

# Nuclear Magnetic Resonance residual dipolar coupling parameters in organic molecular structure identification in Application

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**Abstract:** Residual dipolar Coupling (Residuals dipolar coupling RDC) As an Nuclear Magnetic Resonance the to the opposite sex parameters in analysis organic molecular configuration and advantage conformation and other aspects of application has strong of advantage It can reflect molecular Central Plains sub-in Magnetic Field in space distance and angle information Molecular three-dimensional space of Construction. This paper on residual dipolar coupling in organic molecular structure identification of Progress Review Detailed summary the determination RDC Of directional medium and detection analysis methods And use instance show RDC In natural product, synthesis drug, organic reaction intermediate or complex And the mapping isomers and stereo chemical aspects of Analysis and Application.

**Keywords:** Nuclear Magnetic Resonance Spectroscopy Residual dipolar Coupling Directional Media Organic Small Molecule Structure Analysis

## 1. Introduction

Natural or Synthesis organic molecular of Structure Identification Especially stereo chemical analysis has been is organic chemical and drug chemical of core task one And nuclear magnetic resonance spectroscopy in its structure identification and analysis has not alternative of Role. As an classic of Nuclear Magnetic Resonance Parameters: Chemical displacement ( $\Delta$ ), Coupling Constant ( $J$ ) And Ophir Hauser nuclear (Nuclear Overhauser effect NOE) Effect Is organic chemist daily experimental in for identification Organic Small Molecules and biological big molecular structure of commonly used information. Due to chemical displacement  $\Delta$  By around chemical environment of influence very big So there's only one qualitative role; Whether the same or the same  $J$  Coupling,  $^3J$  Coupling Constant is an important constraint for Structural Calculation, It passed Karplus The empirical formula is related to the dihedral angle, However  $^3J$  Coupling only limited to no more 3. The dihedral angle formed by a covalent bond; But Noe The effect is that the space is closer to the two (Group)

For  $^1H$  Nuclear speaking, When distance is greater 5 Å Time, Noe Limited role. Yin

Based on Noe And  $^3J$  The coupling constants provide only local structural information, It is difficult to analyze the relative configuration of molecules after being separated or blocked by inert nuclei..

Dipole coupling is the interaction between two magnetic nuclei through space.

With, IN SOLID STATE NMR, The dipole coupling is usually measured in thousands of Hertz., The dipole coupling is too strong to make the peak extremely wide, Cannot parse due to poor resolution; And in the solution, Because of the Brown Movement of molecules, The dipole coupling is averaged zero., Although the measured spectral image has a high resolution, the structural information attached to the dipole coupling is lost.. However, When the movement of molecules

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in the solution is limited, Dipole coupling may not be fully averaged, And retain smaller residual values, Called residual couple

Polar Coupling (Residential dipole coupling, RDC)<sup>[1-2 ~ 12]</sup>. RDC Can provide structural information between two directly or indirectly connected Cores, Its size is related to the distance between the two nuclei and the angular orientation of the bond vector between the two nuclei relative to the external magnetic field, Its value is commonly used  $D_{IS}$  Express, Among them  $M_0$  Is the dielectric constant of space,  $h$  Planck Constant,  $\gamma$  Magnetic Ratio  $R$ . Said two spin nuclear between the vector distance  $\theta$  Said

And  $\theta$  of nuclear between vector relative plus magnetic field between of the size of the Angle (Figure 1 ). So RDC Value and atomic of space arrangement related Can reflect molecular

Configuration and advantage Conformation Is study molecular stereo structure of a important nuclear magnetic resonance parameters And NOE And  $^3J$  Coupling constant of information complementary<sup>[13,14]</sup>.

In recent years With the field study of in-depth Residual dipolar Coupling Parameters is gradually in organic molecular Three-Dimensional Structure (Configuration and Conformation) Determination in play important role By widely attention<sup>[15 ~ Natural 20]</sup>. This paper review the nearly ten years to Development of Organic Small Molecule residual dipolar coupling Determination of directional medium and pulse methods And summarize the use the to the opposite sex parameters to solve natural product stereo structure, organic reaction intermediate determination and chiral the mapping isomers distinguish between and instance.

## 2. Directional Media

Accurate Determination RDC Must meet two conditions: A is by certain of methods to make molecular of movement limited or constraint its into the to the opposite sex Make dipole coupling role can't completely offset To produce is weak "Residual dipolar Coupling"; Two is dipole coupling role can't too strong The map quality to High Resolution Line width to in Extraction RDC Value. So Must be Will solute molecular placed a non-The to same-sex environment That is a kind of directional Media (Alignment Media) In This is organic molecular RDC The premise. At present Development and Construction Structure novel, simple practical and organic solvent compatible with RDC Extraction media and methods become organic chemical workers urgent pursuit of target.

1963 Years Saupe Professor and<sup>[21,22]</sup> Reported the first liquid crystal phase organic small molecule Hydrogen Spectrum: Will benzene soluble in oxidation azobenzene methyl ether liquid crystal medium in get H-H Coupling up 2.5 kHz Of multiplet Spectrum Regret Of is

Coupling is too strong and can't actual application. 40 Years Later With RDC Theory of improving More and more of directional medium development and to the actual application<sup>[23 ~ 26]</sup>. At present for Determination of Organic molecular RDC Main have two class directional Media: Can swelling and can tensile or extrusion of gel (SAG ), And solution of Liquid Crystal (LLC ). Gel medium of Directional principle is first by solvent soluble

General time is long, Will be measured molecular mechanical to qualified or constraint in gel cavity in Make its the to same-sex of Brown Movement Limited; And has certain arrangement orientation of soluble induced by liquid crystal make its orientation of spontaneous to part

To be analyte To has Constraint. These directional media can generate weak directional alignment in the magnetic field., Organic Small molecules to be tested

The interaction with the directional medium produces a moderate directional Property, So as to determine the residual dipole-Dipole Interaction (Namely RDC,  $D_{IS}$ ).

### 2.1 Stretch or compress Gel

Gel is a space network structure formed by colloidal particles or polymers under certain conditions., A special dispersion system in which dispersed media can be filled in structural voids. In order to accurately measure RDC, Get the highest resolution spectrum at the same time, The strength of the directional gel needs to be adjusted. Directional strength of crosslinked gel and Properties of gel (Crosslinking degree) Related to the diameter of the rod gel. Directional

angle can be obtained by preparing multiple gel samples of different specifications, To explore the optimal directional conditions after the axial and transverse Free Swelling of the core tube along the wall of the tube, respectively<sup>[27]</sup>; You can also use the earliest German Luy Professor<sup>[28,29]</sup> Invention of drawing device Tool, Find appropriate orientation conditions by changing the alignment strength of a single sample (Figure 2). Depending on the polarity of the gel dissolved in organic solvents, Divide gel directional media into the following 3. Class directional Adhesive.

Crosslinked polystyrene gum (PS) Is two the use of peroxide (DBP) Initiation of divinylbenzene (DVB) Polymerization with Styrene, Gel soluble in conventional non-polar organic solvents, The directional alignment ability is well controlled by changing the proportion of monomer.<sup>[27]</sup> Because PS Too much gum residue, Added RDC Difficulty in measurement and map analysis. To solve the problem of background peak interference, Subsequently Luy Wait.<sup>[30]</sup> And developed the all-deuterated polystyrene gel. (DPS Gum), Greatly reduced the back peak.

And use 10 MeV High Pressure Beta Poly (dimethyl siloxane) with different polymerization chain lengths and crosslinking degrees obtained by ray excitation (PDMS) Gum, Different directional properties in different non-polar organic solvents. Based on the analysis of two relative configurations of spiro two indene compounds RDC Analysis and Structural Verification, Thus established PDMS Practical Application Value. However, the crosslinking process requires unconventional Beta Ray Instrument, Am bassad or PDMS Glue cannot be commercialized<sup>[31]</sup>. 2017. Year Thiele Preparation by Chemical Synthesis PDMS Gum, Hexamethylsiloxane (D)<sub>4</sub>. Crosslinking agent was synthesized from raw materials. (Bis-d<sub>4</sub>) And Initiator, Then the three components are repolymerized to produce inactive PDMS, Last 150 Removal of catalyst components by heat treatment at °C NME<sub>3</sub>. Get PDMS Gum (Figure 3). Synthetic PDMS Gel in chloroform and tetrahydrofuran (THF) Play a directional role in, Subsequently utilized RDC Determination of sesquiterpene-like caryophyllene in chloroform ( $\beta$ -(-)-caryophyllene) The conformation of the complexes and the configuration of the intermediates between organic phosphine amide and Palladium, But the orientation ability is weak<sup>[32]</sup>.

Gil Professor, *et al*<sup>[33]</sup> Initially developed crosslinked poly (methyl methacrylate) Gum (PMMA) Directional Media, On Natural Products Ludartin Preliminary confirmation in the Absolute Configuration Analysis. PMMA The orientation ability in chloroform is also proportional to the degree of crosslinking, And the background peak of the collection map is weak.

The traditional method of Free Swelling, PMMA Preparation of gum is time-consuming (Required 20 ~ 20 ~ 30 D), Testing molecular diffusion inside the gel is also required 2 ~ D. In. Subsequently Gil Professor, *et al*<sup>[34]</sup> By implanting it in a magnetic tube Shigemi Piston, Extrusion gel with chloroform was added to rapidly prepare different orientation angles. PMMA Gum, Fixed the plastic cumbersome and other shortcomings, At present, this kind of piston extrusion device has been commercialized. (Figure 4)<sup>[35]</sup>; Also, Recovery of gum by Solvent washing, These advantages undoubtedly broaden its applicability.

Gel is difficult to prepare chiral directional Media, Well known poly benzyl glutamate (PBLG) Polymer with Helical Structure. To fill this gap, 2013 Year Thiele Wait.<sup>[36]</sup> Triethylene tetramine in crosslinking agent (TETA) Chiral Compounds with helical structure were synthesized under the action PBLG Gum (Figure 5). Pinol (IPC) And camphor Sulfonamide (CS) Discrimination of Enantiomers, Its disadvantage is that the glue making and balancing process takes a long time (40 Equilibrium 1 ~ 2. Moon), And the glue is easy to break during application.

### 2.1.1 Polar Organic Solvent directional Adhesive

2005 Year, Griesinger Professor's equal Monomer 2-Acrylamide-2-Methyl propyl sulfonic acid (AMPS) With N,N-Dimethylacrylate amide (DMAA) In N,N-Methylene bisacrylamide (Bis) And initiator ammonium persulfate (APS) Polymerization under action, Get crosslinked polyacrylamide Copolymer (PH Glue or weigh PH-PDMAA Gum) Is the first one soluble in dimethyl sulfoxide. (DMSO) Directional Adhesive, It can also be connected with water, N,N-Dimethyl formamide (DMF) Concurrently dissolve. PH The directional ability of glue is moderate, BiPBLG Little directional capability; Hydrogen spectrum width, Good RDC Collection and analysis<sup>[37]</sup>. 2012 Year Reins chid Wait.<sup>[38]</sup> Through retouching PH Gum Monomer (AMPS), Adopted (R)-Aphes Or (S)-Aphes As monomer according to the above Griesinger

Methods of aggregation for professors, Developed a chiral PHGum, In DMSO Suitable for methanol and water Solvents, Can effectively distinguish the enantiomers of menthol, Enantiomers of Mefloquine hydrochloride and Brucine hydrochloride and other organic small molecules (Figure 6).

Luy Wait.<sup>[39]</sup> Developing Polyvinyl Acetate (PVA) Gel, The synthesis process and PS Glue similar. PVA Adhesive has a wide range of solvent Universality, Especially in Polar Organic Solvents increased its practicability. By reducing camphor to Natural Products Norcamphor And antibiotics Sphaeropsidin Of RDC Value Analysis, Verified PVA Practical Application Value of adhesive as Directional Medium.

Pan gel crosslinked with acrylonitrile excited by Electron Energy (PAN) Soluble in DMSO And DMF China, Can be adjusted for the right directional arrangement ( $\Delta V_Q = 10 \sim 20 \text{ Hz}$ ). Because Pan Glue not charged, Can be miscible with peptides and Other Molecules, Wide range of applications<sup>[40]</sup>. Deuterium PS Gum inspired, 2010 Year, Luy Wait.<sup>[41]</sup> And the entire deuterium generation. Dpan Gum, Overcome the disadvantage of background peak interference, The sample size is small and contains RDC Less information about the natural product structure provides the possibility.

2013 Year, Luy Wait.<sup>[42]</sup> A new Crosslinked Polyethylene Glycol adhesive was reported. (PEO). It can be categorized into two categories according to the composition method: One is to use Gamma Ray-stimulated crosslinking Gamma-PEO Gel; Another a kind of is chemical modified Polymerization Of PEO MMA Glue. PEO Can soluble in water and various organic solvent and mixed solvent in Its widely of solubility almost become a kind "Universal" Directional glue. PEO Glue also exist some shortcomings: In strong acid environment under Will degeneration; Higher than that  $50^\circ \text{C}$  Under Will softening metamorphic. In addition PEO Glue don't has chiral So in the mapping isomers area time-sharing need to add enough of chiral Adduct of to implementation (Figure 7).

Recent Gil Professor and<sup>[43,44]</sup> Development the hydroxyethyl methacrylate glue (P-HEMA) And ju yi er chun jia mi benzoyl ester Gum (P-degmema), Its physical characteristics and preparation process and PMMA Glue similar. In addition two kind of new of, respectively, soluble in DMSO And methanol of polarity gel directional Media. In JSB-HSQC Experimental on flexible molecular menthol (Menthol) And natural product down Senecio scandens Buch.-alkali (Retrorsine) Collection of data Get the quality higher, data better of Map.

### 2.1.2 Water-soluble directional glue

Water-soluble polyacrylamide hydrogel (PAA) Is first applied to the determination of biological big molecular structure of directional Gel In NMR tubes in by compression or tensile the directional angle regulation<sup>[45,46]</sup>. 2005 Years Luy Professor and<sup>[47]</sup> Found A containing gelatin of Germany candy (Gummib ä rchen) In after simple treatment of purified after By swelling preparation Quadrupole deuterium Spectrum  $V_Q$  Can produce 21 Hz Of splitting. By this inspired Then the daily life with the gelatin (Gelatin) The study Found gelatin not only can as an weak directional medium determination of the relative Configuration Also can as an chiral directional medium to distinguish mapping isomers. Then By electronic to accelerate gelatin crosslinking with negative charge E-gelatin Also can as an chiral directional Media Use RDC Or Rqcs (Residual quadrupole coupling) And the to the opposite sex parameters can of alanine on mapping effective recognition<sup>[48]</sup>. And gelatin similar Collagen (Collagen) Polymer also can be as an effective distinguish between amino acid isomers and Determination of Biological Macromolecules Glutamine combined with protein Gln BPO of the to the opposite sex parameters Directional Media<sup>[49,50]</sup>.

## 2.2 Soluble induced by Liquid Crystal

Liquid Crystal is a kind of between liquid and crystallization state between of material state With liquid liquidity and crystal the to the opposite sex of Properties In a lot of biological system in can observe the to Liquid Crystal Such as lipid, cellulose and DNA Can

Formation liquid crystal phase<sup>[51]</sup>. According to the formation of Environment of conditions different can be to liquid crystal divided into two categories: A is in a temperature range in show of liquid crystal phase material is called the heat of Liquid Crystal; Two is some material dissolved in water or organic solvent after in a concentration under present of liquid crystal phase called soluble induced by Liquid Crystal. Soluble of liquid crystal of morphology and solution of concentration, temperature, PH And ion strength have certain relationship. According to molecular

arrangement of style Liquid Crystal also can be divided into nearly crystal phase liquid crystal, to Column Phase Liquid Crystal and cholesteric phase liquid crystal and<sup>[52]</sup>. And gel compared Liquid Crystal has a most important of advantages: It sample preparation quickly Balance time

So by widely attention To broaden the directional Media Development For RDC The extraction and molecular structure identification play the important of Role. According to solution of liquid crystal of composition and properties Can Will liquid crystal orientation media is divided into the following several type.

### 2.2.1 Poly polypeptide Liquid Crystal

As early 1954 Years Doty Such.<sup>[53]</sup> Found Poly L-Glutamic Acid-γ-Bian Ester (PBLG) Can formation to Column Phase Liquid Crystal. Then, France Courtieu And Lesot Professor and<sup>[54 ~ 60]</sup> Use PBLG Of directional role in non-polar organic solvent in "with isotope markers analyte or deuterium spectrum experimental and Methods Study organic small molecule isomers recognition and distinguish Make PBLG Of Application vigorous development. 2003 Years MERLET Thiele And Griesinger<sup>[61 ~ 63]</sup> A independent research group almost at the same time reported the in PBLG In of small molecule of relative Configuration Successful development. RDC In Organic molecular and natural product of stereo structure analysis aspects of wide world Has landmark significance. Then more of poly peptide α-Spiral polymer was used as a weak directional Media Main

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Including PBLG The enantiomers Pbdg, pcbll/pcbdl And Pelg/pedg Wait.. Because PBLG Directional energy is too strong to complicate the coupling, Problems caused by atlas analysis, After Thiele Professors and others have conducted a more detailed study of this liquid crystal., Mainly focus on reducing the orientation ability, changing the solute orientation and strengthening the recognition ability of enantiomers. Currently PBLG Liquid Crystal has developed into a commercial directional Medium (Figure 8 ). By increasing the molecular weight of the polymer, Increase the polymer chain introduced, PBLG Can show a more uniform liquid crystal phase, Also reduces directional strength, Enhance its applicability, Even at a critical concentration below 10 wt % Can also produce a good map. This is important for studying other peptide copolymers.

Directional performance, And even other types of polymer liquid crystal formation mechanisms provide Theoretical Basis<sup>[64 ~ 70]</sup>.

The secondary structure Alpha-Helically speaking, Beta-Poly peptides form liquid crystals with shorter chain lengths, Lower critical concentration, Directional The ability is relatively weak., More suitable for small molecules RDC Extraction. 2011 Years Thiele Professor and<sup>[71]</sup> Development the poly β-Ach-Polypeptide Liquid Crystal. This liquid crystal in water of critical concentration can be low 1 wt %. By the proline RDC

, China Science: Chemical 2017 Years The To of Liquid Crystal And can achieve IPC Of the mapping isomers distinguish. However high concentration liquid crystal will cause map half peak width increase Limit RDC The accurate analysis; Directional strength even though the PBLG Liquid Crystal small a lot But still 1000 Hz, Coupling role is too strong; Sample Preparation Process in purification not formation liquid crystal of Polymer or not Polymerization of monomer process too tedious (Figure 11 ). For looking for a kind of can instead poly guanidine of directional Media On the one hand keep Poly guanidine one-handed Spiral Structure of advantages On the other hand the directional ability more More suitable for Extraction RDC. 2012 Years Reggeline Such.<sup>[74,75]</sup> And Berger

Such.<sup>[76]</sup> Respectively development the chiral amino acid is yeah esters acetylene directional Media They of Long-chain structure and high of molecular weight make its in low of strong

Degree under it can formation liquid crystal phase Reduce the liquid crystal of critical concentration. RDC Value-10 ~ 15 Hz Appropriate of range in And peak-narrow Greatly improve

The extraction RDC Of Accuracy.

2012 Years Berger Such.<sup>[77]</sup> In accordance with the similar of ideas synthesis The alanine is decyl ester ju dayi nitrile polymer Ju dayi nitrile in chloroform, THF, Dichloromethane in CAN formation Liquid Crystal This liquid crystal

medium in to be measured molecular horse

Money sub-alkali can present is weak the orientation of But no reported its chiral recognition performance (Figure 12). 2017 Years Reggeline Professor<sup>[78]</sup> By heat treatment of methods This Polymer Liquid Crystal the Optimization Heat treatment after liquid crystal performance more

And Stability And success applied to distinguish between the mapping body IPC. This before This research group<sup>[79,80]</sup> Have synthesis the valine is decyl ester and phenylalanine benzyl ester for side chain of spiral ju dayi nitrile polymer weak directional Media By collection of related residual dipolar coupling value show that this kind of Amino Acid class spiral ju dayi nitrile polymer in the hand of model compounds of mapping body partition are

Has is good recognition performance (Figure 12).

This research group<sup>[81]</sup> Also development. A new two peptide ju dayi nitrile Liquid Crystal (LL-Piaf-obn) Weak directional Media The structure in rigid of Nitrile main chain of spiral External Force role under self-assembly for ordered aggregates And peptide side of the introduction of the hydrogen bond role can be stable this a kind of Biological simulation of screw

Spin advantage Conformation To build this a kind of new of directional media provides collaborative Effect It can be in low concentration of chloroform solution in its own liquid crystal phase. This a characteristics success for Semen strychni alkali, Tripterygium Wilfordii A of and complex natural

Molecular of stereo Chemical Research; RDC Calculation results with Single Crystal atomic coordinates of space configuration phase agreement And get the map High Resolution (Figure 13).

2017 Years Thiele Professor and<sup>[82]</sup> The  $C_3$  Symmetric of N-dodecane-based and chiral decane-based replace of benzene three amide (BTA), Use its molecular structure special of geometric configuration by hydrogen bond and  $\pi$ - $\pi$  Accumulation role will molecular extension for three-dimensional super-Molecular Structure (Figure 14), Its non-Chiral twelve alkyl benzene three amide polymer can be in weak polarity Solvent  $CdCl_3$  And  $CCL_4$  In assembly into liquid crystal phase (Critical Concentration respectively 26.0 wt % And 14.9 wt %), Can accurate collection of double-loop dicyclopentadiene small molecule RDC Value. And chiral decane benzene three amide spiral polymer separate in organic solvent in can't formation liquid crystal phase But and non-Chiral twelve alkyl benzene three amide composition of copolymer under will produce chiral amplification effect (The phenomenon in Copolymer Super-molecular chemical in called typical "Officer-Soldiers Effect", The SAS), They can in  $CdCl_3$  And THF- $D_3$  In assembly for Chiral spiral Liquid Crystal Accordingly they study the mapping body  $\beta$ -Pinene this liquid crystal in Chiral distinguish between performance<sup>[82]</sup>.

### 2.2.2 Oxidation graphene Liquid Crystal

Oxidation graphene (GO) As an in recent years of scientific research hot Because its characteristics of Physical and Chemical Properties: Structure symmetric, rigid big, aspect ratio and High Molecular Weight Can be in 1 mg/mL Concentration under formation liquid crystal phase. 2014 Years This research group<sup>[83]</sup> Will GO Liquid Crystal as an weak directional medium for organic small molecule RDC Of extraction Analysis Compared with in the polymer Polymer Liquid Crystal (PBLG, Ju dayi nitrile, Polyacetylene and) GO Liquid Crystal preparation process more express simple Just will be measured molecular and right amount oxidation graphene and solvent Mount NMR tubes in Shaking Mixing Centrifugal balance after can be Application Without long time balance preparation Samples The whole process a few minutes in can be complete. And GO Has wide of solvent Applicability Not only can soluble in water Also can be soluble in Mixed Solution Such as water-DMSO, Water-Acetonitrile, water-Acetone in. In addition GO Liquid Crystal Properties very stable In PH 1 ~ 14 And Temperature 5 ~ 80 °C Range in were keep liquid crystal phase Measured of spectrum figure no back prime This is

Other directional medium the don't have of characteristics. GO Directional ability moderate Extraction RDC Value suitable for of range in Its  $V_Q$  With graphene liquid crystal of concentration regularly change Can by change the concentration to Regulation Its directional ability (Figure 15). Even though GO As an directional media has as many advantages But there are still some defects: Can't all soluble in organic solvent Because  $\pi$ - $\pi$  Accumulation Effect of there

substrate broadness Limited Viscosity is high lead to line width wide.

For solve GO Liquid Crystal in conventional pure organic solvent the orientation of the ask

Ethyl Ester (Tfema) Grafting in GO Surface Get with Two-Dimensional Molecular Brush Structure GO-G-Tfema, Increase GO In pure DMSO In the dispersion Success observation to Liquid Crystal Phase Behavior And was  $^2\text{H}$  NMR Experimental and Synchronous Radiation Small Angle X-Ray Scattering (SAXS) Technology The confirmed; And then to anti-malaria drug double hydrogen artemisinin and female of for mode molecular The RDC Of Determination Calculation results with Single Crystal atomic coordinates of space configuration phase kiss

(Figure 16). Because grafting of oxidation graphene liquid crystal no background signal GO-G-Tfema Liquid Crystal Orientation medium at present by Germany Griesinger

Professor and <sup>[85]</sup> Of favor The liquid crystal in study female hormone drug Ethinylestradiol of configuration, conformation analysis provide the kind of new of directional Methods. trum crack score  $V_Q$ ; (C) NMR tubes in the liquid crystal pictures <sup>[84]</sup> (Color online)

### 2.2.3 Other water-soluble liquid crystal

As early Natural 20 Years ago Rod or fibrous of Mosaic Virus (TMV), Phage (Pfl phage), Disc-phospholipid double Molecular Layer (Bicelle) Colloidal Particles and famous of surface active agent/Alcohol system formation Otting Medium phase Was found in Aqueous Solution System in has directional role Then widely used in biological macromolecules of Structure Determination. But because these liquid crystal on organic small molecule of signal too much interference and few for Small Molecular Structure of Determination <sup>[86,87]</sup>.

And soluble in water and DMSO Of five glycol single twelve Alkyl Ether ( $\text{C}_{12}\text{E}_5$ ) Liquid Crystal Its directional ability can be changed by adjusting the temperature and concentration., The method can be used to determine the residual dipole coupling value of amino acids and Pentacyclic lactones in small polar organic molecules. (Figure 17) <sup>[88,89]</sup>.

2013 Year Berger Wait. <sup>[90]</sup> Using Bromination N-Dodecyl-N-Methyl pyrrolidine salt ( $\text{C}_{12}\text{MPB}$ ) Ionic Type in water, alcohol or DMSO Liquid Crystal formed in ternary system for the determination of glucose RDC Value (Figure 17), And Ionic Liquid Crystals of imidazolium modified by the above pyrrole salt structure recently ( $\text{C}_{12}\text{Mimbf}_4$ ), The liquid crystal is used in the same nucleus of theophylline organic molecules RDC Value

Determination <sup>[91]</sup>.

2014 Year Navarro-Vázquez Professor, *et al* <sup>[92]</sup> Discovery of weak directional medium disodium seganate (Dscg), Successful Extraction of residual dipole coupling value of water-soluble organic molecules, And by changing the concentration, temperature and adding saline 3. Method To adjust directional strength. Adding salt water can weaken the orientation of the medium, So that the residual dipole coupling value is within easy control, Isotropic and anisotropic samples can be collected by controlling the temperature in the same sample. RDC Value (Figure 17).

2013 Year Suryaprakash Professor, *et al* <sup>[93]</sup> A New Chiral Liquid Crystal with nucleotide monophosphate has been developed., Separation of water-soluble proline isomers and tripeptide using residual dipole coupling parameters in this weakly oriented medium (Gly-Glu-Cys) DETERMINATION OF THE STRUCTURE OF COMPOUNDS (Figure 18).

## 3. RDC Determination of Organic stereo chemical analysis methods of construction

RDC Of extraction is by nuclear magnetic resonance two-dimensional experimental get General determination with nuclear or of Nuclear: Such C-H C-C N-H And H-H Nuclear between of residual coupling Value Coupling value can determination single or remote coupling Value ( $^N\text{DN} = 1\ 2\ \dots$ ). In principle Most two-dimensional NMR Pulse experimental technology can be used for measurement extraction dipole coupling Scalar Coupling. However Due to sample placed directional media after Will make  $T_2$  Narrow Especially is viscosity is big of Liquid Crystal System in Makes the line width increases Reduce sensitivity At the same time also influence nuclear magnetic resonance Experiment of evolution Delay. And isotope markers Biological Macromolecules different Organic molecular Especially

is natural product molecular of samples of Limited In order to improve the sensitivity and accuracy Luy Thiele Bax And Griesinger And are committed to development nuclear magnetic resonance pulse technology applied to the determination of Organic Small Molecule and natural product of the to the opposite sex Parameters Table 2 Simple list the part RDC Extraction analysis experiment of various pulse sequence and Characteristics<sup>[94 ~ 111]</sup>. Because in weak of directional media in With nuclear Kai coupling and remote coupling RDC Value is too small Accuracy not enough In actual application in limitations Here not as the main introduced. At present the most popular of is a key C-H RDCs, Its determination methods main is of Nuclear Single Quantum Coherent experimental (Hsqc), Commonly used of sequence Luy Professor and Development of pure with phase of pulse (Clean inphase CLIP) And pure reversed-phase of pulse (Clean antiphase CLAP). Conventional F<sub>2</sub>-Coupled HSQC Due to non-sensitive nuclear between of don't matching produce relaxation Henan Delay (INEPT) And cause is strong of dispersion reversed-phase Often will signal peak Deformation Sensitivity low Spectrum figure quality is not up to the requirements (Figure 19 (A)). If in conventional HSQC Pulse Sequence the end of the applied <sup>13</sup>C Axis 90° Pulse for compensation corresponding of delay signal The applied CLIP, Can get clear of spectrum figure (Figure 19 (B)), For overlap of Signal "With pure reversed-phase of Pulse Sequence (Clean antiphase CLAP) Also can make signal strengthen Map Simplification, Good experimental results can be obtained., To improve accuracy, F<sub>2</sub> Number of axes in 4 K Above is appropriate<sup>[94]</sup>.

But if there are more molecules H-H When there is, Line width will increase, Resolution may decrease, Especially for the cases where there are many methylene compounds such as steroids, triterpenoids and complex alkaloids., May affect the increase in coupling leading to spectral broadening, Cannot be accurately measured

RDC. Recently, Luy, Thiele And Gil Professor<sup>[112 ~ 116]</sup> Corrected pulse acquisition phase, Via F<sub>1</sub>, J-Scaled hsqc, F<sub>1</sub>, J-Scaled bird hsqc (JSB-HSQC) (Figure 20) Or Homodecoupled J-Resolved hsqc (HD-J-Hs qc) And other pulse experiments to get a more perfect map.

RDC The following principles apply to the calculation of Values: Select the previously reported or newly developed targeted media. (Gel or Liquid Crystal), Jing

H NMR After the experimental investigation of its spatial orientation ability, Diffusion of the compounds to the targeted Medium, Using appropriate NMR pulse experiments, Pre-Determination of Scalar Coupling of compounds under Isotropic Conditions (<sup>N</sup>J); Second, Under anisotropic Conditions (Weak directional Medium) Determination of Scalar Coupling

Sum of joint and dipole Coupling (Compound Coupling Value, <sup>N</sup>T), The residual dipole coupling is obtained by the difference between the two. (<sup>N</sup>D = <sup>N</sup>T - <sup>N</sup>J, General Measurement 5. More than one orthogonal <sup>N</sup>D Value, The more the better). Extracted by appropriate software calculation experiments. RDC And predict possible configurations RDC Matching (SVD Method fitting Prediction), Fitting results generally passed Q Value reflected (Q Value is <sup>N</sup>D Root mean square of measured and predicted values, Earliest Cornilescu Validation of protein structure in Liquid Crystal Media), Q Lower Value, It shows that the architecture of modeling prediction is consistent with its actual configuration, So as to establish the application RDC Analytical organic

Method for relative configuration of Small Molecules (Figure 21). For synthetic molecules or natural products whose configuration cannot be determined, Process using the above model method, Via RDC Extraction Analysis, Or Union Noe Correlation spectra and Circular Dichroism Spectra of compounds (Cd) Or rotary Chromatography (ORD) Density Functional Theory (Density functional theory, DfT) Calculation and other necessary 3D Models

: According to the above RDC Flow chart of Value Calculation, Chiral enantiomers were detected in Chiral Liquid Crystals. NMR Experiment, Determination of corresponding RDC Value, Then the two systems RDC The directional permutation tensor calculated from the value is calculated by the following formula:

Non-similarity of Tensor, The larger the value is, Beta Smaller angle, The smaller the difference is; Vice versa, The smaller the value is, Beta Larger Angle, The greater the difference. This method was used early in protein Dynamics Studies., Evaluation of the ability to differentiate. When a pair of chiral enantiomers were detected, two



sets RDC Value, Perform calculations, If you get  $\beta$  When the angle is larger, Representation of enantiomers under the action of Chiral Media, The greater the azimuth difference in the magnetic field, That is, the stronger the chiral discrimination ability of this directional Medium. Construction of Chiral Recognition Model, Theoretical and Experimental Studies on Chiral recognition mechanisms, For RDC Established

#### 4. RDC Application in structural identification of natural products

The residual dipole coupling has been successfully used in the identification of biological macromolecules such as polysaccharides, peptides, proteins and nucleic acids. It has been successfully applied to many small organic molecules. The measuring range is very wide. From simple structural molecules to very complex molecules, From rigid molecules to flexible molecules are reported one after another. In recent years, there have been further developments in the determination of the absolute configuration of natural products with high flexibility and multiple chiral centers. This section summarizes 14. Within the year (2003 ~ 2017 Year) Utilization RDC An example of Determining Natural Product Structure (Figure 22. And table 3 ), Including Utilization RDC Determination of conformation, relative configuration and absolute configuration of Natural Products.

#### 5. RDC Application in Structural Analysis of Organic Synthesis

In addition to natural product structure identification, Utilization RDC Some achievements have been made in the study of the stereochemical structure of organic synthesis or the dominant conformation of the Complex Intermediates in the reaction mechanism. Determination of relative or absolute configurations of synthetic drug molecules with different physiological activities; Involves different types of organic reactions: Different conformation forms generated by optically controlled Reactions; Gold in asymmetric allyl Alkylation

- Study on the conformation of ligand Complexes; Transition Metal Catalyzed Michael Determination of absolute configuration of addition products (Figure 23. And table 4 ).

#### 6. RDC Application of Chiral enantiomers discrimination

The development of chiral directional Media RDC The Application of anisotropic parameters is of great value. For example, the difference and Analysis of chiral small molecule isomers. Currently, PBLG/pbdg, pelg/pedg, pcbll/pcbdl As the most widely used Chiral Liquid Crystal for the study of enantiomers recognition, Early research was basically using deuterium or  $^{13}\text{C}$  Natural abundance to distinguish the enantiomers, The method requires more samples, And it takes a long sampling time, Later focused on research RDC Difference Analysis of anisotropic parameters in Chiral Media. Currently, The Research of chiral isomers is still in the stage of continuously seeking and developing excellent chiral directional media. That is, we generally use the more common rigid structure of the enantiomers mode molecules (Such IPC) Discrimination of Chiral Media as analytes, And for the water soluble directional medium is generally used L-Or D- Natural Amino acids such as alanine or proline

2013 Year Thiele Wait.<sup>[36]</sup> Using converged PBLG Polymer directional Media, Via  $F_1$ , SB-HSQC Experimental record isomers IPC And CST Two-dimensional spectrum, A key to computing them C-H Residual dipole coupling difference 7 Hz To, Its Enantiomers IPC Distinguish Angle  $27^\circ$ , And in PBLG Liquid Crystal Medium

The discrimination angle is only  $8.1^\circ$ , Successfully implemented the mapping distinction. 2016. Year Thiele Professor<sup>[170]</sup> By increasing the molecular weight of poly peptides, Add LCD

141, China Science: Chemical 2017 Years The Self-assembly Length, The synthesis of higher molecular weight PBLG And PELG, And compare the they recognition of mapping body IPC And Pinene  $\beta$ -pinene Of Ability: Pelg Liquid Crystal of recognition performance to is better PBLG Liquid Crystal. 2017 Years Thiele Professor and<sup>[171]</sup> And by Modified PBLG Or PELG The end of the ester-based structure Introduced (S)-Chiral isoprene Kiev-Based Edge chain formation of Chiral Liquid Crystal Psmblg And Psmbdg (Figure 25 ), They (-)-IPC And (-)-IPC Of Chiral Recognition  $\beta$  Angle respectively is  $16.6^\circ$  And  $23.4^\circ$ , At the same time in Psmbdg Liquid Crystal also study the natural product (-)-Curcumol Of Structure. The same year Thiele Professor

Such.<sup>[172]</sup>And development. A kind of Temperature Control of chiral poly glutamic acid Benzene Ethyl EsterPPLAAndPPDAOf TETRACHLOROETHANE Liquid CrystalOkay()-IPCAnd(-)-IPCOF Chiral Recognition $\beta$ Angle respectively43.4 °And44.3 °,When liquid crystal temperature improve120 °C WhenIts recognition effect still considerable( $\beta$ = 19.1 ° 19.8 ° )(Figure25 ).

CarageenanGlue in aqueous solution can distinguish between alanine racemic and determine glycine of latent chiralHAtomicAndlota-carageenanMedia can observe theDMSO-D<sub>6</sub>Solvent inCD<sub>3</sub>Of deuterium splittingIts properties andLuyAnd reports of GelatinGelatinChiral Medium similar.Will valine of the Mapping isomers in accordanceL-Valine/D-Valine= 1.2: 1Of Proportion diffusion into chiral gelatin inSuccess implementation. The mapping isomers of distinguish<sup>[47]</sup>.AndReinscheidSuch.<sup>[38]</sup>To polyacrylamide for basic development.(R)-AphesOr(S)-Aphes-pHGlue Chiral Media(See2.1SectionFigure6 ),Can dissolved in water and organic solvent dimethyl sulfoxide, methanol inCan achieve the organic amine of the Mapping body distinguish.Can effective distinguish between mefloquine Hydrochloride( $\beta$ = 11.3 °), Brucine alkali Hydrochloride( $\beta$ = 16.8 °), Mint Amine Hydrochloride( $\beta$ = 40.5 °)Of the mapping isomersIts mechanism may be is directional medium in containing acid group and to be measured compounds of Amino happen the weak of each other role.

2007YearsThrough relatedRDCParameters Study.(R)Or(S)-Ibuprofen

(Ibuprofen)Isomers inPBLG/CdCl<sub>3</sub>Liquid Crystal in differentThis A methods of have a or two chiral centerCan be soluble in Low Viscosity organic solvent and not crystallization precipitation of Organic Small Molecule also Application<sup>[174]</sup>.And SuryaprakashProfessor and<sup>[175,176]</sup>Use two-dimensionalC-HETSERF INAD-EQUATEEExperimental inPBLG/CdCl<sub>3</sub>Chiral Liquid Crystal inExtraction with nuclear or complex nuclear<sup>1</sup>D<sub>C-H</sub><sup>1</sup>D<sub>C-C</sub>And<sup>1</sup>D<sub>H-H</sub>AfterDFTModel CalculationClear to confirm the acrylic acid carbonate to mapping body.

## 7. Summary and Prospect

Use residual dipolar coupling construction molecular of space structure is nuclear magnetic resonance spectroscopy of, biological big molecular structure, organic analysis research field of frontier and hot. RDCParameters of Determination Methods and ApplicationRDCAnalysis Related Molecular Structure of research work at present has been vigorous development of potential.And Application residual dipolar coupling of pre-conditions is weak directional medium of Structure

So with the performance excellent of directional medium was continuous developmentMore more structure complex changeable of Organic molecular of identification bottleneck problem was gradually broken

In addition.For implementation this a kind of methods in laboratory of conventional detectionMore excellent of chiral directional media development is future development of a important orientationFor solve many new structure of absolute configuration or the mapping body excess Analysis of Determination

Provide more select.At the same time with the directional medium in detection pulse technology optimization and correctionFor solve remote residual the to the opposite sex parameters of determination provide may.And flexible molecular conformation distribution of calculation at present still with challengesLimit the currentRDCMain for rigid and semi-rigid molecularOr flexible macromolecules in the larger of the rigid fragment of analysis.However, the computer-aided of Molecular Simulation configuration and Conformation Analysis Software of DevelopmentFor flexible organic molecular of structure model of provide convenient.More imagine space of is with the artificial intelligent of DevelopmentTheRDCGlobal constraint of characteristics May be for organic molecular structure of map automatic and Structure Learning and Inference MethodsImplementationRDCTechnology in Organic Chemical field of widely set.In several yearsRDCMay become laboratory commonly used of Structure Learning application.

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