



Seventy-three years riding heterocycles

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Received: 12 March 2024 / Accepted: 16 April 2024
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Abstract

The Chemical Intelligencer, 1997, 3, 61–64.

IH: When you returned to Spain, you were 45.

Did you build up a new lab and a new research group then?

JE: It was difficult because the financial resources were not in place. There were no positions, no fellowships, no instrumentation. I tried to survive by building up an extensive system of cooperation with different places in Spain, in France, and in other countries.

I tried to do inexpensive but interesting chemistry. This is one of the reasons why I developed a project on the solid-state properties of heteroaromatic compounds.

They are stable, cheap, and friendly, are easy to prepare, and are crystalline, not volatile.

Keywords Madrid · Montpellier · Jacquier · Cyclopropanones · Katritzky · NMR · Limbach · Ernst · Alkorta

I entered the University of Madrid when I was 16 years old; I am now 89 years old. That's 73 years learning and doing chemistry. Good and bad things happened, none tragic but some unpleasant and some other rather pleasant.

One of the rare advantages of advanced age is that one has many points to generate a robust surface using, for instance, the magical spline interpolation method that works so well unless you have outsiders (this is not the case in my research). Thinking about my about 2000 publications, I remember the classical question about “Bad news or good news first?” I always preferred bad first and I was thinking that attitude was peculiar to me and others close to me, but, and this is one reason that statistics are important in social sciences, most recipients of good and bad news prefer to hear the bad news first.

A life in sciences results in a sort of two-dimensional mosaic, with parts complete, parts just started and some islands far away from the core (Fig. 1). My mosaic began with my PhD thesis that I defended in 1961 under the direction of Professor Robert Jacquier (Fig. 2; Montpellier

University, France): it was centered on the chemistry of pyrazoles.

A little tale

It was the year 1958. I had been working for a few weeks in Jacquier's Laboratory at the Ecole Nationale Supérieure de Chimie, ENSCM, in Montpellier when Max Mousseron, the head of the school, organized a Franco-Belgian colloquium, which I attended sitting discreetly at the back of the amphitheater. His Belgian counterpart was Richard Henri Martin of the Free University of Brussels (1914–1995), one of the great chemists of those times, universally known for his work on helicenes.

In one of the communications, Jacquier presented his synthesis of bicyclo[4.1.0] heptan-7-one or 7-norcaranone (Fig. 3) that he had published in 1956 with Jacquier and Fraisse [1] and Mousseron et al. [2]. It was a notable success because no one had been able to prepare it before, being a bicyclic cyclopropanone. In the 1956 publication, only its physical constants, its ultraviolet spectrum, and a crystalline derivative, 2,4-dinitrophenylhydrazone (DNFH), were given, the usual way at that time, pre-NMR (the first NMR spectrometer, a Varian V-4311 working at 56.4 MHz for

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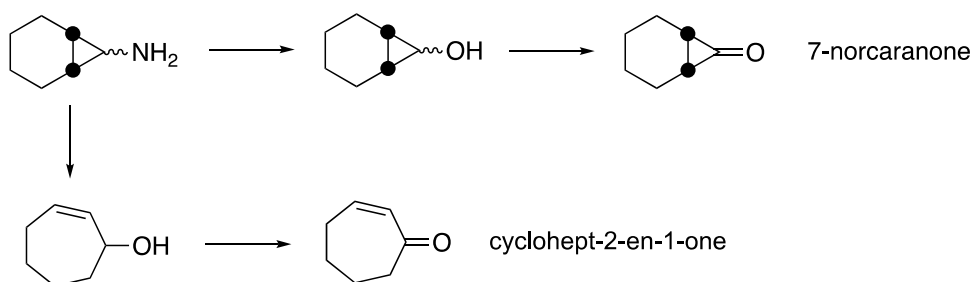
Fig. 1 An incomplete Roman mosaic



Fig. 2 Robert Jacquier



Fig. 3 Cyclohept-2-en-1-one vs. 7-norcaranone



^{19}F and 60 MHz for ^1H arrived at Montpellier in 1961) and pre-mass spectrometry, to characterize a liquid compound.

But at the 1958 mini-congress, Jacquier gave the supplementary information of its infrared spectrum: carbonyl band at 1730 cm^{-1} (I don't remember the exact figure but it must have been something like that). Martin raised his hand and said, "if the carbonyl appears at 1730 cm^{-1} it can't be the structure you propose; the carbonyl of 7-norcaranone must come out around 1900 cm^{-1} ."

Silence in the room. No one questions Martin's argument. They have made a fool of themselves. The congress continues in melancholy. The consequences were dramatic. Jacquier gave an excellent infrared course the following year that I still have. There, the effect of angular tension on the elongation vibration of the carbonyl is explained.

In 2009, with Ibon Alkorta and Fernando Blanco, we published a theoretical paper where the reactions and properties of the structures of the above scheme were explored including the still unknown 7-norcaranone and the known cycloheptenone, the compound they isolated [3].

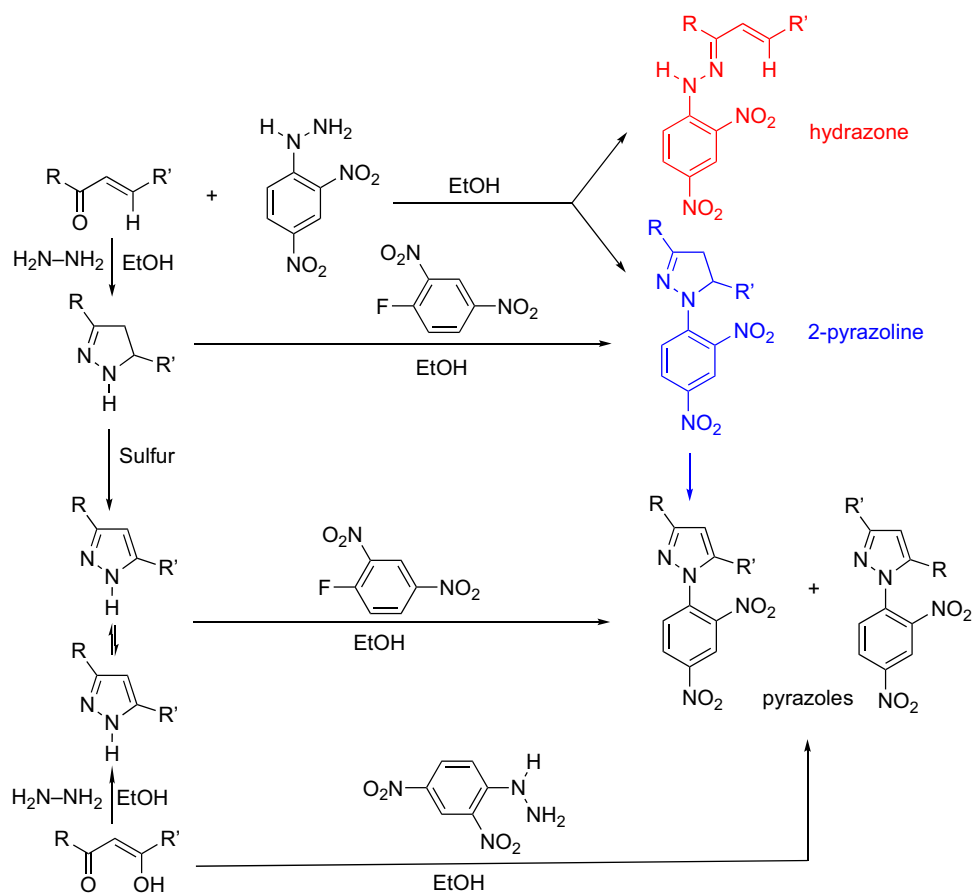
The connection between 1-pyrazolines and cyclopropanes and the characterization of carbonyl compounds using 2,4-dinitrophenylhydrazine (DNPH) led Jacquier to abandon the cyclopropanones and move to answer the

question of the results of the reaction of DNPH with α, β -unsaturated carbonyl compounds: 2,4-dinitrophenylhydrazones or 1-(2,4-dinitrophenyl)-2-pyrazolines? The answer would be easy to get with any spectroscopic method but at that time, we used *pure classical heterocyclic chemistry!* And since the 2-pyrazolines are easily oxidized to pyrazoles, I entered a field that I haven't left since then (Fig. 4).

A sentence by Leon Ghosez from an autobiography published in 2019: "At that time Jacquier was widely recognized for his work in heterocyclic chemistry. Both he and his close coworker Elguero contributed a lot to our understanding of the behavior of heterocyclic compounds. Their work was a harmonious blend of synthetic and physical organic chemistry. Elguero left France when democracy was re-established in Spain and became a major player in the development of chemical research in Spain since 1978. I had the privilege to be a friend of both Robert and José" [4].

In November 2009 on the occasion of an obituary meeting in memoriam of my mentor, held in the ENSCM, I spoke on "Robert Jacquier et la renaissance de la chimie hétérocyclique en France"; other lectures were given by Prof. Seebach and Ghosez.

Fig. 4 The 2,4-dinitrophenyl derivatives



Bad things

Of both bad and good memories, one has to consider pure academic matters and more personal things. Let's start with academic matters. One of the things that has always worried me is why some publications were never cited (or cited one or two times). I think it is the same as not having been published. All bibliometric studies indicate that if a paper is not cited in the five years after its appearance, it will never be cited (there are some rare exceptions (Sleeping Beauty papers)). The journal is usually blamed.

If a paper is much cited, it means that it is good. The contrary is not true. Of two papers of similar merits, one is honorably cited (say, one hundred times) and the other is lost. The position on the mosaic contributes; our papers on natural compounds are much less cited than heterocyclic chemistry ones.

I have tried to understand the reasons so as not to fall into the same mistake again but I failed. Still, I love some of these lost papers very much; they remind me of The Parable of the Prodigal Son. To cite one example, in 2019, we published in *Structural Chemistry* this paper reported in Fig. 5 (the most famous "Strange Case" is that of Robert Louis Stevenson, Fig. 6).

It has been cited by other authors only one time in 2021, fortunately by one of the leading groups in this field, Fig. 7 [5].

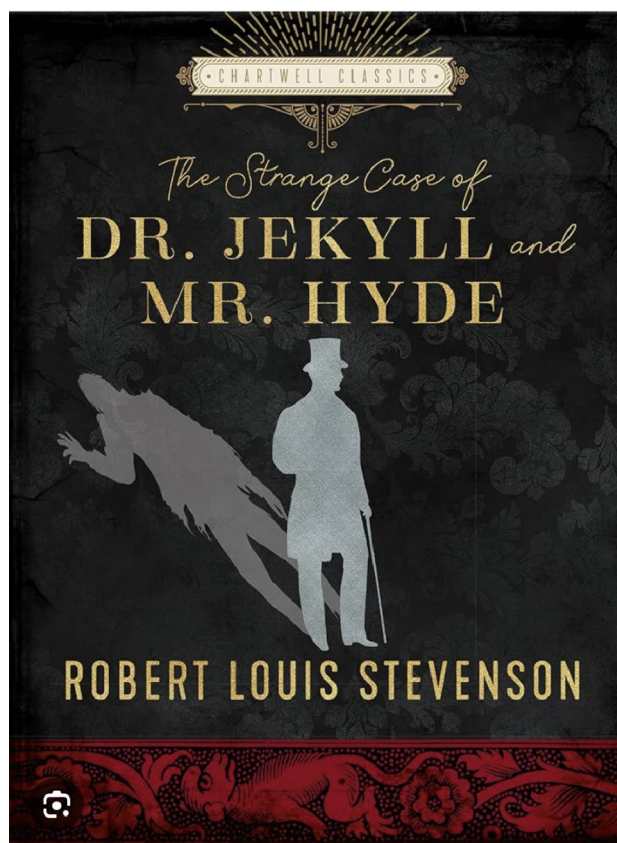


Fig. 6 Robert Louis Stevenson's book

Structural Chemistry (2019) 30:633–636
<https://doi.org/10.1007/s11224-018-1276-0>

REVIEW ARTICLE



The strange case of achiral compounds which were reported to always crystallize in the same chiral group

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Received: 7 November 2018 / Accepted: 26 December 2018 / Published online: 18 January 2019
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Abstract

In the present review, one of the mysteries of chemistry, the non-stochastic preference for one enantiomer during crystallization processes, is discussed with some examples of the literature and one published by our own group.

Keywords Cryptochirality · Bayesian model · Scalemic · Absolute asymmetric synthesis · Viedma ripening

Fig. 5 The strange case of achiral compounds

Spontaneous Deracemizations

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Cite This: *Chem. Rev.* 2021, 121, 2147–2229

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It constitutes one of the rare examples of something that seems to be in contradiction with thermodynamics. Chemistry is a science so consolidated that surprises are very rare. Contrary to physicists (dark matter) and biologists (Bayesian mind), chemists find difficulties but are usually well inside the paradigm. You could be wrong in proposing a given mechanism but your proposal and the right one are both reasonable. This is to the point that bright students find chemistry not difficult enough.

More personal problems. Editors vs. reviewers. I have been Associate Editor of the *European Journal of Organic Chemistry* for a short period. I discovered that editors quickly know that there are two extreme categories of reviewers, the kind and the fierce, and the fact to choose amongst them has a clear influence on the acceptance/rejection of a manuscript.

In 1984, Breitmaier and his collaborators published a well-known paper: “Enantioselective reactions in a static magnetic field” [6]. Reading it led us to perform an experiment that seemed more appropriate to demonstrate the Breitmaier effect, rather than the reduction of a carbonyl compound, the reaction of chloroform with 2-methyl-1*H*-benzimidazole that gives a racemic mixture of tris-(2-methyl-1*H*-benzimidazol-1-yl)methane (percentages determined by NMR in the presence of Pirkle’s alcohol). We did the experiments outside and inside a 300-MHz spectrometer, and in both cases, we got a 50/50 mixture. We sent it to a journal and it was rejected saying the magazine did not publish negative results. So we sent it to an Indian journal that had just appeared. It was published in *Heterocyclic Communications* (received June 30, 1994) [7]. Shortly after, a series of articles appeared showing that it was impossible to obtain enantiomeric excesses using a static magnetic field [8–10].

Twenty-seven years later, we made the same mistake again. We sent a review entitled “Not Only Hydrogen Bonds: Other Noncovalent Interactions” that we thought was worth publication but the Editor replied that they had many reviews waiting and that we should send it to a sister journal. We did so and their publisher rejected it because they had already

signed a contract with another group for a similar review that was about to appear. We quickly sent it to a very different journal where it was published in 2020 having been cited 268 times as of today (February 26, 2024) [11]. No other article on this topic has been published.

Good things

Amongst the personal good things that happened to me was the European Project led by Hans-Heinrich Limbach which was renovated once. On the second time, Richard R. Ernst was part of the project (Fig. 8).

From 1961, NMR spectroscopy has been my favorite technique, but the level of this discipline in the hands of Limbach and Ernst was so high that I learned many things. I remember when the University of Marseille got a 100-MHz machine that was only free on night time. Marseille was 175 km from Montpellier at that time (no highways). With Alain Fruchier, we leave late in the afternoon and work all night there, coming back in the morning. I have a very fond remembrance of that time.

Sartre wrote “L’enfer c’est les autres” but in my life, meeting the others has been one of the most enriching experiences. My students grooved old and became my friends, changing the French “vous” to “tu.” In France, Fruchier,



H.H.L. (1943). Photograph, courtesy of Bernd Wannemacher R.R.E. (1933-2021). Photograph by José Elguero

Fig. 8 Professors H. H. Limbach and R. E. Ernst

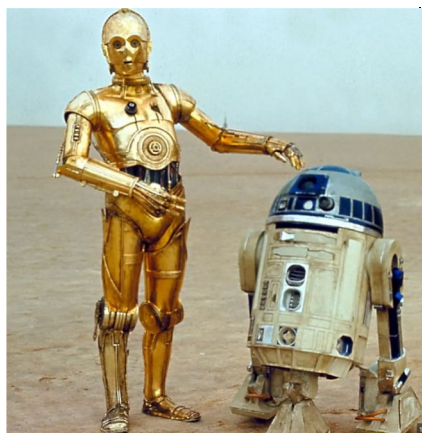
C₃PO & R₂D₂

Fig. 9 Star Wars

Tarrago, Galy, Roussel, and Phan Tan Luu... and Spain, José Luis Serrano, Carlos Cativiela, Antonio de la Hoz, Pilar Goya, Pedro Molina, Nadine Jagerovic, Fernando Cosío, Antonio Frontera, Otilia Mó, Manuel Yáñez, and Ibon Alkorta (CSIC, 756 papers) and Rosa M. Claramunt (UNED, 450 papers) (they are not independent, with both authors, 132 papers), and many others in many countries. Some years ago, I counted them, more than 2000 co-authors. Amongst them were Alan R. Katritzky, Paul von Ragué Schleyer, Alexander T. Balaban, Vladimir I. Minkin, Vladimir A. Ostrovskii, Zvonimir B. Maksić, Swiatoslaw Trofimenko, Robert W. Taft, Janet del Bene, Paul Popelier, Fumio Toda, Artur M. S. Silva, Stephan P. A. Sauer, H. V. Rasika Dias,

The work? Tautomerism (the book with Alan Katritzky, Paolo Linda, and Claude Marzin has been cited more than a thousand times), aromaticity, proton transfer, non-covalent interactions (rather covalent by the way), rare coupling constants (a rather obsolete subject today), solid-state NMR, and X-ray structures (although I am not a crystallographer, the CCSD find 559 hits for Elguero).

I have published many opinion papers, almost all in Spanish, but also in *Chemistry International* (an almost forgotten paper on “Is it possible to extend the Cahn-Ingold-Prelog priority rules to supramolecular structures and coordination compounds using lone pairs?” [12–14]) and some winks about the theoretical structure of C₃PO and R₂D₂, Fig. 9 [15].

As with many scientists, Sherlock Holmes is present in our papers: “A study in desmotropy,” Fig. 10 [16]; its unforgettable sentence “It is a capital mistake to theorize before one has data or one begins to twist facts to suit theories, instead of theories to suit facts,” in *A Scandal in Bohemia*, Fig. 11 [17], etc.

The structure of C₃PO with C_{3v} symmetry and charge −3 is a second order transition state (4TS) which following any of its imaginary frequencies it leads to the compound 4. This 4TS lays 278.1 kJ mol^{−1} higher with respect to compound 4.

A study in desmotropy

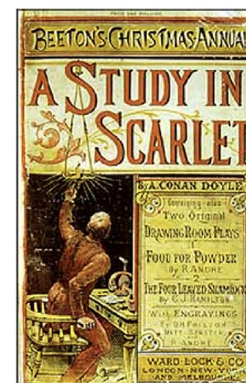


Fig. 10 A Study in Scarlet

In conclusion, when discussing tautomeric equilibria in solution it is important to remind that the position of the equilibrium depends not only on the intrinsic difference in energies but also on the solvation effects, which, in turn, relies on the dipole moment. Otherwise, people could make the capital mistake to force the theory (calculations) to suit the experiments (solution measurements), instead of facts to suit theories.

Fig. 11 A Scandal in Bohemia

Author contribution J.E. wrote the original version of the manuscript.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Competing interests The author declare no competing interests.

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