

## Professor Gerasimos J. Karabatos

### A Tribute



G. J. Karabatsos was born on May 17, 1932, in the village of Homatada, Greece where his father was a physician. "Mike", as he is known to his friends and family, knew the war years when Greece was occupied by the Nazis. In 1950, he went to the USA to study. He took an A.B. degree at Adelphi College in 1954, then entered Harvard where he received the M.A. in 1956 and the Ph.D. in 1959, working with Professor P.D. Bartlett. He stayed on there for a short while as a postdoc, then joined the Michigan State University faculty as an assistant professor. He rose quickly through the ranks, becoming full professor in 1966.

In January 1975, Mike became associate chairman of the Chemistry Department; then that fall became chairman, where he served for eleven years. He was especially effective in bringing major equipment grants, and in expanding the faculty to include many exceptional young scientists. Since 1987, while remaining Professor at MSU, he became Professor at the University of Crete in Greece, helping establish the Department of Chemistry there and serving as its chairman in 1989-91. He is currently Professor Emeritus at both Michigan State University and the University of Crete.

Mike has been particularly active in professional affairs. With his colleague and friend, Harold Hart, he served as co-editor of *Advances in Alicyclic Chemistry*, 1964-72. He served as Scientific Director of the Greek Atomic Energy Commission in Athens, Greece, 1974-75. At the invitation of the International Committee on Education and the Ford Foundation, he acted as visiting professor at the National University of San Marcos in Lima, Peru, teaching a four-week course on Nuclear Magnetic Resonance, in March-April 1967. From 1989-91, he headed a team of External Examiners that evaluated the Faculty of Sciences of the United Arab Emirates

University. Over the years, he guided 34 graduate students to their Ph.D. degrees, and 9 to their M.S.

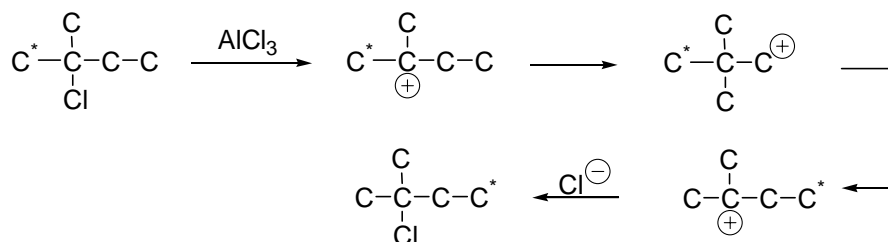
He has been an Alfred P. Sloan Fellow (1963-66) and a NSF Senior Post-doctoral Fellow at Berkeley (1965-66). Among his awards are the ACS Award in Petroleum Chemistry (1971), the Distinguished Faculty Awards at MSU (1971) and the MSU Sigma Xi Junior Faculty Research Award (1970). Mike and his wife, Marianna (married in 1956), divide their time between East Lansing, Michigan and Greece (Athens and Crete). They have four children, Lelena, Yanna, Jason and Byron, and four grandchildren, André, Aris, Nikolas and Sophia.

## Research Contributions

G.J. Karabatsos' research contributions will be discussed under five general headings. The unifying thread which runs throughout these investigations is the brilliant application of modern physical methods, particularly NMR, spectroscopy, to the solution of organic chemical problems.

### 1. Carbonium Ions

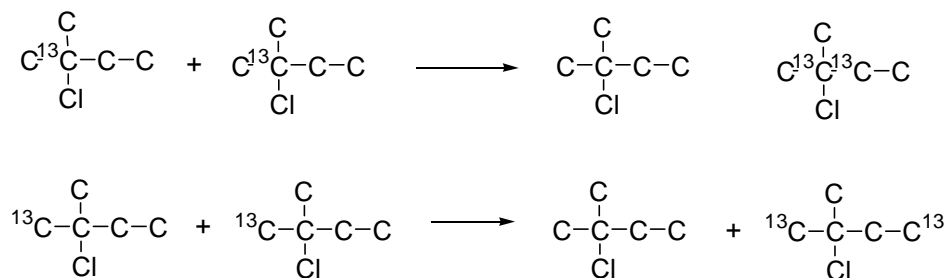
Primary carbonium ions were frequently proposed as intermediates to rationalize the products obtained from systems in which initial ionization leads to secondary or tertiary carbonium ions. For example, the faster than expected redistribution of the label in 2-methyl-2-chlorobutane between positions 1 and 4 when compared to the redistribution between positions 2 and 3 could be explained as shown:



A most unsatisfactory aspect of this mechanism is the rearrangement of a 3° to a 1° carbonium ion.

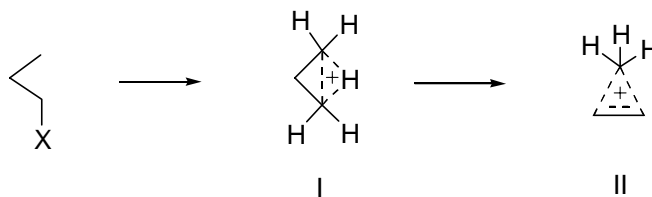
An alternate mechanism proposed by Professor Karabatsos was a bimolecular path, in which a 3° carbonium ion loses a proton to form an alkene which is then attacked by another 3° carbonium ion to form a C<sub>10</sub> cation. This can, by appropriate rearrangement and disproportionation, lead to redistribution of the label and explain the faster redistribution of the label between positions 1 and 4. No uphill process (to primary cations) need be included. The importance of such paths was demonstrated in papers 2, 5 and 6 by the use of C<sup>13</sup> (rather than

C<sup>14</sup>) labeling, and demonstration of the positions of labeling by NMR and mass spectrometric analysis. The results, which show the equilibration of C<sub>1</sub>-C<sub>4</sub> and C<sub>2</sub>-C<sub>3</sub>, can be summarized in the equations:



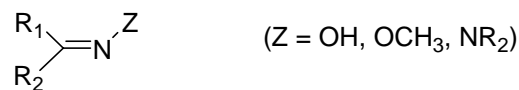
in which a doubly-labeled product is obtained.

Protonated cyclopropanes were implicated in the rearrangements which accompany the generation of the “nominal” n-propyl cation by various paths (as, for example, the action of nitrous acid on n-propylamine, or the reaction of n-propyl bromide with aluminum bromide). In one of his first independent papers (paper 4) Professor Karabatsos demonstrated the possibility of such a species using deuterium labeling (other eminent investigators, Professor Skell in the USA and Professor Reutov in Russia had published similar but somewhat less definitive results at about the same time). Refinements in the description of such reactions and the uniqueness of the n-propyl system were established (papers 1, 7, 8, 9, and 10). By appropriate deuterium and C-13 labeling of the propyl system, it was shown that the “edge” protonated cyclopropane (I) precedes the “corner” protonated cyclopropane (II) in the sequence of rearrangement.



## 2. Conformational Analysis

The conformations of aromatic aldehydes were evaluated by a cleancut demonstration of the stereospecificity of long-range coupling between protons separated by five bonds (paper 16). In other applications of NMR, and especially from a study of solvent effects on chemical shifts, the ratios of syn/anti isomers were established (papers 11-15, 17-19) for compounds of the type:



It thus became possible to establish very quickly, for a number of derivatives of carbonyl compounds, the relative populations of syn/anti isomers, and to evaluate the factors which affect this ratio.

Professor Karabatsos extended these studies to the rotational isomerism about  $sp^2$ - $sp^3$  carbon-carbon bonds. For example, the effect of variations in R, X and Y on the relative stabilities of III and IV has been studied, using NMR:



In the case of aliphatic aldehydes ( $X=O$ ,  $Y=H$ , paper 20) IV is more stable than III, even when R is isopropyl. These studies led to an evaluation of the relative contributions of dipole moments and London forces to the relative stability of these rotamers (papers 21, 22). Furthermore, these studies also led to the formulation of a new model for asymmetric induction, based on the relative stabilities of the transition states, on the basis of which semiquantitative predictions of product stereospecificity were feasible (papers 39-43).

### 3. Proton- $^{13}C$ Spin-Spin Coupling

Professor Karabatsos was the first investigator to observe long-range coupling between a proton and carbon-13. A series of papers (Nos. 23-26, 28-30) established the relative importance of factors (hybridization, conformation and heteroatom effect) that affect the magnitude of such coupling. In paper 31, he and his co-workers showed how this coupling may be applied to the study of rotational isomerism about the alkyl-oxygen bond of esters.

### 4. Enzymatic Oxidation-Reduction Reactions

In three important papers, in collaboration with R.H. Abeles, the relationship between substrate and coenzyme in the NADH-ADH reduction of carbonyl compounds was established (papers 32-34). Through a clever application of NMR, the absolute configuration of C-1 in  $^3CH_3$   $^2CH(OH)$   $^1CHDOH$  obtained from reduction of D- and L-lactaldehyde with NADD and liver alcohol dehydrogenase was established. It was also established that the transfer of hydrogen from C-1 to C-2 was stereospecific and went with inversion at C-2.

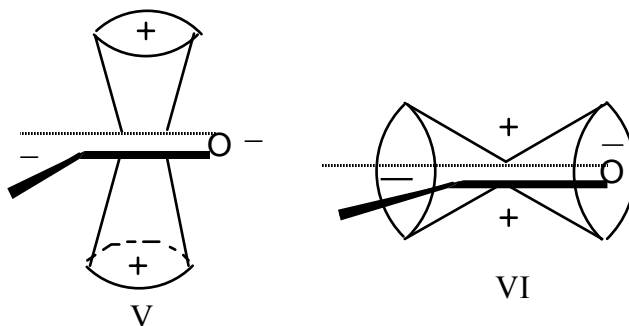
### 5. Miscellaneous

In two early papers (papers 35 and 36) Professor Karabatsos found that the  $C^{13}$  carbonyl frequency is easily distinguishable from the  $C^{12}$  frequency in some simple ketones. These papers

provide the only experimental verification (S.A. Francis, *J. Chem. Phys.* 19, 942 (1951); J.V. Halford, *ibid.*, 24, 830 (1956); T. Miyazawa, *J. Chem. Soc. Japan*, 74, 915 (1953); *ibid.*, 77, 366 (1956) of Halford, Francis and Miyazawa's suggestion that the carbonyl frequency in ketones actually includes about a 20% contribution from C-C motions.

In two key publications (papers 37, 38), Karabatsos and his group demonstrated that nonbonded interactions are responsible for only a small fraction of the secondary kinetic isotope effects in systems where both hyperconjugation and nonbonded interactions are possible.

From their NMR studies on rotational isomerism about the  $sp^2$ - $sp^3$  bonds of aldehydes, Karabatsos and his group demonstrated that the commonly accepted model (V) for the anisotropy of the carbonyl group



was incorrect, as some protons in the plane of the carbonyl group are shielded, rather than deshielded as predicted by the model. From the three principal magnetic susceptibilities of the carbonyl bond, they constructed model VI for the anisotropy of the carbonyl group (paper 44) from the experimental results.

## Selected Publications of G. J. Karabatos

### Carbonium Ions

1. "Carbonium ion rearrangement of the neopentyl system" (with Graham, J.D) *J. Am. Chem. Soc.* **1960**, 82, 5250.
2. "Bimolecular reactions in carbonium ion rearrangements" (with Vane, F.M.; Meyerson, S) *ibid.* **1961**, 83, 4297.
3. "The acid-catalyzed conversion of diethyl ketone to methyl propyl ketone-a reinvestigation" (with Fry, A.; Ookuni, I.; Graham, J. D.; Vane, F. M.) *J. Org. Chem.* **1962**, 27, 1914.
4. "Carbonium ion rearrangements. V. 1,3-hydride shifts in the 1-propyl cation" (with Orzech, C. E. Jr.) *ibid.* **1962**, 84, 2838.

5. "Carbonium ion rearrangements. III. The question of primary carbonium ions" (with Vane, F. M) *ibid.* **1963**, 85, 729.
6. "Carbonium ion rearrangements. IV. The reaction of  $^{13}\text{C}$ -labeled *t*-amyl chlorides with aluminum chloride; bimolecular reactions" (with Vane, F. M.; Meyerson, S) *ibid.* **1963**, 85, 733.
7. "Carbonium ion rearrangements. VI. Mechanism of the rearrangement of neopentyl compounds" (with Orzech, C. E. Jr.; Meyerson, S) *ibid.* **1964**, 86, 1994.
8. "Carbonium ion rearrangements. VII. Protonated cyclopropanes in the nitrous acid deamination of *n*-propylamine" (with Orzech, C. E. Jr.; Meyerson, S) *ibid.* **1965**, 87, 4394.
9. "Carbonium ions. XII. Reaction paths in the isomerization of bromopropanes with aluminum bromide" (with Fry, J. L.; Myerson, S) *ibid.* **1970**, 92, 614.
10. "Carbonium ions. XVI. The question of protonated cyclopropanes in the reactions of zinc chloride with 1-propanol and 1-chloropropane" (with Zioudrou, C.; Myerson, S) *ibid.* **1970**, 92, 5996.

### Conformational Analysis and Nuclear Magnetic Resonance Spectroscopy

11. "*Syn-anti* isomer determination of 2,4-dinitrophenylhydrazones and semi-carbazones by NMR" (with Graham, J.D.; Vane, F.M) *J. Am. Chem. Soc.* **1962**, 84, 753.
12. "Structural studies by nuclear magnetic resonance. II. Aldehyde 2,4-dinitrophenylhydrazones" (with Shapiero, B. L.; Vane, F. M.; Fleming, J. S.; Ratka, J. S) *ibid.* **1963**, 85, 2784.
13. "Structural studies by nuclear magnetic resonance. III. *Syn-anti* assignments from solvent effects" (with Taller, R.A.; Vane, F.M) *ibid.* **1963**, 85, 2326.
14. "Structural studies by nuclear magnetic resonance. IV. Conformation of *syn-anti* isomers from chemical shifts and spin-spin coupling constants" (with Taller, R.A.; Vane, F.M) *ibid.* **1963**, 85, 2327.
15. "Structural studies by nuclear magnetic resonance. V. Phenylhydrazones" (with Taller, R.A) *ibid.* **1963**, 85, 3624.
16. "Structural studies by nuclear magnetic resonance. VI. The stereospecificity of coupling between protons separated by five bonds and conformations of some aromatic aldehydes" (with Vane, F.M) *ibid.* **1963**, 85, 3886.
17. "Structural studies by nuclear magnetic resonance. VII. The stereospecificity of coupling between protons separated by six bonds" (with Taller, R. A.; Vane, F.M) *Tetrahedron Lett.* **1964**, 18, 1081.
18. "Structural studies by nuclear magnetic resonance. VIII. Ring-substituted phenylhydrazones, semicarbazones and thiosemicarbazones" (with Vane, F.M.; Taller, R.A.; His, N) *J. Am. Chem. Soc.* **1964**, 86, 3351.
19. "Structural studies by nuclear magnetic resonance. IX. Configurations and conformations of N-nitrosamines" (with Taller, R. A) *ibid.* **1964**, 86, 4373.

20. "Structural studies by nuclear magnetic resonance. X. Conformation of aliphatic aldehydes" (with His, N) *ibid.* **1965**, 87, 2864.
21. "Structure by NMR. XI. Conformations and configurations of oxime-O-methyl ethers" (with His, N.) *Tetrahedron* **1967**.
22. "Structure by NMR. XII. Conformations and configurations of N-methylphenylhydrozones" (with Krumel, K.L) *ibid.* **1967**, 23, 1079.
23. "Spin-spin coupling constants between non-bonded  $^{13}\text{C}$  and protons in some  $^{13}\text{C}$ -labeled compounds" *J. Am. Chem. Soc.* **1961**, 83, 1230.
24. "Spin-spin coupling constants between non-bonded  $^{13}\text{C}$ -C-H on hybridization of  $^{13}\text{C}$ " (with Graham, J.D.; Vane, F.M) *J. Phys. Chem.* **1961**, 65, 1657.
25. "Spin-spin coupling constants between non-bonded  $^{13}\text{C}$  and proton III. Anomalies in  $J^{13}\text{C}$ -C-C-H" (with Graham, J.D.; Vane, F) *J. Am. Chem. Soc.* **1961**, 83, 2778.
26. "Spin-spin coupling constants between non-bonded  $^{13}\text{C}$  and proton IV. The  $\text{CH}_2\text{CH}_2 - ^{13}\text{C}$  Group" (with Graham, J.D.; Vane, F.M) *ibid.* **1962**, 84, 37.
27. Geminal proton-proton coupling constants in  $\text{CH}_2=\text{N}$ -systems" (with Shapiro, B.L.; Ebersole, S.J.; Vane, F.M.; Manatt, S.L) *ibid.* **1963**, 85, 4041.
28. "Proton- $^{13}\text{C}$  spin-spin coupling. V. Inadequacy of correlation of proton- $^{13}\text{C}$  coupling with s-character" (with Orzech, C.E. Jr.) *ibid.* **1964**, 86, 3574.
29. "Proton- $^{13}\text{C}$  spin-spin coupling. VI. Factors affecting  $J^{13}\text{C}\text{CCH}$ . The  $(\text{CH}_3)_3\text{C}-^{13}\text{C}$  system" (with Orzech, C.E. Jr.) *ibid.* **1965**, 87, 560.
30. "Proton-carbon- $^{13}\text{C}$  spin-spin coupling. VII. The relative magnitudes of *trans* and *gauche*  $J^{13}\text{C}\text{CCH}$ " (with Orzech, C.E. Jr.; His, N) *ibid.* **1966**, 88, 1817.
31. "Structure by NMR. XIII. Rotational isomerism about the alkyl-oxygen bond of acetates" (with His, N.; Orzech, C.E. Jr.) *Tetrahedron Lett.* **1966**, 38, 4639.

### Enzymatic Redox Reactions

32. "The stereochemistry of the conversion of propanediol to propionaldehyde" (with Frey, P.A.; Abeles, R.H) *Biochem. Biophys. Res. Commun.* **1965**, 18, 551.
33. "Comments on the factors controlling product stereospecificity in the reduction of carbonyl compounds with alcohol dehydrogenase and diphosphopyridine nucleotide" (with Fleming, J.S, His, N.; Abeles, R.H) *J. Am. Chem. Soc.* **1966**, 88, 849.
34. "The stereochemistry of the conversion of D and L 1,2-propanediols to propionaldehyde" (with Zagalak, B.; Frey, P.A.; Abeles, R.H) *J. Biol. Chem.* **1966**, 241, 3028.

### Miscellaneous

35. "Infrared spectra of isotopically labeled compounds. I. Diisopropyl ketones" *J. Org. Chem.* **1960**, 25, 315.

36. "Infrared spectra of isotopically labeled compounds. II. Compounds possessing the 2,4-dimethyl-3-pentyl skeleton" *ibid.* **1960**, 25, 1409.
37. "Relative contributions of hyperconjugation and nonbonded interactions to secondary isotope effects" (with Sonnichsen, G.C.; Papaioannou, C.G.; Scheppele, S.E.; Shone, R.L) *J. Am. Chem. Soc.* **1967**, 89, 463.
38. "Isotope effects. II. Further comments on the contribution of nonbonded interactions to secondary deuterium isotope effects" (with Papaioannou, C.G) *Tetrahedron Lett.* **1968**, 22, 2629.
39. "Asymmetric induction. A model for additions to carbonyls directly bonded to asymmetric carbons". *J. Amer. Chem. Soc.* **1967**, 89, 1367.
40. "Asymmetric induction II. On the extent of bond breaking in the transition states of some additions to carbonyls" (with Althuis, T.H) *Tetrahedron Lett.* **1967**, 49, 4911.
41. "Asymmetric induction. III. Effect of the *t*-butyl group directly bonded to the carbonyl" (with Zioudrou, C.; Moustakali, I) *ibid.* **1972**, 52, 5289.
42. "Asymmetric induction. IV. Dependence of some diastereomeric product ratios on  $\Delta\Delta H^\ddagger$  and  $\Delta\Delta S^\ddagger$ " (with Zioudrou, C.; Chrysochou, P.; Herlem, D.; Nipe, R.M) *ibid.* **1972**, 5293.
43. "Asymmetric induction. V. Effect of R on Asymmetric induction in additions to abcC-COR compounds" (with Zioudrou, C.; Moustakali-Mavridis, I.; Chrysochou, P) *Tetrahedron* **1978**, 34, 3181.
44. "Structure by nuclear magnetic resonance. XIV. On the anisotropic effect of the carbonyl group" (with Sonnichsen, G.C.; His, N.; Fenoglio, D.J) *J. Amer. Chem. Soc.* **1967**, 89, 5067.