Current Opinion in Colloid & Interface Science 32 (2017) 94–107

Contents lists available at ScienceDirect

Current Opinion in Colloid & Interface Science

journal homepage: www.elsevier.com/locate/cocis

Chiral surfaces: The many faces of chiral recognition

John C. Lang *, Daniel W. Armstrong

Department of Chemistry & Biochemistry, University of Texas at Arlington, Arlington, TX 76019, United States

ARTICLE INFO

Article history:
Received 24 October 2017
Accepted 25 October 2017
Available online 7 November 2017

Keywords:
Chiral recognition
Intermolecular interaction sites
Enantiomeric chromatographic separations
Chirality in drug design
Selector surface

ABSTRACT

Molecular recognition is integral to many biological, synthetic, and supramolecular systems. Recognition is often the nexus that controls the path, kinetics, and mechanism of chemical and biochemical processes. Recognition can be static in the case of more rigid molecular environments, or dynamic in which either the selector, selector target, or both respond altering conformations in response to the local environment, or the intended partner. The recognition may be simple, with just a pair interacting, or complex with multiple partners and the pairing can be concurrent or sequential. The partnering may be at an active site or in its vicinity where not only recognition occurs, but also subsequent chemical reactivity is regulated, or distant from that location yet altering the chemical architecture in a manner seeding longer-range consequences. Because it need involve relatively few dominant interactions and structural requirements, chiral recognition is often integral to the more intricate and complex concatenated influences on the chemical landscape. In this review we have identified several forms of chiral recognition, noted their efficacy can involve combinations of chirality, and have highlighted numerous functionalities that by their complementarity encompass a wide array of applications. We conclude by suggesting the variety of means available for regulating recognition.

1. Introduction

Interest in chiral surfaces draws from awareness of the vastness of chiral influence on the specificity of biological systems, the significance of their functions, and the capacity for exploiting their utility. In recent years, considerable progress has been achieved in understanding enantioselectivity of particular protein or nucleic acid active sites, either directly from investigations of their structure, or indirectly through investigations of the dependence of efficacy on ligand energetics and molecular morphology. To put this in perspective, >2500 chiral drugs have been developed and catalogued. These span a large number of therapeutic classes including anesthetic, antibiotic, anti-cancer, anti-inflammatory, cardiovascular, CNS (central nervous system, and for other abbreviations see Table 1), hormone, ion-channel modulators, and respiratory drug classes [1]. Chirality impacts efficacy from considerations of potency at an active site to drug targeting and delivery, assessed from a drug's ADME (adsorption, distribution, metabolism, excretion) and toxicity. All of these stages can be influenced by chirality, elements attributable to multiple receptor-site controls. Investigations of chiral discrimination for multiple enzymatic classes, including oxidoreductases, transferases, hydrolases, lyases, and ligases, suggest that stereospecific constraints, beyond the simple constraint of restrictions to predominantly L-amino acids, can be highly efficient [2–4]. Functionally significant configurational changes in either a protein or its small-molecular ligand often are controlled by modifications of chiral centers. A simple example is the influence of amino acid sequence on conformation and functionality [5–7]. In other instances, a choice of ligand chirality, one enantiomer of a chiral pair, may influence efficacy, toxicity, or both, and substitution with a racemate may vary from synergistic to antagonistic. The high probability of influence on a drug's therapeutic index has led to strict governmental regulation.

Unlike more transient changes in biopolymeric architecture induced by exchangeable small molecules, ions, or even altered redox state, modifications in chirality are longer lasting. Phosphorylation, glycation, lipidation, and oxidation of disulfide bonds are biochemical modifications that are enzymatically available and reversible. The modifications are intended as dynamic means of altering protein structure or function and often engender a response to a modified environment, which can be either transient or long-term. Covalent chiral structural modifications, alternatively, appear to be design changes in protein architecture that become established, and may be incorporated in and regulated by genetic modification. A recently reported example is the genetic or epigenetic influence on an isomerase affecting the chirality of carotenoid generation and distribution [8]. The ability to recognize such chiral subtleties has contributed to the identification of unique structural targets and of new means for controlling biochemical outcomes. These outcomes range from enhancing or limiting bioactivity to empowering industrial applications [2,3,5,9].

The influence of chirality is pervasive. While vision is highly dependent on geometric isomerization of retinoids, olfaction and taste can be

* Corresponding author.
E-mail address: jclang@UTA.edu (J.C. Lang).

https://doi.org/10.1016/j.cocis.2017.10.004
1359-0294/

Table 1
Definitions & acronyms.

Acronym	Definition	Acronym	Definition
Chirality		Chromatography	
BMA	Boehm-Martire-Armstrong	CCC	countercurrent chromatography
CDA	chiral derivatizing agent	CE	capillary electrophoresis
CF6	cyclofructan with 6 fructofuranose rings	CEC	capillary electrochromatography
CIL	chiral ionic liquid	CMM	crosslinked modified micelles
CLSR	chiral lanthanide shift reagent	EOF	electroosmotic flow
CMPA	chiral mobile phase additive	ESI-MS	electrospray ionization MS
CNT	carbon nanotube	GC	gas chromatography
CS	chiral selector	HILIC	hydrophilic interaction liquid chromatography
CSA	chiral solvating agent	HPLC	high performance liquid chromatography
CSP	chiral stationary phase	HWHM	half width at half maximum
ee	enantiomeric excess	IC	ion chromatography
EF	enantiomeric fraction	k, k′	solute retention factor
er	enantiomeric ratio	LSER	linear solvation energy relationship
MWCNT	multi-walled CNT	MECC, MEKC	micellar electrokinetic chromatography
PCM	polymerized chiral micelle	MS	mass spectrometry
SWCNT	single-walled CNT	NP	normal phase
TPI	three-point interaction model	OR	optical rotation
Selectors		PCA	principal component analysis
AGP	acid glycoprotein	PI	polar ionic
BSA/HSA	bovine or human serum albumin	PO	polar organic
CD	cyclodextrin	RP	reversed phase
NEC-CD	naphthylethylcarbamoylated CD	SEC	size exclusion chromatography
QD	quinidine	SFC	supercritical fluid chromatography
QN	quinine	SPE	solid phase extraction
T	teicoplanin	TLC	thin layer chromatography
TAG	teicoplanin aglycone	α	selectivity factor, ratio of k's
V	vancomycin	Regulatory bodies	
RSP	ristocetin	CDC	US Center for Disease Control
Detectors		EMEA	European Medicines Agency
BID	barrier ionization detector	FDA	US Food & Drug Administration
CD	circular dichroism	MHRA	British Medicines & Healthcare Products Regulatory Agency
FID	flame ionization detector		
FTIR	Fourier transform infrared	Pharmaceuticals & Biosciences	
NMR	nuclear magnetic resonance	ADME	absorption, distribution, metabolism, excretion
NOE	nuclear overhauser effect	ATR	ataxia telangiectasia & Rad3 protein
NOESY	NOE spectroscopy	CNS	central nervous system
ORD	optical rotatory dispersion	DFT	density functional theory
PAD	photoarray detector	DNA	deoxyribonucleic acid
ROESY	rotating frame overhauser effect	MRSA	methicillin resistant for of *Staph a.*
TCD	thermal conductivity detector	PBP	penicillin binding protein

sensitive to the chirality of the stimulants, with R and S isomers chemically and sensually discernible. Many pheromones, for example, are chiral and sex-specific [10]. Biosensors are themselves chiral as are their ligands. Because many narcotic cationic drugs are chiral, forensics often can exploit their chirality to achieve detection, identification, and isolation [11]. In biological systems, handedness and handed preference indicate the unevenness of chiral distribution, and are suggestive of the importance of chirality. In some instances, homochirality is the rule, for example eukaryote proteins are dominated by L-amino acids, saccharides by D-sugars, nucleic acids by α-helices, and natural phospholipids by L-lecithins. The chirality of membrane lipids and alignment of surface dipoles, such as those in phosphatidyl cholines can result in surface aggregations or segregation, domain distortions from competition between dipolar and boundary tensions, and contribute to chiral discrimination [12–15]. Segregation of heterochiral glyceryl esters has been observed [14]. In other instances, diastereomeric heterochirality is the norm. Glycoproteins of physiologic significance are comprised of L-amino acids and D-sugars but their D-α-helical conformations appear to govern optical rotation [16,17]. Protein – Z-DNA complexes combine both left- and right-handed helices [18].

Recent awareness of the chiral superstructure of water surrounding DNA provides a suggestion of the transference of chirality imposed by proximal association, and the impact of thermodynamic constraints on it [19]. Combating drug resistant bacteria, such as MRSA (methicillin resistant *Staphylococcus aureus*), has required adjusting the chirality-dependent drug binding site, to complement changes in bacterial PBPs (penicillin-binding proteins) accompanying drug resistance [20]. This synthetic methodology, involving multiple modifications of previously effective derivatives of vancomycin, was devised in order to diminish drastically the rate of developing drug tolerance. The novel redesigned structures introduced heteroatoms into a now *pseudo* binding pocket domain of the aglycone, and subsequently established optimized glycation with an aryl substituted disaccharide.

Insight into the multiplicity of effects of chiral ligands has been provided by the observation of their extended influence on neighboring sites. An example of an effect on nearest neighbors is the preferentiality for the Λ and Δ stereoisomers of metal complexes dependent on ligand chirality. Noteworthy is the potential for anticipated physiological significance attributable to their influence in enzymatically active sites [21,22]. Interest in the chirality of more stable metal ion complexes, resolvable using chiral selectors, resides in their potential for therapeutic applications, involving disruption of nucleic acids, their synthesis, or function [23,24]. Structures involving chiral transition metal cofactors also can be examples of heterochirality [25–27].

Such diversity in the occurrence and application of chirality motivate this brief survey, where the focus is on manufactured and adapted chiral surfaces. An overview of types of chiral recognition is provided in the next section, and a summary of examples of primarily commercial implementation, in Table 2. This topic is followed by a review of the intermolecular interactions commonly implicated in spatial discrimination. A tabulation of examples of relative magnitudes is reported in Table 3. Numerous formats for chiral separations – including HPLC, GC, CE, SFC, IC (see Table 1 for definition of acronyms) – have contributed to our understanding of the complementarity required for chiral recognition, and