MOLEKULSKA ARHITEKTURA

THE SECRET MECHANISM OF ENEDIYNES

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CRAZY CHEMIST COMICS

THE SECRET MECHANISM OF ENEDIYNES

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RAIN.

MAKES ME THINK ABOUT COOL THINGS.

MAKES ME THINK ABOUT BEAUTIFUL THINGS.

MAKES ME THINK ABOUT ***CHEMISTRY***.

ENEDIYNE ANTIBIOTICS.

THEY ***KILL*** TUMOR CELLS BY UNIQUE MECHANISM.

IT'S CALLED ***BERGMAN CYCLIZATION***.

IT OCCURS UPON ACTIVATION.

BUT THERE ARE DRAWBACKS.

COMPLEX STRUCTURE, NON-SELECTIVITY, UNCONTROLLED REACTIVITY...

SCIENTISTS ARE WORKING 24/7 TO SOLVE THESE ISSUES.

SO AM I.

BUT WHAT IF THERE IS MORE TO ENEDIYNE REACTIVITY?

GOING THROUGH LITERATURE DOESN'T HELP A LOT.

SCIENTISTS PREPARE ENEDIYNE DERIVATIVES AND ACTIVATE THEM THERMICALLY.

THE CONCLUSION: BERGMAN CYCLIZATION OCCURS.

THE THING IS, ALMOST NOBODY ***ISOLATED*** THE BERGMAN PRODUCT.

CONCLUSIONS ARE MADE BASED ON A SINGLE PEAK IN DSC.

IN RARE CASES WHEN PRODUCTS ARE ISOLATED, THEY DON'T KNOW WHAT HAPPENS ***DURING*** THE ACTIVATION.

TAKING INTO ACCOUNT TEMPERATURES USED FOR THE ACTIVATION, THERE ***HAS TO*** BE SOMETHING MORE TO BERGMAN CYCLIZATION MECHANISM. BUT WHAT?

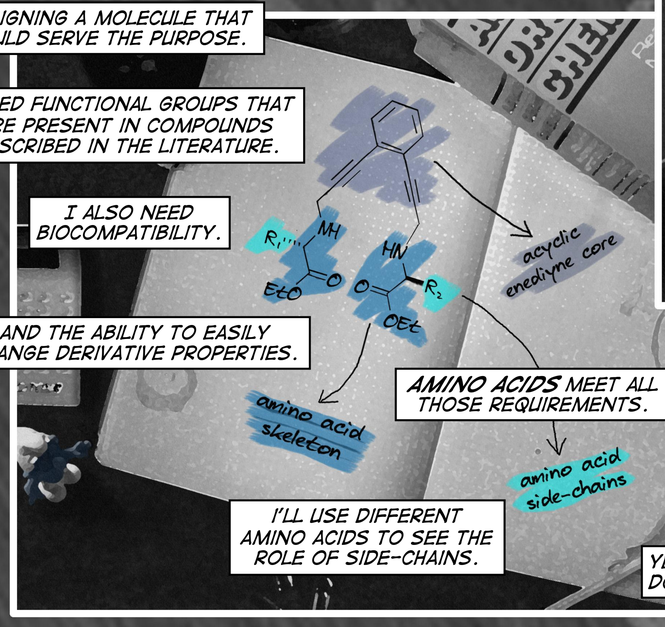
IT'S WORTH INVESTIGATING.

DESIGNING A MOLECULE THAT COULD SERVE THE PURPOSE.

I NEED FUNCTIONAL GROUPS THAT ARE PRESENT IN COMPOUNDS DESCRIBED IN THE LITERATURE.

I ALSO NEED BIOCOMPATIBILITY.

AND THE ABILITY TO EASILY CHANGE DERIVATIVE PROPERTIES.



AMINO ACIDS MEET ALL THOSE REQUIREMENTS.

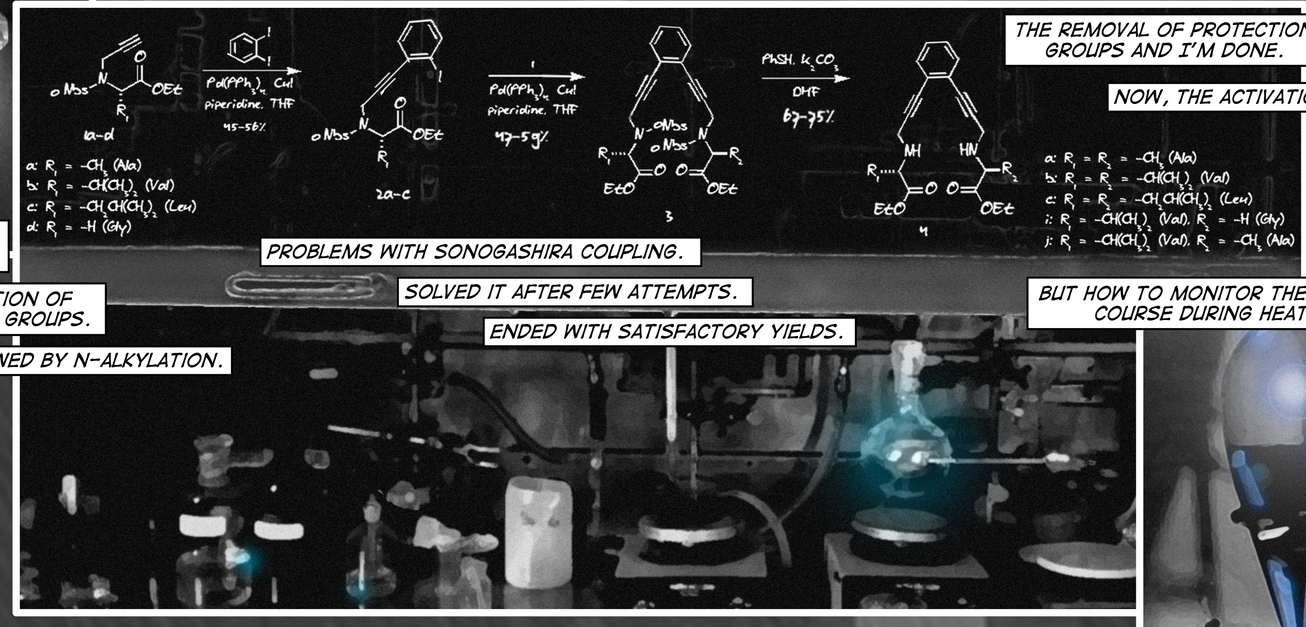
I'LL USE DIFFERENT AMINO ACIDS TO SEE THE ROLE OF SIDE-CHAINS.

YES, IT SHOULD DO THE TRICK.

SYNTHESIS SHOULDN'T BE SO COMPLICATED.

INTRODUCTION OF PROTECTION GROUPS.

FOLLOWED BY N-ALKYLATION.



THE REMOVAL OF PROTECTION GROUPS AND I'M DONE.

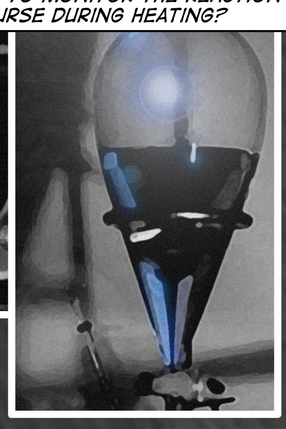
NOW, THE ACTIVATION.

PROBLEMS WITH SONOGASHIRA COUPLING.

SOLVED IT AFTER FEW ATTEMPTS.

ENDED WITH SATISFACTORY YIELDS.

BUT HOW TO MONITOR THE REACTION COURSE DURING HEATING?



CAN IT BE DONE WITH IR SPECTROSCOPY?

LUCKILY, I KNOW A GUY...

YES, IT CAN. BUT IT'S NOT TRIVIAL. EXTENSIVE MEASUREMENTS, TONS OF SPECTRAL DATA. AND TIME... LOTS AND LOTS OF TIME. MOREOVER, I'LL PROBABLY NEED TO MONITOR SEVERAL MOLECULAR VIBRATIONS.

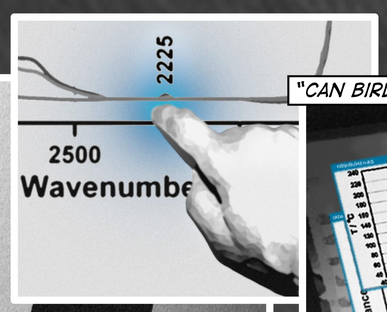
YOU MEAN LIKE SOME SORT OF DISTINCTIVE SIGNAL?

EXACTLY. FOR EXAMPLE, RIGHT HERE, AT 2226 CM^{-1}, ARE ACETYLENES. NO SIGNAL, NO ACETYLENES.

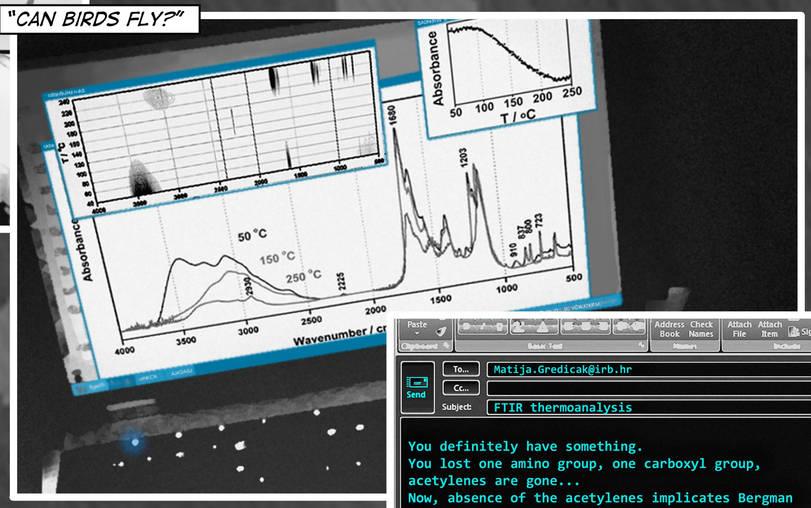
I SEE. AND IF YOU COLLECT SPECTRA AT DIFFERENT TEMPERATURES...

...I'LL BE ABLE TO SEE EVERYTHING THAT HAPPENS WITH YOUR COMPOUND AT DESIGNATED TEMPERATURE.

COOL! CAN YOU DO THAT?



"CAN BIRDS FLY?"



IT WAS HARD.

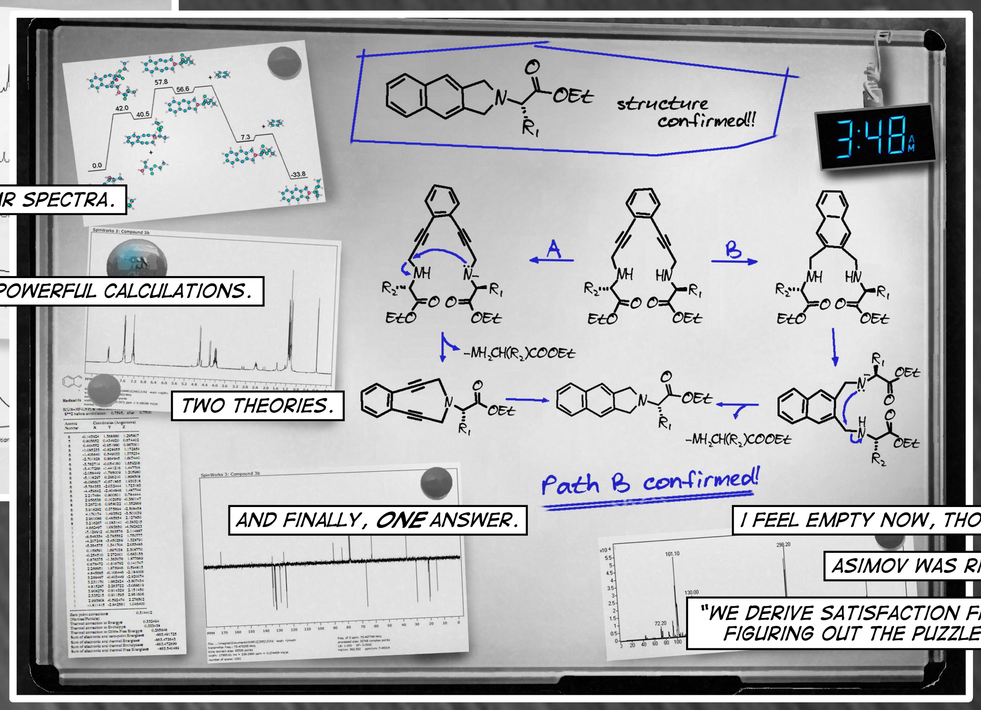
HARD AS HELL.

A TON OF MS SPECTRA.

EVEN MORE NMR SPECTRA.

POWERFUL CALCULATIONS.

TWO THEORIES.



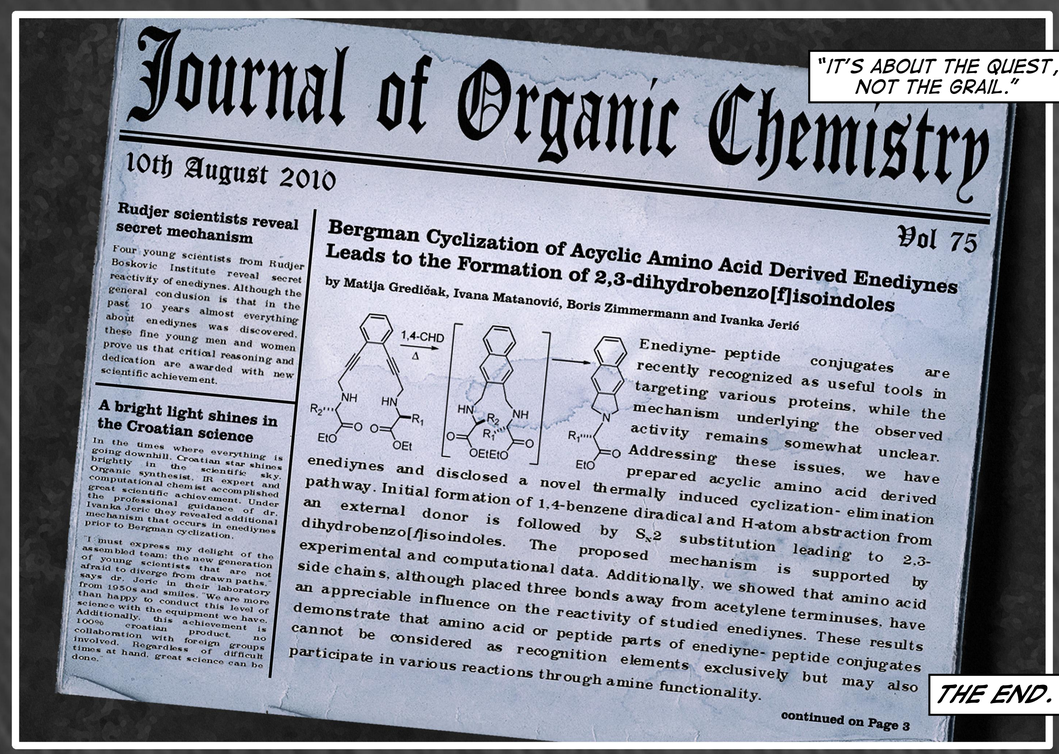
AND FINALLY, ***ONE*** ANSWER.

I FEEL EMPTY NOW, THOUGH.

ASIMOV WAS RIGHT.

"WE DERIVE SATISFACTION FROM FIGURING OUT THE PUZZLE."

"IT'S ABOUT THE QUEST, NOT THE GRAIL."



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Rudjer scientists reveal secret mechanism

Four young scientists from Rudjer Boskovic Institute reveal secret reactivity of enediynes. Although the general conclusion is that in the past 10 years almost everything about enediynes was discovered, these fine young men and women prove us that critical reasoning and dedication are awarded with new scientific achievement.

A bright light shines in the Croatian science

In the times where everything is going downhill, Croatian star shines brightly in the scientific sky. Organic synthesist, IR expert and computational chemist accomplished the professional guidance of dr. Ivanka Jerić they revealed additional mechanism that occurs in enediynes prior to Bergman cyclization.

I must express my delight of the assembled team; the new generation of young scientists that are not afraid to diverge from drawn paths, says dr. Jeric in their laboratory from 1950s and smiles. We are more than happy to conduct this level of science with the equipment we have. Additionally, this achievement is 100% croatian product, no collaboration with foreign groups involved. Regardless of difficult times at hand, great science can be done.

Bergman Cyclization of Acyclic Amino Acid Derived Enediynes Leads to the Formation of 2,3-dihydrobenzo[*f*]isoindoles

by Matija Gredičak, Ivana Matanović, Boris Zimmermann and Ivanka Jerić

Enediyne- peptide conjugates are recently recognized as useful tools in targeting various proteins, while the mechanism underlying the observed activity remains somewhat unclear. Addressing these issues, we have prepared acyclic amino acid derived enediynes and disclosed a novel thermally induced cyclization- elimination pathway. Initial formation of 1,4-benzene diradical and H-atom abstraction from an external donor is followed by S_N2 substitution leading to 2,3-dihydrobenzo[*f*]isoindoles. The proposed mechanism is supported by experimental and computational data. Additionally, we showed that amino acid side chains, although placed three bonds away from acetylene terminuses, have an appreciable influence on the reactivity of studied enediynes. These results demonstrate that amino acid or peptide parts of enediyne- peptide conjugates cannot be considered as recognition elements exclusively but may also participate in various reactions through amine functionality.

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THE END.