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DONALD J. CRAM

Transcript of an Interview  
Conducted by

Leon Gortler

at

University of California, Los Angeles

on

14 January 1981

(With Subsequent Corrections and Additions)

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## DONALD JAMES CRAM

1919 Born in Chester, Vermont on 22 April

### Education

1941 B.S., chemistry, Rollins College,  
1942 M.S., chemistry, University of Nebraska,  
1947 Ph.D., chemistry, Harvard University,

### Professional Experience

1942-1945 Research chemist, Merck & Co.  
  
University of California at Los Angeles  
1947-1948 American Chemical Society Fellow/Instructor  
1948-1950 Assistant Professor  
1950-1956 Associate Professor  
1956-1990 Professor  
1985-1995 Saul Winstein Professor of Chemistry  
1988-1990 University Professor  
1990- Emeritus Professor

Consultant

1952-1987 Upjohn Co.  
1961-1981 Union Carbide  
1981-1991 Eastman Kodak  
1984-1992 Technion Co.  
1988-1991 Inst. Guido Donegani, Milan

### Honors and Awards

1953 Western Sectional Award, American Chemical Society  
1954-1955 Guggenheim Fellow  
1961 Member, National Academy of Sciences  
1965 Herbert Newby McCoy Award for Contributions to Chemistry  
1965 Award for Creative Work in Synthetic Organic Chemistry,  
American Chemical Society  
1965 Award for Creative Work in Organic Chemistry, Society of  
Chemical Manufacturers Association  
1967 Member, American Academy of Arts and Sciences

- 1974 Arthur C. Cope Award for Distinguished Achievement in Organic Chemistry, American Chemical Society
- 1974 California Scientist of the Year, Los Angeles Museum of Science and Industry
- 1975 Herbert Newby McCoy Award for Contributions to Chemistry
- 1975 Rollins College Distinguished Alumni Award
- 1977 Honorary doctorate, Uppsala University, Sweden
- 1983 Honorary doctorate, University of Southern California
- 1985 Roger Adams Award, American Chemical Society
- 1985 Richard Tolman Medal, Southern California Section, American Chemical Society
- 1985 Willard Gibbs Award, Chicago Section, American Chemical Society
- 1987 Nobel Prize in Chemistry
- 1988 Honorary doctorate, Rollins College
- 1989 Honorary doctorate, University of Nebraska
- 1989 Honorary doctorate, University of Western Ontario
- 1989 Glenn Seaborg Award
- 1991 Honorary doctorate, University of Sheffield
- 1992 National Academy of Sciences Award in Chemical Sciences

## ABSTRACT

In this interview Donald Cram talks briefly about his family and growing up in Vermont, Florida and New York, and this is followed by a description of his experiences at Rollins College and his start in the world of chemistry. Next he talks about his graduate work at the University of Nebraska with Norman Cromwell, the circumstances which led him to work at Merck during World War II, and his work at Merck and the chemists with whom he collaborated. He then talks at length about his doctoral work at Harvard, his research, his coursework, cumulative and foreign language exams, and his interaction with various members of the faculty. In 1947 he took a position at UCLA, and he describes much of his research through the early 1960s, Saul Winstein and his interactions with Winstein, and the changes that took place over thirty years in the UCLA chemistry department. The last part of the interview includes comments on the changes that have taken place in organic chemistry as a result of various factors, the advantages to the academic community of interactions with industry, the state and future of organic chemistry, and a description of his major research effort in the late 1970s, guest-host chemistry. It was this research that led to his sharing the Nobel Prize in 1987. In the final pages of the interview he talks about the influence of theory and theoretical papers on the development of chemistry.

## INTERVIEWER

Leon Gortler is Professor of Chemistry at Brooklyn College of the City University of New York. He holds A.B. and M.S. degrees from the University of Chicago, and a Ph.D. from Harvard University where he worked with Paul Bartlett. He has long been interested in the history of chemistry, in particular the development of physical organic chemistry, and has conducted over fifty oral and videotaped interviews with major American chemists.

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INTERVIEWER: Leon Gortler  
INTERVIEWEE: Donald Cram  
LOCATION: University of California, Los Angeles  
DATE: 14 January 1981

GORTLER: I know you were born in Chester, Vermont, in 1919, but beyond that I know very little about your early history, and perhaps you can start there.

CRAM: I was born of Canadian parents, my mother [Joanna Shelley Cram] having been a first generation immigrant from Germany to Canada, and my father's family, having been of Scottish background, had been in Canada for some years. My sisters are Canadian. I have four of them. I have no brothers. I was the fourth of five. I was next to the youngest. My father [William Moffet Cram] died when I was not quite four years old and left my mother with the children, and no means of support, and so I was raised with a great deal of challenge in a financial sense. But I was fortunate enough to have had a decent father, on the one hand, and a very energetic, provident, and very enterprising mother. My father had been a lawyer. My mother had essentially no education. In fact, she was raised as a Mennonite, and had obtained an instant set of values by going completely against the religion in which she had been raised, which is sort of a bleak religion. She embraced all the things they were against, and raised us in a most liberal way. We were brought up with all the advantages that a much more wealthy family might have had, from the point of view of music lessons, sports, plays, some of the things that tend to embellish life. We were also raised to be hard working and ambitious, and also with the general notion that education is the path to righteousness.

I suspect this is why I'm a college professor today. Brattleboro, Vermont was a good place, too. It was a town of ten thousand, with a lot of work for youngsters, a lot of different jobs, odd jobs after school. We were partially self-supporting at a very early age. I worked for probably ten, fifteen, or twenty different employers at one time or another, doing just about everything you can imagine.

I left Brattleboro when my home broke up because my older sisters were all going to school. I went to Florida, the beginning of my third year in high school, to work for friends of the family in a store. I worked there for a year, went to school in Lakeworth and West Palm Beach, Florida, and then for the fourth year, moved to a private school on Long Island where I worked as a janitor to support myself.

GORTLER: What school is that?

CRAM: That was a school that's no longer in existence. It's Winwood School. That was a small private school, pretty good—I took Regents exams and did quite well on them without really being very much instructed, except I learned early a lot of self-discipline and I instructed myself pretty much. I remember, I took a course in solid geometry, where the teacher didn't know anything about it, and all I did was to work all the problems in the book. That's an example. That type of thing. I think I got a ninety-four on the Regents exam, out of a hundred, so that wasn't too bad, with no competition and no instruction.

I never did very well in my grades in school but did reasonably well—but I engaged in sports somewhat successfully, and was looked upon as being well rounded. I did some singing, some dramatics. On the basis probably of more well-roundedness than anything else, I got a six thousand-dollar scholarship to attend Rollins College in Florida in 1937, and spent four years down there, and got a bachelor's degree. This was liberal arts college, at that time, of about four hundred fifty students, co-ed.

GORTLER: Who provided that money?

CRAM: They had four scholarships, I think, and they had some rich donor who donated these as sort of a trial run.

GORTLER: This was from Rollins?

CRAM: This was from Rollins. It was a national competition. There were applications to be filled out, interviews to be given, and presentations to be made. I went to Rollins, and had a very good time. It isn't a first class school, but it's a school where you could get a first class education if you wanted to dig in.

I worked, not very hard, but reasonably hard, particularly my last two years. I remember particularly that they only had a two-person chemistry department, and I took four courses in chemistry. That's all I had. But I found later that those courses held up very well. I had missed some things, but what I had was great.

GORTLER: Who were the people there?

CRAM: Guy Waddington, who was a Caltech Ph.D. After leaving Rollins—this was during the Depression—he went to the Bureau of Mines in Bartlesville, Oklahoma, and I think he became head of it for a while. Then he worked for the National Academy of Sciences. So he was good. And Gene Farley, who got his Ph.D. at the University of Illinois, taught me organic chemistry.

Then he became a patent lawyer, and works as a patent lawyer in Eugene, Oregon, the last I knew. He was a first class person. He used [James] Conant's book, which at that time was standard, but you could put it in a corner of a current textbook. It really was not all that great, looking back on it, in my view. Having written a book, I can evaluate better.

GORTLER: Yes, I know what you mean. When you were growing up in Brattleboro, aside from your mother, were there any people you can think of, teachers, for example, who might have influenced you in any great way?

CRAM: Only in the sense that I had a Latin teacher who was a strict disciplinarian and who constantly worked at me, from the point of view of trying to extract more from me. I remember her because she challenged me and did so very ably. Also there were some good English teachers.

Then I had some good coaches and I played hockey, football, and tennis. I was lucky in the sense that I got interested in athletics, and it's something I have maintained. By interest, I don't mean as a spectator. I mean as a participant. I had a very fine childhood in an ideal place and a fine family.

GORTLER: When did you decide you were going to college?

CRAM: Well, that had always been understood. The means were not understood. But there was no question, so, by some device or another—and all of us did get to college. Not all of us got through four years of it, but all of us attended college, and two of my sisters went all the way through. One didn't. Another died in the meantime.

GORTLER: At Rollins, were there other particularly influential people, aside from the two chemists who were there?

CRAM: I took a course in high school in chemistry, and knew I was going to be a chemist at the end of that course. The teacher was not very good, but the book was. Well, the book was all right, but it really simply showed me the subject. There was a natural complementary relationship between me and the subject. After that I knew I wanted to be a chemist. I knew I wanted to be a college professor when Guy Waddington told me at the end of my freshman year that I wasn't good enough to be a college professor.

GORTLER: Threw down the gauntlet.

CRAM: He told me I wasn't good enough. That meant to me that he thought that that profession was the ultimate. Not having had a father, I was always looking around for father figures. I never found a perfect one, but I found a piece of one here and a piece of one there, and over a period of time I assembled one. I took a piece from him, just as I've taken pieces from quite a number of people over the years. In some ways I was lucky not to have a father, because I got a chance to assemble my own. And that's sort of nice if you can do it. It takes longer and there is a certain amount of trouble associated with it, but at least you aren't stuck with a bum.

GORTLER: When you decided to be a chemist, after let's say, a short while at Rollins, what were your perceptions of being a chemist?

CRAM: Well, I had done a whole lot of very repetitive jobs as a child, frequently on a barter basis: my labor for goods. Whether it be apples, or strawberries, or God knows what—socks, clothes, whatever, and I knew what I didn't want to do. What I knew was, I didn't want to do anything repetitive. To me the word "research" meant something that was non-repetitive. Now, of course, there's an awful lot of repetitive research, I learned later. On the other hand, the notion of research, and the notion of repetition, seemed to me to be antithetical. This is why the idea of doing research, in other words, doing something new every day, appeared to be very attractive. I learned that in academia you could do your own research, that you'd come and go to some extent on your own initiative, that it really only depended on you, and that you were, in effect, unlimited by institutions. All of that added up to academic research. When I learned that I could do chemistry and had a lot of fun doing it, it was a natural thing that I go into chemistry and go into academic chemistry.

Then I planned to be a physical chemist until I got to the University of Nebraska, and they had no proper physical chemistry. They had some pretty good organickers, so I decided to become an organic chemist, because I was simply making use of what was there.

GORTLER: You obviously had some laboratory courses at Rollins. How were they?

CRAM: Pretty poor, even by standards of that time. On the other hand, it was a small school. There might have been two or three people majoring in chemistry. What was good about it was that I became sort of a TA my second year and had to build equipment, and got to blow glass and got to design some equipment for the physical chem course, which I then took. The department was dependent on students more than would be found at a better-endowed place. Again, I took courses out of books and things like that on my own, and got to be sort of a do-it-yourself type. This was good because taking a course was between you and the staff, and the two people there, and you could more or less design whatever you wanted to do. So I got a little bit of introduction to the fact that things weren't cut and dried in research, and that you could design stuff, and make stuff.

GORTLER: Did you do a little bit of research there as well?

CRAM: A little bit, but it didn't come to anything, looking back on it. It was pretty shallow and unsophisticated.

GORTLER: What happened to the other "two" students? Did any of the others go on to graduate school?

CRAM: Oh yes. One fellow who got his Ph.D. and worked for Shell Development is Robin Hood Rae. The other fellow's name was Walter Danlicker. He works at Scripps [Institute]. These two people provided good competition. The fact is, they got better grades than I did.

GORTLER: That's absolutely amazing. Out of an undergraduate population of three, they all ended up in research careers. A very good percentage.

CRAM: That might have been some kind of chance of some sort. I learned how to fly down there. I was in dramatics. I sang in the choir for four years. I started going out for athletics, but then decided I didn't get a big enough yield on the time, and that it was incompatible with a science education. But I engaged in intramural swimming, diving, touch football, tennis, and what-not. And of course I enjoyed it.

GORTLER: During that period you didn't have to work because you had enough money.

CRAM: That's right. I had all this money. That was a packet of money in those days. It paid for everything. Fifteen hundred dollars paid for tuition and room and board. Then in the summer I worked for the National Biscuit Company in New York City, the first year as a salesman working the East Side. I got a class in ethnics. I got tossed out of a lot of little delicatessens and got to know all the A&P managers, and I also saw the seamy side of New York: prostitution, drugs, gang warfare. Things I didn't know the possibility of existing before that.

GORTLER: Not from your background, you wouldn't.

CRAM: Oh, no, it was very good for me because it told me what that part of the world was like.

And also I got a good course in ethnics. I got a chance to see the differences between people with different histories and cultures and what-not. That was very rewarding. I lost 40 pounds in the process, in three months. But that's all right. I was a little overweight going into the positions.

GORTLER: How did you decide to go to Nebraska?

CRAM: Rollins not being the best school in the world, and 1941 not being the most prosperous year in the twentieth century, led me to apply to seventeen different schools for a teaching assistant-ship. I got four offers—University of Pittsburgh, if I remember correctly, University of Nebraska, Iowa State, involving [Henry] Gilman, and I forget the fourth. As a matter of fact, I've lectured at most of the schools in the meantime that turned me down and I always congratulate the students on having been admitted there—the good taste of those places—not only good taste but they were good enough to be accepted.

So, although I knew I shouldn't get a Ph.D. from the University of Nebraska, I looked upon their M.S. as a stepping stone. I knew I had to get a Ph.D. degree from a better place to get a good academic job.

GORTLER: You already understood that.

CRAM: I already understood that. I understood a lot of things earlier than most people, because when you aren't given things, you go out to get them on your own.

GORTLER: That's right, you were really fending for yourself early.

CRAM: Exactly. So I was, oh, I was four or five years ahead of my time in all sorts of ways, like political development. I went through a political development when I was about fourteen or fifteen. My mother used to start reading me things and when she'd get me interested she'd quit, and I'd have to finish them on my own. So I digested everything that came along in the way of reading, and I went through various stages of getting interested in politics and then interested in cultural anthropology and interested in history and interested in English literature particularly. I was raised on English literature pretty much, and English literature values, with a pretty big dose of Victorian ethics thrown in. Of course, Vermont at that time was a little bit that way anyway.

But of course, the business of being uprooted and going away from home early, that was pretty tough. It took me a long time to wash New England out of my hair. It took me seven, eight years to get my roots out, but I ultimately got them out. I've never completely put them down anywhere else.

GORTLER: The comparison always was between you and Paul Bartlett. He came out of the Midwest, and there was no greater New Englander than Paul Bartlett—at least it appeared that way. You came out of New England and you always, it seemed to me, belonged here on the West Coast.

CRAM: I took on some of the aspects of the West Coast, but I'm very New England in my fundamentals. My values are very New Englandish.

GORTLER: That's good to hear. New England values are good ones. What was the nature of the courses you took at Nebraska, and what kind of research did you do there?

CRAM: I was there ten months. I worked for Norman Cromwell. I was a TA the whole time, including over summer session. I got a master's degree, wrote a thesis, and published three papers based on the master's thesis (1). I did all my own combustion analyses. I did, I think, forty-five analyses: carbon, hydrogen and nitrogen analyses. These were all new compounds. With Cromwell, I worked on the neighboring nitrogen in substitution reactions. We were actually, I think, very close to being the first to discover the migration of nitrogen from carbon to carbon via ethylenimine intermediates, for  $\beta$ -amino- $\alpha$ -bromo ketones. For example, we would make  $\beta$ -morpholino- $\alpha$ -bromo ketones and treat them with piperidine, and the morpholine would migrate to the alpha position, and the piperidine would come into the beta position. At least, this is what we'd see in the product, and we interpreted it as going through the bridging iminium ion. Norman was right at the beginning of that, and we worked out a couple of systems, and of course that, at that time, was hot stuff.

So I had, I think, really in some ways, a better master's thesis than I did a Ph.D. thesis.

GORTLER: You got a taste of mechanistic organic chemistry at that point.

CRAM: That's right, yes. I became a pretty good lab man. I'd been pretty bad at Rollins, getting my hands under control. I broke a lot of stuff, partly because of my impatience. I worked very fast and all. But I got things under control at Nebraska and moved very fast. In fact, I moved in and out of there with a thesis better than most of the Ph.D. theses that were coming out of there at that time.

And also I learned that I liked research, and I liked research done with my own hands. As I said, I did my own—you had to in those days.

GORTLER: Did you have some courses there as well?

CRAM: Oh, I had many courses. Oh, yes.

GORTLER: Do you remember any of them in particular and the textbooks you were using there?

CRAM: I don't remember textbooks, but I remember a course in heterocycles given by Hamilton. It was a "marching-down-Fifth-Avenue" type of course. It was an encyclopedic type course where we talked about the various heterocyclic systems: how they're made, what their reactions are. A very classical but very substantial course.

There was a fellow by the name of Demming who wrote many textbooks, a physical chemist, who was one of the world's worst teachers, just awful. He'd forget what lecture he'd given the day before, so he'd start to give the same lecture over again. The class would tell him he'd given that one yesterday, and then without embarrassment, he'd give the next one. He never prepared. He was bad. He's one of the people who turned me against physical chemistry. He was known locally as "Hogfat" Demming. Nobody respected him. He used to entertain the pretty girls in his office.

GORTLER: Who else was there at Nebraska University?

CRAM: Well, there was an analytical chemist who taught me how to do these analyses, and worry about error analysis, whose name escapes me. I think his name started with a P and it was a French name. I can't bring it to mind. But what I do remember is, he used to leave in the middle of the lecture and say he had to do something that nobody could do for him and then he'd reappear three or four minutes later.

Actually, when I was in Nebraska, I did nothing but work. I got up probably in the neighborhood of a hundred to a hundred twenty hours a week, on that kind of schedule, and I moved very well. I'd go to a movie every other week maybe. That would be my entertainment. But then Lincoln isn't rich in outdoor life and didn't offer many neat things to do.

GORTLER: Were you married then?

CRAM: I got married while I was there. I took a weekend off, got married, to somebody I'd known at Rollins and had gone around with for four years.

GORTLER: I see. You were supporting the two of you on a TA?

CRAM: Yes. As a matter of fact, I got fifty dollars a month for my TA job, but then you have to remember that you could buy a reasonable dinner for a quarter. And a milk shake was a nickel. Steak was thirty-five cents a pound. So this gives you a financial framework. I paid eight dollars a month when I first went there for a room where I slept in a bed with another guy. We shared a room and a bed for eight dollars a month, so that gives you some impression of prices.

GORTLER: Did you take an advanced organic course, aside from the heterocycle course?

CRAM: No course in physical organic chemistry. Whitmore's book, I had a look at it. I think it had just come out in 1939 or 1940 or something like that. I remember the benzil-benzilic acid rearrangement, being astonished at how complicated that mechanism was, written in the book, with all the electrons showing. And, of course, you get into a tremendous amount of electron counting. And I remember being impressed with its complicatedness. And that's all I recall. Outside of my research, there was some, of course, involved in this imine rearrangement, but I didn't really have a good feeling for it.

GORTLER: How about just general papers? Aside from your research and your course work, were you being introduced to the literature at that point? Did you know what was going on outside?

CRAM: Very little. I was operationally oriented: "How do you get through?" I was not scholarly oriented.

GORTLER: No reason why one should be at that age.

CRAM: Well, people have different inclinations, and I've always been inclined toward doing things.

GORTLER: Then you went off to Merck. How did that all take place?

CRAM: That's an interesting story too, at least to me. The first time the government offered a Civilian Pilot Training Program, I took it at Rollins. You got a private flying license,

under government auspices. They paid the bill.

[END OF TAPE, SIDE 1]

CRAM: I took the Civilian Pilot Training Program, and then came back to New York City and got my summer job for twenty dollars a week. Then, I got a telegram and they wanted me to come down to Florida and take an advanced course. If that telegram had come two days earlier, before I got that job, I would have taken it. And, if I'd taken it, I would have undoubtedly been a pilot in the war. Because the five people who did, two or three of them ended up as brigadier generals, one was killed, and one ended up as an instructor. I liked flying, and I probably would've accepted that, but I didn't. As a result, I went on and got a master's degree. My draft board was in the middle of Harlem because my mother lived on Morningside Heights, and the draft board in the middle of Harlem was over-subscribed with people. They wrote me a letter while I was in Nebraska and said: "We have been deferring you all this time so that you could get a job and do something for the war effort." They suggested that I go ahead and get a job, and do something for the war effort. So I applied for jobs at several of the pharmaceutical houses, and accepted one at Merck because my wife wanted to go to the New York School of Social Work, and get a master's degree while I worked during the war. She got her master's degree at Columbia while we lived in New York City, and I commuted to Rahway, New Jersey, which was a sort of a poor arrangement.

GORTLER: Now, the twenty dollars a week job, that was the one you had summers when you were a student at Rollins.

CRAM: Yes. The draft and the Army, all that came later.

The sequence of events is that I took the Civilian Pilot Training Program and got to be a pilot. I got my bachelor's degree at Rollins, went to Nebraska, got a master's degree, came back to New York in 1942, summer. Left Nebraska in a wind storm, temperature 95°, by Greyhound bus. I'll never forget that day. Arrived in New York, went to work at Merck. And I worked at Merck for three years then during the war. Worked for Max Tishler (2).

GORTLER: And you also had some work with John Sheehan (3).

CRAM: John Sheehan was in the next lab. Merck had quite a distinguished group of scientists at that time, and large numbers of them left. Merck is an institution that has large numbers of alumni.

GORTLER: Who else was there at that time?

CRAM: J.C. Keresztesy, for example, and Stanton [Stan] Harris and Ralph Mozingo, and Kurt Laudenberg, Bittenbender, Bulhoffer, Jack Little, those are some of the names that come to mind. There are large numbers of others but I can't bring them to mind.

There was a steroid chemist, Jacob Van de Kamp. He was making cortisone, as I recall. And of course, John Sheehan, working on Vitamin A, if I remember correctly, or penicillin. And of course Karl Folkers was there.

I worked on the isolation of penicillin, and purification. This is the time, of course, when we were recovering penicillin from the urine of patients, to recycle it, because it was very valuable. So I got a lot of training in isolation chemistry. I did some chromatography on alumina, which in 1942 was just starting to be fairly common. I had run some chromatograph columns in Nebraska, that were more primitive, and on a much smaller scale.

Well, then I worked on the riboflavin process, I worked on the papaverine process, and then I worked on the isolation and purification of streptomycin. Those are the things that I worked on while I was at Merck. I did quite a bit of development work. I did some basic research. I even did pilot plant work. I converted a four hundred-pound batch of ribose to ribotylamine. The reaction involved several hundred pounds of Raney nickel and about eight hydrogen tanks, pouring hydrogen into a great big kettle. Everything happening at once and the reaction had to be over in four minutes or you lost about seventy or eighty thousand dollars worth of stuff. I remember running that out in the open, essentially in an open shed.

GORTLER: You got an enormous amount of training.

CRAM: So I got a lot of training.

GORTLER: Who was your adviser, Tishler?

CRAM: Tishler was my boss's boss. I had a series of about three bosses. Kurt Laudenberg was one and, gosh, I can't remember the second fellow's name. He's now an executive some place. I talked to him a couple of years ago.

I had two or three bosses, but Max took a particular interest in me and used to come around and see me directly. So I always felt that I worked for him, because he provided the continuity. Well, the moment VJ Day came along, I applied to get into Harvard as quickly as I could. As a matter of fact, I moved to Harvard three months after VJ Day, if I remember correctly, on a teaching assistantship. Then I got a National Research Council Fellowship a

few months later.

GORTLER: They were available for graduate students at that time? I know the post-docs very often had them, but they were—

CRAM: There were some graduate student fellowships. And I remember going to try to get out of my TA-ship and we entered into a compromise arrangement whereby I worked for nothing for one half of a semester in return for being released for the other half of the semester.

GORTLER: Who was it you had to deal with during that time?

CRAM: It was some old fellow who was an inorganic chemist but was chairman of the department at that time. I can't remember his name.

GORTLER: Was [Arthur Beckett] Lamb gone by that time?

CRAM: No, Lamb was there, but he was the *JACS* editor; he was not chairman. The chairman was an inorganic chemist, George Shannon Forbes.

I get to Harvard and who's there but George Hammond and Ted Lewis, and they were sort of left over from an earlier period.

GORTLER: Yes, right. They had been working with Bartlett during the war.

CRAM: That's right, and of course Louis [Fieser] was there and Mary [Fieser] was very much there.

GORTLER: Were you called upon to get the cookies, too? That's what Tom Jacobs was telling me. He used to get the cookies for the tea.

CRAM: Well, there were quite a large number of things that I was called upon to do which I never did and, as a matter of fact, got into Mary's ill graces as a result. But actually, Max Tishler probably as much as anybody was responsible for my going to Harvard.

GORTLER: Yes, I wondered whether he had influenced you.

CRAM: He had encouraged me to do this, and he'd also encouraged me to work with Fieser. Actually, it didn't take me very long to think that I probably had made a bad mistake. But looking back on it, I think it was the best thing I could ever have done. In other words, on Max Tishler's advice I went to work for Fieser. When I got to Harvard, I found that Fieser really was a pre-war rather than a post-war chemist in this thinking, and that there were much better people. I had already committed to Fieser by the time I'd gone there.

GORTLER: You had written him before?

CRAM: I had written to him. I had in effect signed up.

GORTLER: Bartlett was there?

CRAM: Bartlett was there and [Robert B.] Woodward was there and, of course, both of them were relatively young men then. I envied the people that worked for them, and I wondered why I hadn't been smarter in working for them myself. But in looking back on it, my analysis is that I had the best of all worlds. I had the independence that went with working with somebody that didn't know what I was doing and didn't care very much, and the ability to learn from the best that were around, and on my own terms.

GORTLER: You were probably mature enough, as a result of everything else that had happened to you, to do that kind of thing.

CRAM: Yes. I was only two years younger than Woodward, and I didn't look upon him as any different than someone my age. Although I admired him as a scientist, I thought, "Here is another interesting person." And Paul was maybe eight, ten years older than me, I guess. I don't know just exactly. I'm sixty-one now and he's about seventy-one?

GORTLER: Yes, he was born in 1907. He is seventy-three now.

CRAM: Yes, and so he's about ten years different in age from me, and of course I looked up to him more as a person a generation removed from me. I took a course from him, and George Hammond was the TA who corrected my papers. That course was a revelation. This was Chem 5, if I remember correctly.

GORTLER: That was the advanced organic course.

CRAM: As I recall, I got an A in it and enjoyed it thoroughly. Got a big kick out of it. Then I started taking cumes [cumulative exams]. They'd just invented cumes. The first few cumes, they announced the topic they were going to be on. Now, I remember for example, there was going to be one on the use of isotopes in organic chemistry. I looked up every paper that was published on isotopes in organic chemistry at that time, and as a result, I learned a whole lot of stuff that was very interesting. Of course they changed the system after about four cumes, because people were spending all their time studying for these cumes and weren't doing any research. The staff thought this was not so great so they changed it, and left the cume topics unannounced. I can't remember how many. I think we had to pass seven, and I think I passed seven out of eight, if I remember correctly, or five out of six. I forget. It was one or the other. As I recall, the one I flunked was on the history of organic chemistry, and it was given by Louis Fieser, and I misspelled some things. In fact, there's a story: the famous chemist, Emil Fischer; I spelled Emil Fischer "Amyl." When Fieser came to this, there was a big red mark on the paper, and a great big arrow to this, and he said, "I can't stand this any longer," and there were no red marks after that. So I knew that it hadn't been corrected past that point and I'd just flunked.

GORTLER: It seems to me that that was perfectly chemical and he should have been willing to overlook it.

CRAM: I've never been able to spell proper names. I can spell non-capitalized names reasonably well, but I can't handle proper names for some peculiar historical reason.

Well then, I got through the cumes. I took the four placement tests that I had to take when I first arrived. I had been preparing for those tests by working problems in all sorts of books. Passed them all, so I had no courses to make up. And I started doing research.

GORTLER: You took the advanced organic. Did you take the thermodynamics course, for example?

CRAM: I took the thermodynamics course. Kisty [George Kistiakowsky] was not there when I first came. That course was taught by a fellow who went to Columbia after Harvard. Very nice person. Good teacher. I may bring his name to mind as time goes on. Got a B in it, I think. It had some statistical mechanics and quantum mechanics in it. I think it was a year course, if I remember correctly. Henry Kuivila and I studied together, and as I recall, we both got Bs. I had to stretch on that course. I had to really work hard. I didn't have the proper mathematical

background at Rollins, and I had to go back and learn partial differentiation math, which I did. I think that was probably the only B I got at Harvard. I didn't go to Bartlett's seminars but I went to Woodward's seminars. They were held reasonably frequently then. They used to be four or five hours long.

GORTLER: They were still that way about ten years later. I was there then.

CRAM: I listened to all of Woodward's courses and I got to know him quite well personally. In fact, I'd done some work on the structure of a compound on the side, and had it almost fully elucidated, and tried it out on him, and he helped me with some suggestions. We arrived at the final structure, and then I confirmed it later—a natural product. I earned his respect in the process of doing this, and also, we weren't all that different in age. Also, I went skiing with him, probably the only time he ever went skiing, and it was a disaster. I mean, he nearly got hurt. I was concerned about him. I had skied since I was a kid, and was a reasonably good skier. Not super but pretty good.

GORTLER: You were a pretty good athlete. Was he?

CRAM: Oh, he was the antithesis of an athlete. In fact, he always had a set of derogatory jokes about people that engaged in athletics.

I got a good look at his mind, of course, in these seminars, and he taught a whole course on morphine. Woodward's courses were a lot about a little, to summarize. Also he would show up for class only when he felt like it. Nobody would quite know beforehand whether he was going to show up or not.

GORTLER: That's interesting. I thought maybe earlier on he was more conscientious than he was later. When I was there in the late 1950s, sometimes his course would never meet at all.

CRAM: I think he probably met three-quarters of the time at the beginning and maybe half in the middle period, and none at the end. As he got to be more famous there was more slippage. I remember when he was promoted to associate professor. I remember congratulating him on getting tenure—coming in the door of Converse Laboratory.

I shared a lab with Martin Etlinger who you may have heard of, or you may not have. Martin was a Texan, and after he got his Ph.D., he came out to Caltech for a year, and then he went to Rice and he was on the staff at Rice for a while. Then he went from Rice to Copenhagen and he's teaching in Copenhagen. I saw him last year. He was a prodigy. Both his father and mother were mathematicians, and he had a photographic memory, and was a

real intellectual.

We all used to play touch football, Harry Wasserman and Jack Roberts and George Hammond, out in the back of Converse, until we broke a window, and then somebody got mad and decreed we couldn't play touch football out there any more.

I got to know Jack quite well, got to know George. We talked about the possibility of writing a textbook some time together, while we were—

GORTLER: At least two [Cram and Hammond] of you did.

CRAM: Two of us did.

GORTLER: And the third [Jack Roberts] went off on this own.

CRAM: Yes, except that later on, we almost got Jack to join us. In fact, if we'd given him more time, I think he would have. But we put a deadline on him, so he said that he couldn't fulfill it, but if we'd given him more time he'd join us. But we had put in a lot of time already and I didn't want to delay it, so we went ahead.

Well then, what happened? I finished Harvard in about eighteen months. I came in September, then got all my courses out of the way, took the tests, passed all the tests, got my French and German out of the way, and those were comical. They were fictional type of tests.

GORTLER: You'd go down to the basement, somebody would hand you an article, and if you could read that—

CRAM: Well, you had to sit down at a table and do a translating job and hand it in, and somebody would glance at it and that was it.

GORTLER: Professor Albert Sprague Coolidge would give you the exam.

CRAM: Yes, that's right. And it didn't come to anything.

GORTLER: If you were lucky, French would be an experimental section, and you could—

CRAM: Interpolate it pretty much.

GORTLER: That's how I managed to get past my French exam.

CRAM: Those were non-events.

I knew how to do research already, and I got a problem working on naphthoquinones, 2-acyl naphthoquinones, so I became the world authority on 2-acyl-3-hydroxynaphthoquinones. And I made something like seventy-five new compounds for testing as anti-malarials (4). After I'd been there about a year, I thought, gee, I really should write a report on this. So I wrote a report. I never talked chemistry with Fieser essentially after the first time I came in to get a problem.

GORTLER: Oh, really?

CRAM: I saw a lot of Mary but I never saw Louis. Louis was in doing lab work. After about a year, I thought, gee, maybe Louis ought to know what I was doing, so I wrote a report for him. He gave it to Mary to read. She was at that time doing a lot of writing and learning how to write. She was giving a course in creative scientific writing, which we all had to take, and which was good for me, although I didn't like it at the time. So I wrote this report, and she marked it up and gave it back to me, and Louis never saw it. And there were no comments on the science of it. It all had to do with English. It was a good job that Mary did. It was good for me.

Well, I had some trouble with the analyst. Those were the days when you had to pay your own lab bills for the most part, or a good portion of them, and Harold Kwart and Bill Sager were there, and they were in the glass blowing business. I remember, I ordered four hundred fifty dollars worth of glassware—micro ground glass equipment that I designed for my research and paid for myself. And I had an eight hundred-dollar storeroom bill that I had to pay for at the end, when I left, I remember that.

GORTLER: After only eighteen months?

CRAM: Well, some of the tab had been picked up by my fellowship. But I had overrun it by that much. Also I remember being very disgusted: somebody called me up one Christmas vacation and asked me if I was working, and I proudly said, "Yes, of course." Then they were going to charge me, personally, rental on the lab. I raised a big fuss about it and they didn't. But things were a little different then.

Well, it became pretty clear that Louis wasn't going to get to know me or get to know my abilities, except through Mary. It was also very visible—this is turning into quite a biography—it was also very visible that Mary didn't like me very much because I wouldn't do things to accommodate her.

GORTLER: What kinds of things would she call on you to do?

CRAM: Order compounds, do this chore or that chore. I did it the first few times, but then as time went on, I thought it improper that I'd be spending my time this way, so I refused to. I kept on working, and accumulating results, and then the question came up as to just when was I finished?

So I went to the library to look over theses. I looked over Louis' thesis, which is very heavy, big. He did a very substantial thesis.

GORTLER: He worked with [James] Conant.

CRAM: Conant, yes. He had a very nice thesis. But I figured I had a master's degree so I could take my master's thesis and my Ph.D. thesis and put them together and I'd get something somewhere near his. So I decided, after I'd been there about sixteen months, that I could finish in eighteen months. So I wrote the whole thing up and gave it to Louis as a thesis.

In the meantime, there was this analyst. I had had some problems with the analyst, in the sense that I had given her a compound with boron and fluorine in it, not knowing that I had a chelated compound. I'd had to use  $\text{BF}_3$  and, of course, she had an ash and it fouled up her furnace. Then it ruined a whole lot of subsequent analyses. So this resulted in my not being able to use her. And I came down to the wire and I had something like forty analyses that needed to be done. I went to the storeroom and signed out a whole bunch of antiquated combustion equipment and did fifteen-milligram analyses on forty compounds in something like ten days. Set it up, standardized it, went through the whole bit. Fieser saw all this equipment. He was walking by the door and he looked in and saw all this equipment. "What in the world are you doing?"

So I told him what I was doing. He admired me more for doing that than he did for anything else because he understood it. You may recall that he did analytical work himself back in the days when they were determining the atomic weight of carbon. He combusted very large samples. That's one of the first things he did.

GORTLER: I didn't know that.

CRAM: Yes, this was back in the days when the exact atomic weight of carbon wasn't known. He polished the atomic weight of carbon, got a much more accurate value by carbon-hydrogen combustion analysis.

So he admired this. Well, I wanted to apply for a fellowship for the next year. So I wrote this all up and gave it to Louis and he said, "What's this?" I said, "It's my thesis. My Ph.D. thesis." He said, "What's in it?" I said, "Well, what's in that report, plus what I've done in the meantime." He was very surprised, and so he gave it to Mary again. Mary went over it and said, "It looks like a pretty good thesis."

In the meantime I'd gotten to know Jack Roberts really quite well, and he offered me a post-doc job with him. I was going to start in April of my second year, but Louis said, "Well, now that you've done your thesis, there are several other things that we'd like to have you do."

GORTLER: He wasn't going to let that good man go that easily.

CRAM: So I got out in June, but I submitted my thesis in April. I made a few more compounds of his design. These others had been of my design.

GORTLER: That must have been one of the fastest Ph.D.'s.

CRAM: I got out pretty fast. I was raised in the Depression, and I figured that there were going to be all sorts of people knocking at the academic doors, and there were going to be a limited number of jobs and I wanted to be out early. So I got out. I got my Ph.D. in June with George Hammond and Ted Lewis, and got an American Chemical Society fellowship that paid me twenty-five hundred dollars a year to come to an institution where I'd be a half-time teacher and half-time my own investigator. I wanted to come out West because I hadn't been in that part of the country, so I asked Jack Roberts, "What's the best organic chemistry place? What's the best organic chemistry place on the West Coast?" He said, "UCLA." I said, "Is it near the ocean?" He said, "Yes." I said, "Fine, that's where I'll go." So I applied to UCLA and asked if they would give me a part-time teaching job for a thousand dollars. The ACS gave me twenty-five hundred, and the institution had to give me a thousand, so I got thirty-five hundred, which was enough to live on.

But I needed some money to go across country with, so I went down and worked as a post-doc with Jack. He had, in the meantime, gotten a teaching job at MIT, and so he hired me. I went down and worked for him for three months, from June to August, or maybe it was May, June—I think it was May, June and July—and then I came out here.

[END OF TAPE, SIDE 2]

CRAM: I was about to say that Louis gave me a relatively poor letter of recommendation for a fellowship, and I happened to see the letter because his secretary mixed a copy of the letter in with the forms that she was to return to me. Then I approached Fieser and asked him why he had written me a relatively poor letter. He said I wasn't supposed to see that letter, and that I should have returned it to him without looking at it. I said I didn't know that, and I apologized.

But in the meantime I'd gotten to know Bartlett. I'd been skiing with him and had taught him how to ski. And I'd gotten to know Arthur Cope, and had taken Art Cope out and bought ski clothes with him, and these people wrote me very good letters.

I remember Paul Bartlett told me that a negative letter from Louis would probably do me more good in some quarters.

And Woodward wrote me a very nice supporting letter, too. So I had the advantage of working with someone who left me essentially strictly alone, which was good, and learning a great deal from Woodward and Bartlett at my own leisure and choice and disposition. And I also got to know them well personally. There were very few graduate students around then. People hadn't gotten back to school yet. And so I really went through Harvard when there was hardly anybody there.

GORTLER: So you were really talking to the staff more than anyone else?

CRAM: Exactly.

GORTLER: What kinds of things were you reading then? By then you must have been really reading the literature.

CRAM: No, I wasn't.

GORTLER: You weren't?

CRAM: No. Again, I didn't learn anywhere near as much as I should have at Harvard. I just couldn't take the time. I just couldn't take the chance. I started reading seriously when I came out here. In fact, I went through—what I did was to take the major journals and page backwards in them for the ten years prior to that time. That's one thing I did. Another thing I did, I took

people whose work I admired and looked up all their early history, early papers and stuff, to see what sorts of things they'd done. I followed their history on paper.

GORTLER: Give me an example of a couple of people.

CRAM: Well, I did it with Bartlett, although his history wasn't that old at that time. I did it with [Christopher K.] Ingold. His history was quite a bit longer, and in fact I remember being quite disgusted at some of the early stuff he did. It was pretty bad.

GORTLER: Yes.

CRAM: Some stuff he did with Thorpe or somebody on some four-membered ring compounds. You could just tell by the way it read that it was bad work. And in fact, I remember Raistrick. I went through all Raistrick's papers on compounds he'd isolated from molds. I remember working very hard to try to solve the structure of the stipitatic acid, which gave rise to the whole tropolone business. Michael Dewar figured that out, and I kicked myself around the block because I'd gone through the same literature without coming up with the tropolone structure. Dewar had done it, which told me that there was enough stuff there to come up with that structure, and I had not been able to do it. I remember being very chagrined about this.

At that time, I decided to work on mold metabolites. That was going to be one of my fields, because of the antibiotics on the one hand, and because I'd done some structural work on compounds and I liked degradative procedures, and the kind of inductive reasoning you do, and reasoning back from properties to structure (5).

But then I leafed through these early literatures of various people that I looked up to, and decided I ought to broaden out a little bit. I got interested in the paracyclophanes as a result of Dewar's ideas on the benzidine rearrangement; you remember the  $\pi$ -complex business? I thought, well, let's build an intramolecular  $\pi$ -complex by tying two benzene rings together in the 1,4 positions, and let's pull them in on each other and see what kinds of effects turned up. I had that idea about 1947, 1948, something like that.

GORTLER: When did you start the paracyclophane work?

CRAM: I started it in 1947, started working on it. We published our first paper on it in 1951 (6).

That work I did with a graduate student, though. I did all the other work, the early work, with my own hands. I published eighteen papers or something like that with only my name in

the early days. I decided I wasn't about to risk not getting tenure by depending on somebody else's hands. So I essentially got tenure based on my own hands. I worked—again, I worked a hundred, a hundred twenty hours a week. Worked all the time, and had a ball. Really.

GORTLER: If you enjoy what you're doing, you're okay.

CRAM: Now, the phenonium ion work I got into completely serendipitously, in 1948. We were working on the structure of citrinin, and ran into a system that was a 3-aryl-2-butyl alcohol, which was optically active, and when treated with acid, racemized—even though there were two chiral centers. The aryl group had two meta-methoxyls on it, and also a methyl. So the question was: how do you racemize the two centers?

Well, I was familiar with the Wagner-Meerwein rearrangement, so I postulated that it was by aryl rearrangement, and then I thought I'd do the model work. So I did the 3-phenyl-2-butyl system, and separated all four enantiomers. I worked all that out, and then treated the alcohols with acid and methyl alcohol. Then I thought, I'd better do it so the product itself can't undergo reactions. So I went to tosylates, following what [Joseph] Kenyon had done and what Ingold had done. This allowed me to run acetolysis, and then later formolysis, and we did all that work and published it in 1949 (7).

On the basis of that work, I accomplished two things. I irritated the hell out of [Saul] Winstein who had been looking for just exactly the phenomenon that we had found serendipitously. And on the other, I was offered a job at the University of Wisconsin.

Now, I was picked over [George] Hammond and [Ted] Lewis for the tenure track job that they had at UCLA, on the basis not that I was a better chemist, but on the basis that I was a natural products chemist and they wanted somebody in natural products. That's one of the ironies, of course. I haven't been all that natural product-ish in the meantime.

GORTLER: Right. Bill [William G.] Young was here and Winstein was here, so you must have started to interact with them, and their physical organic bent.

CRAM: Right. Also, I'm a great one for following my nose. My nose rather serendipitously led me into the phenonium ion work. Then in the course of making the compounds, we ran into the rule of steric control of asymmetric induction (8), and I looked up all the earlier literature on this and put it all together. Then of course I learned about the same time—this was about 1951, as I recall—that [Vladimir] Prelog was barking up the same tree, but with a 1,4 rather than a 1,2 asymmetric induction, I guess. He followed up on McKenzie's early work.

So these were all results of my following my nose, to some extent, although the paracyclophane work was really a conception, a general conception. In fact, I laid that whole

program out, about ten years of research before it was done, and asked all the interesting questions. I knew that we could make some formally conjugated, but in reality non-conjugated, olefins, which we did later. I knew we'd get into very interesting inter-annular substituent effects, and so forth. I knew we'd run into interesting ultraviolet spectra, which we did, trans-annular electronic effects, which we ran into.

GORTLER: Yes. Of course, NMR hadn't really come into use at that time.

CRAM: We used UV. That was our main modification of electronic spectra.

So the paracyclophane work was really a concept, a good, nice, central concept. The phenonium ion stuff, once I had got the initial lead, it became a concept. But I had a lead into that, an experimental lead into that, so that was empirical. The rule of steric control was simply a correlation that grew into a sort of correlation based on a mechanistic concept. I haven't worked anywhere near the center of physical organic chemistry. I've always worked on the periphery of it.

Of course, I read [E.D.] Hughes' and [Christopher K.] Ingold's papers. I read [Herbert C.] Brown's papers on elimination and I followed the controversy between the two, and I was interested in the  $E_1$  and  $E_2$ ,  $SN_1$  and  $SN_2$  reactions—as a result of having to teach a course. We used to pass around the courses. Almost every quarter you'd teach a different course, and I had to teach a course in advanced organic, and as a result of this I went to the literature and dug up a whole lot of stuff on these reactions. Kenyon's work impressed me very much, and I always liked stereochemistry anyway, and it occurred to me that Kenyon got a better hold of the structural aspects of a transition state diagram than you could get your hands on with kinetics. So I was always structurally oriented in my physical organic, and that meant stereochemically oriented, using a stereochemical probe as a test of the structural changes that occurred during the mechanistic sequence.

That's the way our work shaped up as time went on. We used a stereochemical probe, and then in later years to some extent I modeled some of our carbanion work after the carbonium ion work done by Kenyon and others. Do you see?

GORTLER: Yes.

CRAM: So I reasoned by analogy. All I did was to change plus to minus. And all our carbanion work was pretty much an outgrowth of reasoning by analogy from the solvation effects from carbonium ions to carbanions.

Now, that started about 1957. No, that started about 1953, 1954, but it really didn't get any momentum up. We published our first papers in 1959 on carbanions (9). The

stereochemical capabilities of carbanions. Up to that time they had been thought not to have any stereochemistry.

GORTLER: Yes, and they maintained their stereochemistry better than—

CRAM: Than carbonium ions, and also they show more flexibility as to what they can do. But it took an awful lot—it took twelve or fourteen years to unravel all the complications you can get into.

Now, Winstein had a big effect on me. In fact, I probably owe Winstein a big debt for a number of reasons. First, he stressed me. And he tempered me. He was a very stressful and stressing person. He had very high standards for himself. He had high standards for those around him. He was a very good competitor, in the sense that he was very good. He didn't have a high-class sense of sportsmanship about his competition, I don't think, but he was a hell of a good competitor because he was high class. He was like a bulldog. He was very, very thorough, extremely thorough in his thinking. In fact, he'd go over and over and over and over things before he was satisfied with them. He was very meticulous. He hated to be wrong. He wanted to be right. You can classify people that way. Some people, like Dewar, don't care whether they're wrong as long as they're stimulating; Winstein always wanted to be right. He would be happy to be stimulating too, but he wanted to be right more than he wanted to be stimulating.

GORTLER: The challenge of Brown really must have bothered him.

CRAM: Oh, the Brown thing tore Winstein apart and contributed, in my opinion, to his early death.

GORTLER: You're not the first person who's said that to me.

CRAM: I lived with this for over thirty years, and watched its effect, and saw how Saul overstressed himself, too. He not only overstressed everybody around him, but he overstressed himself by these high standards and this perfectionism, his hard work and his devotion to science, and his devotion to standards. He and I competed for years with each other, for graduate students, for goodies, and what-not. It was this competition, I think, that probably more than any other single thing contributed to my growth.

It wasn't that he taught me so much. It was that he competed. You had to be good to survive. And this was a tremendous stimulation to me. I didn't approve or like a lot of the ways he went at things, because he always, for my taste, dwelt too long on one thing. I'd rather

study more things less thoroughly. He'd rather study fewer things more thoroughly, and did. In fact, his whole career was much more pyramided than most people's. He worked on neighboring groups all his life.

GORTLER: Yes.

CRAM: In fact, he continued his thesis all his life, and it was a very important field, and of course it was a gold mine. It was more than a gold mine. It was a gold, silver, and platinum mine. With some diamonds thrown in.

GORTLER: Yes. Sure. But in a sense, he may have contributed more if he'd had more breadth.

CRAM: No, I don't think so. I think his character and the problems he picked were a beautiful fit, one with the other. Because he started out with neighboring bromine, with his thesis, with [Howard] Lucas, and he went from neighboring bromine to neighboring oxygen to neighboring nitrogen to neighboring acyl, to neighboring carbon in its various forms, and of course this led into the non-classical ion, and into the non-classical ion controversy. But that was his edifice, his neighboring groups, participation and solvolysis, I think more than any other single thing.

GORTLER: Certainly he mastered synthesis as well. He did some magnificent work.

CRAM: Oh, yes, and that was one of his strengths, the fact that he could design and make, whereas Hughes and Ingold more or less took things off the shelf. They were physical chemists who didn't make things. Winstein made whatever he thought he wanted. And what he designed. That was his strength. That also has been my strength.

GORTLER: So maybe it's useful to have that strength in synthesis. You never think of Bartlett as having done that, and yet he did, too.

CRAM: He did some of that, too. I remember when he wanted to make tri-tertiary-butylcarbinol—and did.

GORTLER: Yes.

CRAM: You're most interested in this early period, I take it?

GORTLER: Yes.

CRAM: Incidentally, Saul and I had an awful lot of trouble with each other the first few years, but as time went on, we became very good friends and did a lot—worked hard for each other's interests.

GORTLER: The trouble was you were competitive with one another?

CRAM: We were competitive. We were both high spirited. Also I think both of us were a little bit roughshod. And we challenged each other.

GORTLER: You came here on an ACS fellowship. Then a year later you became an instructor?

CRAM: Yes. I was appointed on a regular basis as an instructor. Then the next year I became an assistant professor, and then I guess at the end of my fifth year here, I was promoted to associate professor.

GORTLER: Could you characterize the department when you arrived?

CRAM: Yes. We were ill-housed.

GORTLER: Where were you then?

CRAM: We were off in another building, Haynes Hall. We were in places that were fire hazards, with no ventilation to amount to anything. Sometimes we'd do reactions out on the porch when the wind was blowing, and we had benzene fires and we had all sorts of things that happened. But nobody really got hurt, interestingly.

There were something in the neighborhood, if I remember correctly, of fourteen staff in the chemistry department then. And there were Tom Jacobs, Ted Geisman, Robby Robinson, Saul Winstein, and Bill Young as organic chemists, plus myself, plus a temporary person.

This grew, though. The organic group didn't grow all that much, but the chemistry department currently is around forty to forty-four staff members.

The number of graduate students was something like thirty-two or thirty-three. And there hadn't probably been more than ten or fifteen Ph.D.'s granted by the time I came here.

GORTLER: Yes, the first one was granted in 1942.

CRAM: Something of the sort. So 1947 is only five years later, so there couldn't have been very many.

GORTLER: Yes, right.

CRAM: It was a pretty small number. And of course I've been here thirty-three years, and so I've watched this place grow—I've had almost a hundred Ph.D.'s myself, and Winstein had something like seventy-five or eighty before he died. He died at the age of fifty-seven. He was seven years older than I am.

He was not one to do very much administering, and as time went on, I became head of the organic group, more or less. He and I would confer about things, and then we'd confer with everybody else, and then we'd act, and we sort of had a minimum of commotion and got quite a bit done. I did a lot of hiring and firing and recruiting and what-not.

GORTLER: This was in the organic group.

CRAM: Yes, and then I became space czar for the department, and in charge of the curriculum committee and stuff like that. I've avoided being chairman of the department. I've been asked to be chairman twice, but I have avoided it by doing this organic stuff steadily.

GORTLER: When did you move out of the Haynes Building?

CRAM: I guess 1951. I think it was 1952.

GORTLER: All right. You came to this building.

CRAM: We came to this building, and then a new wing went on this building about 1961, something like that. We're in the new wing, so-called new wing. It's twenty years old now.

This is the kind of place where power has never been centralized, and everything gets done because somebody has individual initiative and gets other people to join them. Pretty soon they develop a consensus, and pretty soon you can persuade enough people so that you can move something. That's the way it's been run historically. If you want to change the curriculum, that's the way you do it. If you want to change something, that's the way you do it. Nobody mandates a change.

GORTLER: There was never a problem with—well, interaction between the physical organikers and non-physical organikers?

CRAM: No, that was our great strength, as a matter of fact. The place had been small, very small, historically. It had a very short history, and all the people knew each other and liked each other, got along well and supported each other, and there were not very clean lines of separation between fields. The physical and organic chemists and analytical and biological chemists, biochemists, all were housed close to one another and were all mixed up all over the building. They weren't even segregated.

GORTLER: I see.

CRAM: So we had friends across lines, and cooperative projects, and all sorts of things, so we became more compartmentalized as time went on. But still, there is that feeling. And we've been blessed, I think, historically, by the department never becoming factionalized in a personal sense. Also, we've been blessed with very, very few people who have just been troublesome and nothing else. Almost everybody has been constructive over the years. I'm just amazed at how constructively this place has been run. And how little commotion, wasted motion, there has been over petty things. Or jealousy. Jealousy played a very small part in this operation.

GORTLER: That's good, because you had a lot of very high powered people here.

CRAM: We've been blessed with real men. No pettiness.

GORTLER: Since you started your training in the late 1930s and sort of entered academia officially in the late 1940s, were you aware of a transition taking place in organic chemistry?

CRAM: Oh, very much so. Woodward and Bartlett's work epitomized this to me. And then when I got out here, Winstein's work. In several different ways. First, instrumentation was starting to take hold. UV came in first, then IR. IR came in the early 1940s. And it was pretty obvious that—well, the structure of penicillin was an example. I recall that there had been no beta-lactam isolated in natural products at that time, and there was great instability. This question of the lactone versus the beta-lactam structures. And remember this was a Woodward-Robinson controversy; an English-American controversy over the structure of penicillin.

Well, I think it was settled more than anything else by the infrared stretching frequency of the carbonyl of the four-membered ring. Later, of course, by X-ray structure determination. But, well, that was a dramatic thing to me, that you could settle the structure of a compound by physical methods. I had occasion at Merck to use UV and IR, in fact. I ran into a new strain of bug and a different kind of side chain in the penicillin. The bug mutated, and I couldn't isolate what I'd been formerly able to—it went from benzyl to pentyl penicillin, as the broth had been changed. I got at this through some detective work, and it involved instrumentation. So instrumentation obviously was going to be a big thing. And I was very early impressed by X-rays, the importance of X-rays in structure work, and I knew that was a big thing. In fact, I remember when I started consulting at Upjohn. They had a conference on what's going to be in the future, and I said, "Lots of instruments, including X-ray machines for structure determination, and probably a lot of other forms of spectroscopy." And that's one of the few predictions I've made that was really right.

GORTLER: How about approach to organic in general? Obviously, you saw the distinction between Bartlett, Woodward, and then Fieser on the other hand, and this was clear to you.

CRAM: Yes, this was clear to me. There was a clear discontinuity between before the war and after the war, as far as I'm concerned, looking back on what I've learned since about that time in both Britain and the United States. I'm particularly thinking of the way people were trained. Physical organic research was being done in the 1930s and 1940s, but it wasn't in the textbooks in the 1930s and 1940s. When things get into the textbooks, they get wide currency. So the people that came in, maybe in the middle 1940s, had the benefit of a whole lot of refinement that had been going on in the minds of the people that were doing the work in the 1930s and 1940s.

GORTLER: Hammett's book was published in 1940, but then the war came along.

CRAM: It had a lot of influence, but in a relatively narrow sphere. And, it was very numerically oriented. It was non-structurally oriented. Hammett was non-structurally oriented.

GORTLER: He was a physical chemist.

CRAM: He was a physical chemist and applied physical chemistry principles to organic compounds. And, of course, the center of his work was Bronsted's work. So that came directly out of physical chemistry: the concept of linear free energy relationships.

Of course, even the idea of a carbonium ion or carbanion, as an intermediate, or a radical as an intermediate, for a while was taboo because of the early history of writing radicals and writing ions all over the place, which had been done profligately. There was a reaction against it, and the reaction took a while to shake loose. Radicals, interestingly, became popular again earlier than did carbonium ions and carbanions, in organic chemistry, as intermediates.

[END OF TAPE, SIDE 3]

CRAM: The concept of radicals having earlier currency, then discarded, and then rebirth. And all of this happening before carbonium ions and carbanions really had very much currency.

GORTLER: Of course, Lapworth had some sort of carbanions written in 1900 or thereabouts and, if you look at the structures, they look somewhat modern. They didn't know much about electronic structure then.

CRAM: Yes. I never got into that literature. I went back to about 1910, and I ran into some [A.] Lapworth stuff in 1910, particularly on the base-catalyzed elimination reaction, and I was surprised at its sophistication. I remember that distinctly. I haven't looked at that since.

GORTLER: I'm referring to the bromination of ketones and things of that sort, way back in 1900. He even did some kinetics. Then, Bartlett picked up some of that in the 1930s.

CRAM: Well, he had some 1,2-diphenyl systems of some sort, where he followed the stereochemistry of elimination.

GORTLER: That was the 1910 work you're talking about?

CRAM: Yes, it was very early. And found that he got nice clean trans-elimination, although I don't think he knew all the configurations. But, it was all there. If you know the configurations, it was all there.

GORTLER: I think there was a fair amount of work being done in the early 1900s but people didn't understand it completely, and there were only a few people here and there. It wasn't until people started to accept the [G. N.] Lewis structures that things could begin to take off.

CRAM: Yes. That was the key.

GORTLER: For some reason, the English seemed to accept the Lewis ideas a little bit earlier than the Americans did.

CRAM: They had a bigger operation. Of course, they were not as geographically diluted.

GORTLER: Yes. There wasn't all that much chemistry going on in the United States before World War I.

CRAM: No, there wasn't. In fact, we didn't really get going until after World War II. We didn't become competitive until after World War II. By "competitive," I mean I don't think we were doing as well as the English and Germans.

GORTLER: I wonder—Tom Jacobs suggested that there was a hiatus during the war. I'm not sure that physical organic chemistry didn't get a real boost during the war because a lot of people came together and were beginning to think in those terms. That was certainly true at Harvard from about 1941 to 1945, a lot of the people you mentioned, Gardner Swain, George Hammond, Henry Kuivila, Harold Kwart and Sid Ross were there.

These people were all just there talking about chemistry and they were anxious to do it, too. They were also approaching the wartime problems as physical organic chemists, as opposed to just churning it out to make it useful.

CRAM: Harvard was—well, there were these people there, and they were obviously worrying about problems during that period, but I suspect that their inability to work on these problems didn't help. They were thinking about it more than working on it. They were doing applied research.

GORTLER: Well, I talked to Sid Ross this summer, and he said that they'd be sitting around and they'd worry about some problem, and they figured the only way to solve it was to go into a laboratory. A whole bunch of papers came out that had nothing to do with the war time work.

Because I think they were like you: they were eager to get work done, and they solved the problem by just going in and trying to do it in the laboratory. So, I think the war in some sense may have been an advantage for these people.

CRAM: Well, there's one thing about stopping and starting. When you start afresh, you ask what is the important thing to do, rather than doing what you did yesterday. I think it was important in that sense. Also, it was a period, of course, where people left jobs and new people came into jobs. There was an infusion of youth, and of course, right after the war there was a tremendous mixing of foreign and American chemists, greater than there had ever been before. I think this was a tremendous stimulant. People were coming over from Europe and people were going from here to Europe and then coming back. This undoubtedly gave rise to the sense of excitement people had in the late 1940s and early 1950s.

GORTLER: Who do you have in mind who was doing this kind of thing? I know Ingold came in the late 1940s. Were you talking about other people?

CRAM: Well, Fieser followed the troops, went around and visited all the labs, then came back and told us all about various people he'd encountered, including Hans Meerwein who at the time was probably sixty-five or so. And Butenandt. I forget all who he saw. Who's the chemist who was a pretty big Nazi in Heidelberg?

GORTLER: [Walter] Reppe?

CRAM: No. Reppe. I know Reppe quite well. I remember the stories about Reppe at that time. The fellow who was at the Institute in Heidelberg. He died. I think he made the multiple allene compounds. I believe his name was R. Kuhn. When I was at Harvard, I remember a number of foreigners coming through giving seminars. I'd be a little hard put to say who they were.

GORTLER: So it wasn't just the students?

CRAM: It wasn't just the students, no. No, this was my second year, and that was right after the war.

GORTLER: Okay, so there was a greater interaction that was taking place that hadn't taken place before.

CRAM: And, of course, there was the War Time Corps. Actually the War Time Corps' cooperation on the penicillin project with the British I think had quite an effect on American chemistry. The best were competing with the best in each country on the structure and synthesis of it. That was a tremendous effort, in some ways unparalleled, historically. And of course, the effort on the steroids had been an international effort prior to that time. All the vitamin and co-enzyme co-factors that came through in the 1930s were objects for international competition. I'm sure that there was an accumulative effect of what industry was doing in the United States. See, I think that the American chemical industry—Merck was quite a place, and Squibb was quite a place in those days. They may have been the two best places for natural products and for elucidating structures and total synthesis in the States. A lot of people in effect graduated from those two places. It was like a university in some ways. They went to other industries.

So the educational operation was going on, both, I think, in the universities and in industry. American industry was building up. This is true in the polymer industry too, of course. The fact is that the U.S. had an industry a-building, whereas there wasn't any in Japan and Germany; England had to sort of regroup; France was still staggering under the loss of manpower in World War I, and Russia was in a mess. So it was obvious where the action was going to have to be for the first while. There was a tendency for the whole world in some ways to concentrate its resources on the United States and invest in it, in a sense, sending post-docs. There was a flood of foreign post-docs that came through here in the early 1950s. The fact is we were fortunate enough to have a lot of people who occupied chairs come through here and spend summers with us.

GORTLER: That makes a lot of sense. What about money at that particular time? Suddenly money was becoming available from the government?

CRAM: Well, not very much until Sputnik. Some. Mainly from the armed forces. The Navy first, and then the Army, and the AEC [Atomic Energy Commission] in certain fields.

GORTLER: If you used an isotope it would work.

CRAM: Yes. I never had any problems with money. The storeroom was open to everybody, and we didn't keep track of who paid for what until later on. The students were all on TAs. There weren't any such things as RAs—research assistantships—and I got a little bit of money from Upjohn, as I recall.

GORTLER: When did you start to consult?

CRAM: I started consulting there in 1952. I've consulted about ten days a year ever since. I've spent about a year there in twenty-eight years. That's been good because it's kept me knowledgeable in a lot of fields I wouldn't have otherwise known much about. I've also consulted at Union Carbide since 1962. That's been good for me because I've learned a lot about polymer work, and again it's not in my field of expertise. I really think it's better to consult where you're not expert and where you're non-competitive.

GORTLER: You probably have a more open mind.

CRAM: More than that. There isn't any conflict of interest either.

GORTLER: Yes.

CRAM: Actually, I think those consultancies played quite an important role in the development of American science. I think that's been a very positive thing in American education, because it left the professors a hell of a lot better educated. I'm not sure how much it did for industry, but I think it did a lot for academia.

GORTLER: Someone told me recently, the industrial outfits were doing less and less of this, and they tried to convince them that this was a big mistake.

CRAM: Yes, I think they're doing less of it now. The pharmaceutical houses are not cutting back; they're doing a lot of it still. The oil companies and what-not are doing less.

GORTLER: The oil companies are not even hiring organic chemists these days. I have a friend at ESSO who said there isn't an organic chemist around, even though I think Brown is still consulting.

What would you say about the future of organic chemistry today? Where is it going? What are the big problems going to be?

CRAM: Well, in the present, right now, in organic chemistry as always, there's a center, and the center is synthesis. Then, there are blends of the center with the periphery.

There are all sorts of things on the periphery, which are perhaps in many ways, at least temporarily, more important than the center. One is bio-organic or biotic chemistry. And we're working in this field of what we call host-guest chemistry (10, 11).

GORTLER: I'm not familiar with your host-guest work.

CRAM: We started it about ten years ago. We've been synthesizing compounds designed to do some of the kinds of things that biological systems do. We've been studying complexation, both of transition states—that's catalysis—and of ground states—which is equilibrium—and trying to make a science out of complexation. We've published maybe fifty papers on it so far. It's my total effort now, and it's quite broad. We're trying to assemble, for example, the same kinds of functional groups in the same arrangements as you find in chymotrypsin, to catalyze trans-acylation. We've made chiral-catalysts that will catalyze Michael additions, and get up to 99 percent enantiomeric excess in some cases. We've made compounds that will sort out the enantiomers of amino acids by extraction, by designed synthesis, looking at CPK molecular models beforehand. We have X-ray structures on maybe thirty, thirty-five complexes. So we're getting some feeling for the—see, complexation plays a central role in biochemistry, in regulatory systems, in information storage and retrieval, in genetic systems, and of course in enzymes. So we're trying to do something synthetically with this same thing, starting with just synthesis, not using natural products at all, except as guests. Hosts we define as having “convergent binding sites,” and guests as “divergent binding sites” for complexing partners. And we are dealing with binding energies that range from five to, I guess the highest we've encountered is something like 28 kilocalories per mole. We've designed a host that binds lithium ion by about 28 kilocalories, and a whole lot of stuff like that.

This is one area that I think is going to be a big thing in the future, simply because—well, for a number of reasons. One is that the biotic world is such a wonderful world; it shows what can be done. And there's no reason why the organic chemist can't have a piece of this with completely synthetic systems. That's one direction. Another direction it's going in, of course, is toward the other elements in the periodic table. And that's going to go on for a long time, probably as long as there are chemists doing research.

Separation science is going to get a big play, using very highly designed complexes to separate things, both inorganic and organic, in my opinion. Another thing I think that's going to get a big play is, I think, the making of compounds in the molecular weight range of, maybe, 1500 to 3000. This type of complexation will do remarkable things with regard to being able, for example, to carry reactions out in water as solvent, but in effect carry them out in the center of a hole that's dissolved in water. In other words, phase transfer chemistry of one type or another. This is important simply because water is much easier to dispose of than an organic medium, and it's cheaper.

Also, the compounds in this molecular weight region that have designed and specific structures just haven't been studied very much. Getting the effects of cooperativity of various functions—catalysis, stereospecificity, what not—all of this is going to get a big play, I think. And it's very challenging.

I think natural product chemistry, the waste product side of it, such as alkaloids and terpenes, are going to run out of gas pretty soon. In fact, I think they've run out of gas already.

New reagents, new reactions will go on probably as long as there are organic chemists. Physical organic chemistry, I think, is wearing thinner and it's getting very, very highly refined now, and it really, I think, has had its period from the point of view of affecting the other branches of organic chemistry the most. In other words, I think it's had its rosiest days. There are still some very nice things to be done in it that will be done, I'm sure. But it won't be central to a whole lot of other things the way it was during this renaissance, or whatever you want to call it, in the 1930s, 1940s, and 1950s.

GORTLER: Now, what we considered physical organic chemistry essentially has been integrated.

CRAM: That's right, integrated into the body of organic, and it's no longer thought of as physical organic.

The synthetic people have been so remarkably successful that they're running out of challenges. That's why I say that probably they're going to get into the design business a lot more, and they're going to be making highly sophisticated systems of much higher molecular weight to do things, rather than just to show that you can put an elegant structure together that resembles something nature did, or something of this sort. You get the idea?

GORTLER: Yes.

CRAM: I figure that's going to get quite a big play. It's sort of interesting to me that finally the classical synthetic organic chemist is now sort of re-discovering stereospecificity. In other words, it's a problem that hasn't been solved by the organic chemist. The organic chemist doesn't know how to catalyze specificity and doesn't know how to regulate it. He does in a few cases, and there have been some elegant examples. But things like Johnson's wrap-up of the steroids, for example—beautiful thing. That's an example of how you can work very hard for a long time and get a very high-class result of stereospecificity and wrap-up and multi-chiral center operation. And of course, things like Woodward's synthesis of reserpine—that was a very highly stereospecific type synthesis, as I recall. Beautiful thing. But as far as making chiral centers, making optically active compounds, with chiral catalysts or chiral reagents, that's a relatively untapped field. You are going to see a lot of that. It's just starting up now.

GORTLER: What about the use of natural materials in a more sophisticated way than we've done before? That is, for example, using enzyme systems?

CRAM: They're being used as starting materials now. A lot of things that were looked upon as end products in the old days are now looked upon as starting materials, where you start with a sugar because you want some chiral centers. You start with amino acid because you want some chiral centers, and you don't want to do resolutions.

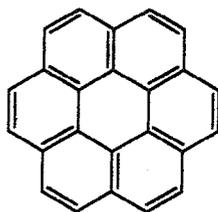
We have taken the other tack. We've stayed away from natural systems and natural chirality, and have tried to work with what we thought was ideal rather than what we thought was available. We worked with chiral-binaphthyl, for example or chiral-paracyclophanyl. Or things of this sort, units that we've designed and made, you see, that are very unnatural. But this kind of organic chemistry is going to have a big play, I'm sure, partly because there's a lot of organic chemists doing a lot of research, and they want to do something new, and they're running out of some of the old things that have already been done. So they're going to be looking for new fields. This is one of the new fields that's almost limitless. Let's just ask the simple question: how many compounds have been made that have holes in them big enough to accommodate other molecules or ions, and the holes are enforced? In other words, the holes exist when there isn't something in them.

Well, the answer is—there weren't any up to very recently. And there are some naturally occurring holes. There are the lipophilic pockets in the proteases. There are the cyclodextrins. They're naturally occurring. They're made by bacteria. But the crowns fold up on themselves, and fill up their own cavities. The cryptands do the same thing. You look at the X-ray structures of those hosts—they don't have any holes in them. They have holes that become holes when guests depart their complexes. The occupants organize them. You get the idea?

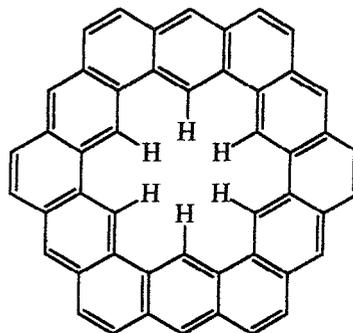
GORTLER: Yes.

CRAM: How about pre-organization? Well, we are addressing this problem intensively. And we've got several pre-organized systems. Now, you have to deal with very rigid groups. These are composed of aryl rings. Kekulene is an example of a compound with a hole in it. You know kekulene? Staab made kekulene. Kekulene is a hydrocarbon made out of benzene rings arranged in a circle. It's like coronene only it's the outer ring. Coronene is composed of fused arranged benzene rings in a circle. Well, if you go one more big ring out further, you've got kekulene.

There's a hole in the middle, and the hole is defined by six inward-looking hydrogens. It's just that much bigger. It melts at something like 600°, 550°, or something like that. Well, we've got some holes, holes that will accommodate sodium, holes that will accommodate lithium, holes that will accommodate cyclohexene, and some holes that are bigger than that.



Coronene



Kekulene

GORTLER: What about porphyrin systems? They normally just accommodate the metals you're talking about.

CRAM: Well, actually porphyrins don't exist unless there's magnesium or cobalt or hydrogen in the hole.

GORTLER: You can't yank that out and just leave the hole?

CRAM: That's right.

GORTLER: I see.

CRAM: In other words, the holes are made by, in a sense, magnesium getting in there, or cobalt getting in there, or made by displacing hydrogen atoms that were there before. Do you understand?

GORTLER: Yes.

CRAM: And you can go through the literature looking for holes and you don't find them. But they're now being invented. [C. David] Gutsche just got his hands on some of the 8-calixarenes that obviously have holes in them (12). There are crystallographic holes, but that's a different matter. That's an intermolecular matter. You get the idea?

GORTLER: Yes.

CRAM: So we're addressing this business of making holes. It's fun. It's never been done. And you run into some very interesting things. Holes don't like to exist. It's quite troublesome to make these things.

GORTLER: Nature abhors a vacuum.

CRAM: Exactly. Well, some Van der Waal's attractive forces are better than none. That's what it comes down to. Even if they have to be intramolecular. Molecules will fold on themselves if they have a chance, because there's something to be gained by it. Do you get the idea?

GORTLER: Yes.

CRAM: Well, here's a field that nobody has fussed with or recognized as an interesting field and phenomenon in its own right until very recently, and I think we're either the first or among the first to do this because there's a lot of profit to be gained by this. A lot of interesting things, hanging functional groups around the periphery of these holes. You can get cooperativity, and you can get separation of charge and concentration of charge gradients that you can make use of in catalysis. All sorts of interesting things.

Now, in inorganic chemistry, the zeolites have holes in them, and of course, zeolites do wonderful things.

GORTLER: That sounds absolutely fascinating.

CRAM: So that's a lot of fun. And we use CPK molecular models as our guide in this work. These are based on x-ray of naturally occurring compounds. Oh, here's [pointing to model] an example of a compound with a hole in it that we've made. It's got six benzene rings attached to one another. This will accommodate sodium or lithium—here, for example, is something of the diameter of sodium. And it holds onto it, this binds—

GORTLER: You have methoxy groups on the other side?

CRAM: Yes, these are two methoxys, and these are two ethylene bridges. You can't turn a methylene inward because the hole is too small to accommodate a methylene, and it's rigid. It can't fold—

GORTLER: So this is like a tunnel.

CRAM: See, this is a hole, lined with electron pairs. That's why it holds onto the metal so well. This holds onto sodium ion with about 23 kilocalories per mole in chloroform.

GORTLER: Now I understand why the binding is so strong.

CRAM: Here's an example of a transition state molecular model, with two binaphthyls, where you have a chiral environment in which you're carrying out an addition of an alkyllithium to a carbonyl. The alkyllithium is complexed by these two amino groups, and you can get something like 95 percent enantiomeric excess when adding butyllithium to benzaldehyde in the presence of this diamine.

This is the kind of research we're doing. Here's another hole that's designed [pointing to another model]. This is what we call a cryptospherand: two nitrogens, inward looking oxygens. These are the kinds of things that we play with all the time. Here's our chymotrypsin model [showing model]. We've made about half of this. Here is a peptide; here is a binding site; here's a carboxyl of aspartic acid; here's an imidazole. Here's the serine hydroxyl equivalent, and here's the proton relay system. Here's the nucleophile right next to the carbonyl group of an amide. This is a designed system. This is the urea unit; it's hydrogen bonded here and here, to an ammonium ion. Here's a pyridine that provides another binding site. And this is all rigid. It's all pre-organized.

GORTLER: I see you put the benzene rings around it just to hold everything in place.

CRAM: Yes. They're all placed in this rigid structure. See, there are very few degrees of conformational freedom in this molecule. We've synthesized this up to here. All this is made and we know that this complexation occurs. All the background work is done. Now we're trying to put catalyzing groups in place.

This is some of the research that's going on. Here's a hole. We haven't made that, but we think we can make it very easily.

[END OF TAPE, SIDE 4]

CRAM: In the old days you couldn't publish an idea without publishing an experiment to go

with it. In other words, it wasn't honorable for an organic chemist to publish a fairly theoretical paper. And it took people like Roald Hoffmann and Michael Dewar and Jack Roberts to break this down. What they did was to write a whole lot of structures that they calculated energies for, and as a result of this, this stimulated a large number of chemists to make compounds that they would never have thought of making before. In other words, the people who can see interest in a given problem aren't always the ones that are able to synthesize the compounds. And if it was taboo to pass that information around in journals—there was sort of a blockage of science by an artificial taboo.

Well, I watched that dissolve. That was a good thing to get rid of. I think probably that's one reason why U.S. science has prospered. It got rid of that taboo much faster than journals in other countries.

GORTLER: Yes.

CRAM: And then of course that opened the idea for other kinds of ideas, not only based on theory, but based more on intuition, or less rational grounds, to get stuff into the literature. I remember publishing my first paper without any kind of experiment at all; it was on the mapping of stereochemical reaction cycles (13). This was a long paper. I was just astonished that here I could make something out of nothing and publish it in the *JACS*. Well, this was some kind of a breakthrough in American education.

GORTLER: There were a lot of thought processes devoted to this. It's a time-consuming process just to formulate all this.

CRAM: The historical outcome of this was that, you see, everybody isn't equally endowed as to thinking about given subjects, nor are they experimentally endowed in effecting a synthesis or carrying out an experiment. Man does a lot better by implementing each other's talents, by complementing each other. [Linus] Pauling would never have amounted to a row of pins if he hadn't gathered around himself some very critical people to check on his wildness. He was a guy just absolutely chock full of new, interesting and wild notions, and he was smart enough to know that some of these were wild. So he got some very clever people, both good experimentalists and good theoreticians, around him to criticize what he did, and as a result of this, why, he did some remarkable things before he was fifty. And, in fact, he had a very profound effect on organic chemistry, among other things. That was complementarity.

Well, if you can do it on a national or even an international basis, you can do it, in effect, by the people who dream getting their dreams in the literature, and the people who act—following up the dreams with actions. The dreams and the action do not have to come from the same person or even the same country.

GORTLER: Yes.

CRAM: So there's vastly more stimulation around. Some people made a profession of feeding on theoreticians' notions. That's been one of the themes, particularly the synthesis of hydrocarbons, particularly strained hydrocarbons or oddly-shaped hydrocarbons, or unusually degenerate hydrocarbons. Bullvalene is an example.

GORTLER: I was just going over one of Jack Roberts' papers, and the thing that he did with Streitwieser in about 1952 or so, where they did this whole series of calculations (14).

CRAM: Yes, that's an example. That was a sort of breakthrough paper. Not so much that it was really beautiful hot stuff. It was very nice stuff. But what it did was to open that door.

GORTLER: Yes. I think some organic chemists had used quantum mechanics before that.

CRAM: But they hadn't published something in a journal that demonstrated that it was possible to publish these kinds of notions in a journal. Then the synthetic organic chemist jumps on it and starts making some of these things.

GORTLER: Yes. What were you going to say about transition state theory?

CRAM: The organic chemist really couldn't think clearly, in my view, about organic reaction mechanisms until the transition state theory was incorporated in the body of knowledge. Now, I haven't combed and looked through Ingold's stuff with the express purpose of asking myself the question: did he really use and understand transition state theory? But I got the impression from reading his papers that he used it less than he should have, and he used it less than the Americans did. He worried about it in the  $S_N2$  and E2 reactions. But once beyond that, he didn't give it much thought. He may have in aromatic substitutions. I haven't looked those papers over carefully, and I haven't looked at them as a historian would want to look at them, because a historian wants to be accurate. Somebody talking the way I'm talking doesn't necessarily have to be; he just has impressions.

GORTLER: Yes.

CRAM: But that was one of Saul's strengths. I think that he had a good command of the ideas

involved in transition state theory, and he was interested in both coordinates, both the reaction coordinate and the energy coordinate. It was the putting of these two together that I think involved a great deal of genius.

What's sort of interesting is that the stereochemical probe helped you on the reaction coordinate a great deal, and of course, kinetics helped you on the energy coordinate a great deal, that and equilibria of various kinds, and thermal burning of compounds and all the rest. But it was the merging of the concept of structure and the concept of rate in transition state theory that really provided a very powerful way of thinking for the organic chemist to put together reaction mechanisms.

Now, what's sort of interesting to me is that, as far as I can see, the Woodward-Hoffmann rules, in the early phases, essentially ignored transition state theory. Later on they deal with it more—Hoffmann does—but not in the early stuff. They worried more about the overall pathway of what orbitals hooked up with what other orbitals, not where the maxima and minima were on the reaction coordinate. It was more of the kineticist and the stereochemist who worried about that.

Now, as the applications of Woodward-Hoffmann notions fell into the hands of the physical organic chemists, transition state theory got applied to it much more. But initially the Woodward-Hoffmann rules and orbital symmetry considerations were really of a lot more use to the synthetic organic chemists than they were, really, to the physical organic chemist. They strengthened the hand of the synthetic organic chemist because they gave him a degree of predictability and design.

GORTLER: Yes. I think that Woodward was probably worried more about the synthetic consequences. I remember his discussing some of the inconsistencies in the Diels-Alder reaction, in the late 1950s, in one of his seminars. He had a hard time explaining these inconsistencies. It wasn't until a few years later that Hoffmann came to work with him.

CRAM: Now, if you read Woodward—both Woodward and Dewar published some of the most asinine papers in the late 1950s, as I recall, having to do with the Diels-Alder reaction. If you read those, they are essentially uninformative. You can't tell what they're saying. But what was obvious was that these papers were the thought processes they were going through. They were asking questions and trying to arrive at orbital symmetry theory in publishing those stupid papers. And they were stupid. It was later that things started to get more orderly.

GORTLER: Woodward was very worried about these Diels-Alder reactions, the way these molecules were coming together. He was concerned about step-wise-ness, and why they always worked in a particular fashion.

CRAM: Those two guys were like Gilbert and Sullivan.

GORTLER: Woodward and Hoffmann?

CRAM: Sure. One without the other couldn't have done a damn thing.

GORTLER: That's right. That's absolutely true. Woodward knew the problem was there.

CRAM: Yes, and he was phenomenologically oriented, and Hoffmann was mathematically and theoretically oriented. So he could understand the mathematical language to handle it.

GORTLER: Sure. He came along just at the right time to solve that aspect of the problem. Woodward could not have done it.

CRAM: Now, I think the tremendous advantage that my generation had that the earlier generation didn't was that we did have transition state theory to hang our hats on. We got it when we were educated. Therefore, it became second nature to think in terms of the difference between an intermediate and a transition state, and how long-lived was it, and how much higher was it in energy, and what was its structure, and all the interesting and right questions. And how do you get at these questions?

Now, this was what to me was the revolution. That and advances in instrumentation that occurred over the period of my lifetime. Instrumentation and the windows that were opened on structure and on mechanism, by the instruments.

NMR revolutionized stereochemistry because it brought a whole domain of stereochemistry into play that had been not on the human time scale. It gave humans another time scale to work with. In fact, there's a great deal of confusion in the field of stereochemistry with regard to terminology that grew out of this conflict between the human time scale and the NMR time scale.

GORTLER: Which is using the same terms.

CRAM: Yes, and confusing them because a lot of the terms are operational, and if something racemizes on the human time scale, or an inversion occurs on the human time scale, it's a different time scale than on the NMR scale. A lot of the terms were transferred back and forth, and pretty soon people don't know what they're talking about. The question is, are you talking

about absolute zero, or are you talking about 120° absolute? A lot of complications. But a lot of interesting complications. This type of thing. We could talk about that for quite a while. I'm just opening up these subjects so as to alert you to notions that other people might be interested in talking about, too.

GORTLER: Let me digest what you've told me already and I may come back.

CRAM: I'm sorry. It's been a little unstructured and a little random.

GORTLER: I think it's better this way.

CRAM: Well, first go-round.

GORTLER: We managed to get a lot of the questions answered. Thank you very much. I really appreciate it.

[END OF TAPE, SIDE 5]

[END OF INTERVIEW]

## NOTES

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