TOWARDS THE TRANSFER OF CHIRALITY FROM MOLECULAR MOTORS TO BIARYLS VIA NON-COVALENT INTERACTIONS

THESIS

As a pre-requisite
to obtain Master Degree from
Insitut Teknologi Bandung

By

Jefri

NIM: 20514062

(Master Program in Chemistry)

INSTITUT TEKNOLOGI BANDUNG

October, 2015

ABSTRACT

TOWARDS THE TRANSFER OF CHIRALITY FROM MOLECULAR MOTORS TO BIARYLS VIA NON-COVALENT INTERACTIONS

By

Jefri

NIM: 20514062

Chirality is a property of molecules which plays a big role in many aspects of living systems. Since its discovery by Louis Pasteur in 1848, much research on the chirality of both natural and synthetic compounds has been carried out. One of the most interesting topics in this field is the chiral induction, in which chirality is transferred from a chiral molecule to an achiral molecule. In this research, a series of complexes was designed for chirality transfer from a chiral 'first-generation' biphenol molecular motor to conformationally flexible biaryls, such as 3,3'-bipyridine, 4,4'-biisoquinoline, 1,1'-dimethyl-4,4'-biisoquinoline, and 1,1'-diphenyl-4,4'-biisoquinoline through hydrogen bonding. The biphenol molecular motor was successfully synthesized in three reaction steps, namely Friedel-Crafts alkylation and subsequent acylation, McMurry homocoupling, and deprotection of methoxy groups in good yield for each step (59–74%). Both enantiomers of the biphenol motor were obtained in high enantiomeric excess (>99%) from resolution of the synthesized motor with (8*S*,9*R*)-*N*-benzylcinchonidinium chloride using either ethyl acetate or acetonitrile as the solvent. Each of the four biaryls was synthesized in one reaction step, either Pd-catalyzed cross coupling, Ni-catalyzed homocoupling, or 1,4-functionalization in low to moderate yields (5–49%). Furthermore, photochemical and thermal isomerization steps of bismethoxy motor, an intermediate in the synthesis of biphenol motor, were studied by means of UV-Vis and ^{1}H NMR spectroscopy. The results showed that the introduction of the methoxy group in the motor does not have a significant influence on the thermal isomerization steps. NMR study revealed that there were no hydrogen bonding between the biphenol motor with either 3,3'-bipyridine or 4,4'-biisoquinoline. Similar result was obtained when the biaryl was substituted with chiral aliphatic diamines. A new design of complex for chirality transfer employing a pyridine-based molecular motor was constructed, but attempts on the synthesis of the motor scaffold were unsuccessful.

Keywords: chirality transfer, biphenol, molecular motor, biaryls, hydrogen bonding.

ABSTRAK

KAJIAN TRANSFER KIRALITAS DARI MOTOR MOLEKUL KE SENYAWA BIARIL MELALUI INTERAKSI NON-KOVALEN

Oleh

Jefri

NIM: 20514062

Kiralitas adalah sifat molekul yang memiliki peranan besar dalam berbagai aspek kehidupan. Sejak penemuannya oleh Louis Pasteur pada tahun 1848, banyak penelitian tentang kiralitas senyawa bahan alam dan sintetik telah dilakukan. Salah satu topik yang paling menarik dalam bidang ini adalah induksi kiralitas, dimana kiralitas ditransfer dari suatu molekul kiral ke molekul akiral lain. Dalam penelitian ini, serangkaian molekul kompleks dirancang untuk transfer kiralitas dari motor molekul bifenol 'generasi pertama' yang kiral ke senyawa biaril yang fleksibel secara konformasi, seperti 3,3'-bipiridin, 4,4'-biisokuinolin, 1,1'-dimetil-4,4'-biisokuinolin, dan 1,1'-difenil-4,4'-biisokuinolin melalui pembentukan ikatan hidrogen. Senyawa motor molekul bifenol berhasil disintesis melalui tiga tahap reaksi, yaitu reaksi alkilasi Friedel-Crafts diikuti asilasi, homokupling McMurry, dan deproteksi gugus metoksi dengan rendemen yang baik untuk setiap tahap (59–74%). Kedua enansiomer motor molekul bifenol diperoleh dalam *enantiomeric excess* tinggi (>99%) dari resolusi motor molekul hasil sintesis dengan (8*S*,9*R*)-*N*-benzilcinchonidinium klorida menggunakan etil asetat atau asetonitril sebagai pelarut. Masing-masing senyawa biaril disintesis melalui satu tahap reaksi, yaitu reaksi kupling-silang-terkatalisis-Pd, homokupling-terkatalisis-Ni, atau fungsionalisasi-1,4 dengan rendemen rendah hingga sedang (5–49%). Selanjutnya, tahap isomerisasi fotokimia dan termal motor molekul bismetoksi, intermediet dalam sintesis motor molekul bifenol, dipelajari menggunakan spektroskopi UV-Vis dan ^{1}H NMR. Hasilnya menunjukkan bahwa gugus metoksi dalam motor molekul tidak memiliki pengaruh signifikan dalam tahap isomerisasi termal. Studi NMR menunjukkan tidak adanya pembentukan ikatan hidrogen antara motor molekul bifenol dengan 3,3'-bipiridin maupun 4,4'-biisokuinolin seperti yang diharapkan. Hasil serupa juga diperoleh ketika senyawa biaril diganti dengan senyawa diamina alifatik kiral. Sebuah kompleks baru untuk transfer kiralitas menggunakan motor molekul berbasis piridin dirancang, tetapi upaya untuk mensintesis kerangka motor tersebut belum berhasil.

Kata kunci: transfer kiralitas, bifenol, motor molekul, biaril, ikatan hidrogen.

TOWARDS THE TRANSFER OF CHIRALITY FROM MOLECULAR MOTORS TO BIARYLS VIA NON-COVALENT INTERACTIONS

By

Jefri

NIM: 20514062

(Master Program in Chemistry)

Institut Teknologi Bandung

Has been approved as a requirement to obtain Master Degree from
Institut Teknologi Bandung

Date 8-9-2015

Daily Supervisor

Thomas van Leeuwen, M.Sc.

Supervisor

Dr. Deana Wahyuningrum

Supervisor

Prof. Dr. Ben L. Feringa

GUIDELINE FOR USING THIS THESIS

This unpublished master thesis is registered and available at the library of Institut Teknologi Bandung and open for public. The writer has the copyright of this thesis which is protected by HaKI law of Institut Teknologi Bandung. In order to cite this thesis, the citer must have the writer's permission and has to be done in a proper way of scientific community.

Copying and publishing some or all part of this thesis has to be under permission of Dean of School of Post-Graduate Study of Institut Teknologi Bandung.

Dedicated to my father, my mother, and my brothers.

ACKNOWLEDGEMENT

First of all, I would like to thank Prof. Ben Feringa for giving me such a great opportunity to work in his group filled with so many great chemists. Thank you for your encouragement, guidance, great suggestions and comments during my research in Groningen. It was a great pleasure and honor for me to work in your group.

I would also give my big thanks to Tom van Leeuwen for being such a great daily supervisor for me. Thanks for your kindness and patience in teaching and guiding me since the beginning of my research, from the lab-work, measurements, discussion, to correcting my presentation as well as my master thesis. I did learn a lot of chemistry from you and I hope my work could contribute in your research.

In this opportunity, I want to acknowledge Dr. Sander Wezenberg for the discussion about binding study and also for reviewing my presentation in Groningen together with Dr. Beatrice Collins. I sincerely thank you both for giving me very good comments and suggestions on my presentation slides. I also want to thank Jos Kistemaker for his help in the Eyring analysis of the motor and Dorus for his help in performing the GC-MS measurement. I would thank Theodora for the HRMS measurements and Peter for his help in NMR measurements.

Furthermore, I would express my gratitude to the members of the molecular motor subgroup for the useful discussion and suggestions during the subgroup meeting. I would also thank the members of the recently-formed smart material subgroup, especially Prof. Wesley Browne for his critical comments and suggestions on my research. I would thank the C-Wing lab-members for their assistance during my work in the laboratory.

As my supervisor in ITB, I would like to thank Dr. Deana Wahyuningrum for encouraging me during my research in Groningen and also for the useful discussion on my research. I would also thank my lecturers in ITB who provided me with so much knowledge about chemistry during my master program.

I would acknowledge Indonesian Directorate General of Higher Education/ DIKTI for giving me the fresh graduate scholarship during my master program in ITB and Zernike Institute of Advanced Material, University of Groningen for the scholarship during my research stay in Groningen.

In this opportunity, I would sincerely thank my parents and brothers who always give me support and encouragement since the beginning of my master program. I would also express my gratitude to all of my friends in ITB and Groningen for their support during my master program.

Bandung, August 2015

Jefri

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

ABBREVIATION	FULL FORM	First time used in page
DNA	Deoxyribonucleic Acid	1
CD	Circular Dichroism	3
NMR	Nuclear Magnetic Resonance	3
CAHB	Charged-Assisted Hydrogen Bond	3
UV-Vis	Ultraviolet-Visible	7
MeLi	Methyllithium	8
PhLi	Phenyllithium	8
HRMS	High Resolution Mass Spectroscopy	8
SFC	Supercritical Fluid Chromatography	8
PSS	Photostationary State	8
kJ	kilo Joule	15
s	second	15
min	minute	15
K	Kelvin	15
TS	Transition State	16
BINOL	1,1'-Bi-2-naphthol	18
R_f	Retention factor	19
CPL	Circularly Polarized Light	20
L-CPL	Left-handed Circularly Polarized Light	20
R-CPL	Right-handed Circularly Polarized Light	20
T	Temperature	23
H	Host	24
G	Guest	24
C	Complex	24
M	Molar	26
TLC	Thin Layer Chromatography	28
PMA	Phosphomolybdic Acid	28
ESI	Electrospray Ionization	28

APCI	Atmospheric Pressure Chemical Ionization	28
μm	micrometer	28
nm	nanometer	28
MHz	Mega Hertz	28
ppm	parts per million	28
eq	equivalent	29
cm	centimeter	29
g	gram	29
mL	milli Liter	29
h	hour	29
Et_2O	Diethylether	29
PPA	Polyphosphoric Acid	29
EtOH	Ethanol	30
lit	literature	30
calcd	calculated	30
THF	Tetrahydrofuran	30
EtOAc	Ethylacetate	30
mmol	millimol	31
PPh_3	Triphenylphosphine	32
Et_4NI	Tetraethylammonium iodide	32
DME	1,2-Dimethoxyethane	33
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone	33
DCM	Dichloromethane	34
DMF	*N,N*-dimethylformamide	34
ee	enantiomeric excess	36
d	day	42
rt	room temperature	49
Phen	1,10-Phenantroline	51
MeOH	Methanol	56
Et_3N	Triethylamine	69
cat	catalytic	70
GC-MS	Gas Chromatography-Mass Spectroscopy	73
EI	Electron Impact	73

LDA	Lithium Diisopropylamide	74
n-BuLi	normal-buthyllithium	75

SYMBOL

pK_a	Acid dissociation constant at logarithmic scale	3
$\Delta H^{\ddagger}$	Entalphy of activation	8
$\Delta S^{\ddagger}$	Entropy of activation	8
$\Delta G^{\ddagger}$	Gibbs free energy of activation	8
τ	Half-life	15
℃	Celcius degree	15
%	Percent	16
$\Delta\varepsilon$	Difference of molar absorptivity	20
A_L	Absorbance of left-handed circularly polarized light	20
A_R	Absorbance of right-handed circularly polarized light	20
ε_L	Molar absorptivity of left-handed circularly polarized light	20
ε_R	Molar absorptivity of right-handed circularly polarized light	20
[J]	Molar concentration of sample	20
l	Path length of sample	20
$k^{\ddagger}$	Rate constant of activation	23
κ	Transmission coefficient	23
ν	Vibrational frequency of relevance	23
k	Rate constant	23
k_B	Boltzmann constant	23
h	Planck's constant	23
R	Gas constant	23
A	Arrhenius constant	23
E_a	Energy of activation	23
K	Binding constant	24
$[H]_t$	Total concentration of host at initial stage	24

$[G]_t$	Total concentration of guest at initial stage	24
$[C]_t$	Total concentration of complex at initial stage	24
[H]	Concentration of host at equilibrium	24
[G]	Concentration of guest at equilibrium	24
[C]	Concentration of complex at equilibrium	24
δ	Chemical shift	25
c	Concentration	29
J	Coupling constant	30
$[\alpha]_D^{20}$	Specific rotation using D line of sodium spectrum at 20 ℃	36
λ	Wavelength	37
π	Phi bond	51