained that Purcell's course was so clear because everything is known and understood about electricity and magnetism, whereas there are many unknowns and uncertainties with organic mechanisms, which was why he was continuing to do research in that field. What an inspiration!

Over the years I have enjoyed teaching many different courses. Each fall I teach the first quarter of our introductory organic chemistry sequence, usually to 300 or 400 students. In earlier years, until we hired additional faculty, I taught all three quarters, which was a heavy load. A repertory of jokes helps to get the attention of many students who are biology majors not interested in chemistry. More satisfying are the graduate courses, which are expanded to qualified upper-division students. Among these are a course on Structure and Properties of

Organic Molecules and another, on Kinetics and Mechanism that I developed as a practical course suitable also for synthetic organic students. These two courses generated a concise and instructive summary of the field of physical organic chemistry,[73] On short notice I inherited from John Faulkner a course on Applied Spectroscopy, which challenged me to keep a chapter ahead of the students.

When I arrived at UCSD, there were only graduate students and no undergraduates. Joe Mayer was teaching Statistical Mechanics and found that he needed to give a few lectures on the mathematical underpinnings. I undertook to create a course, Mathematics for Chemists, to cover the material needed by chemists while recognizing that we are not as mathematically gifted as physicists and engineers, for whom most of the applied mathematics courses have been devised. The course eventually led to a textbook.[74] After it was published I was relieved of teaching the course, because there were greater needs in organic chemistry. However, it did lead to invitations to prepare ACS Audio Courses.[75]

Much of the fun and excitement I have had is in teaching students to do the research described above. We have dealt with the challenges of designing the informative experiments, carrying them out, and figuring out what the results mean. Many of my former research students seem to have enjoyed that and have chosen to embark on careers in college teaching that allow them the opportunity to introduce their students to research. I am grateful to all of my coworkers, listed among the references. This research could not have been accomplished without them.

Future

I have enjoyed these many years of research, and found it exciting to explore the unknown, to uncover something new, and to share with students the excitement and satisfaction

of making discoveries that have made lasting contributions to knowledge. I hope to continue research, teaching, and service for many more years. It's been so much fun that I don't want to give it up.

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