Hierarchical Multi-Scale Molecular Conformer Generation

Jiapeng Hu[1] Weizhi Gao[1] Zhichao Hou[1] Xiaorui Liu[1]
[1]North Carolina State University

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NC STATE UNIVERSITY

Outline

1. Introduction
2. MSGEN Framework
3. Experiments

Introduction

Background

Molecular conformer generation is a fundamental task in computational chemistry with applications in drug discovery, material design, and property prediction, where we predict the 3D geometry of a molecule from its 2D graph representation.

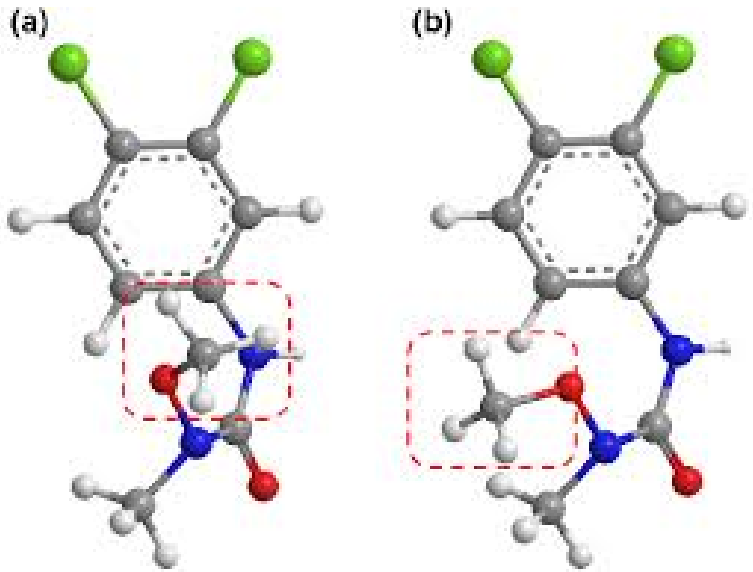


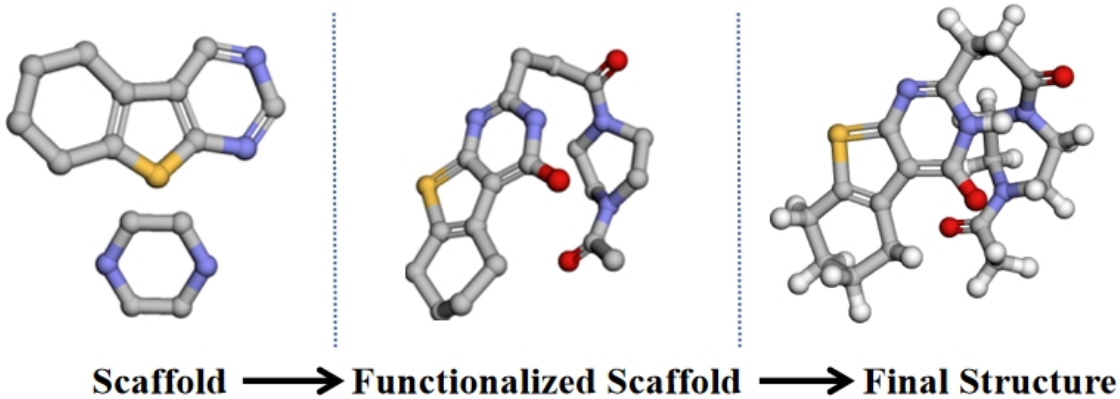
Figure: Picture from Alignment-independent technique for 3D QSAR analysis

Limitation

However, many existing methods focus on generating atomic coordinates or local geometries, such as torsion angles, while **neglecting higher-level structural information**. As a result, **they often fail to preserve essential substructures, such as ring systems, leading to chemically implausible conformers**.

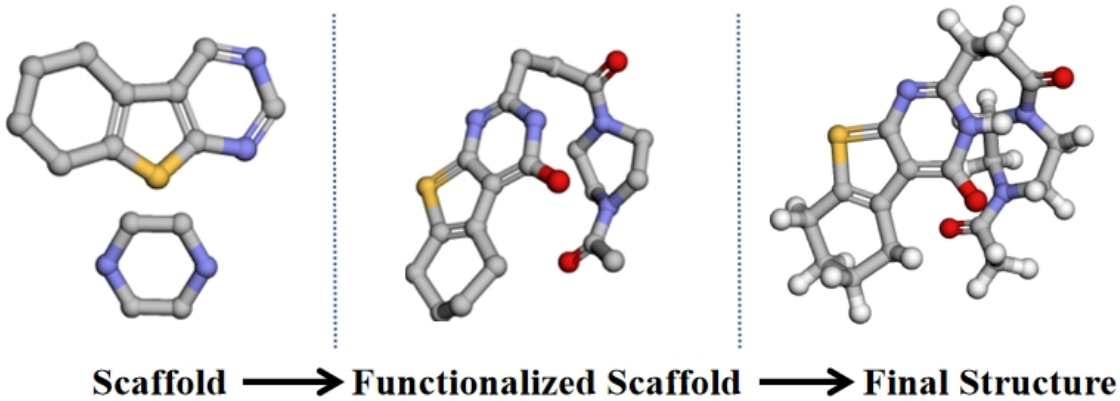
Motivation

As shown in figure, molecular structures naturally exhibit a hierarchical organization. In chemistry, this hierarchical nature reflects how molecules are assembled from basic structural motifs, such as rigid rings and flexible linkers, into complex functional architectures.



Motivation

Several methods attempt to preserve key structures either through subgraph denoising or fragment-level features. These methods improve local connectivity and fragment consistency, but **they neglect the dominant role of key structural components such as ring systems and heavy-atom backbones.**



Preliminary Study

Without explicitly constraining these key substructures, generated conformers may satisfy local validity but still deviate from realistic global arrangements. So, we assume that incorporating geometric structural guidance, such as **the positions of key substructures**, can serve as a more chemically meaningful prior.

Guidance Type	COV-R (%) ↑		MAT-R ($\mathring{A}$) ↓		COV-P (%) ↑		MAT-P ($\mathring{A}$) ↓	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Vanilla	64.12	75.56	1.1444	1.1246	43.16	42.02	1.3806	1.3314
Local	74.30	86.43	1.0003	0.9905	−−	−−	−−	−−
Fragment	84.88	94.97	0.9118	0.8788	64.74	68.19	1.1465	1.0876
Geometric(ours)	**99.58**	**100.00**	**0.5035**	**0.4899**	**88.56**	**94.70**	**0.7816**	**0.7515**

Table: Geometric Evaluation on GEOM-Drugs ($\delta = 1.25\mathring{A}$). The results show that the geometric structural guidance effectively enhances the generation quality.

MSGEN Framework

Multi-Scale Design

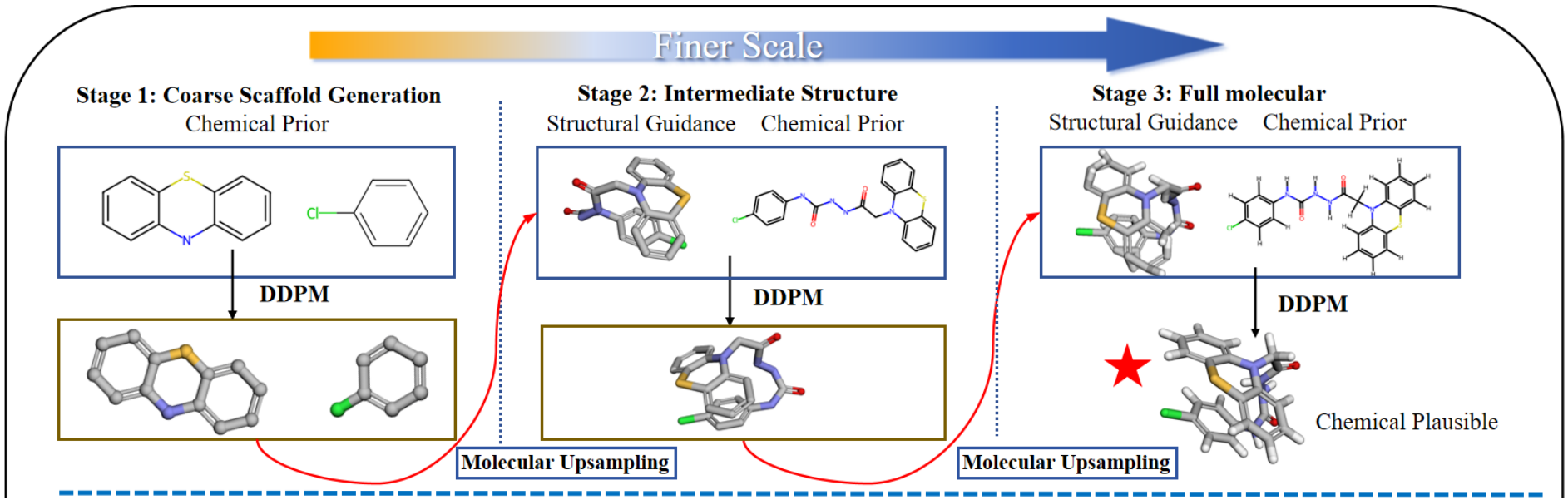


Figure: Multi-Scale Framework Design

Molecular Upsampling

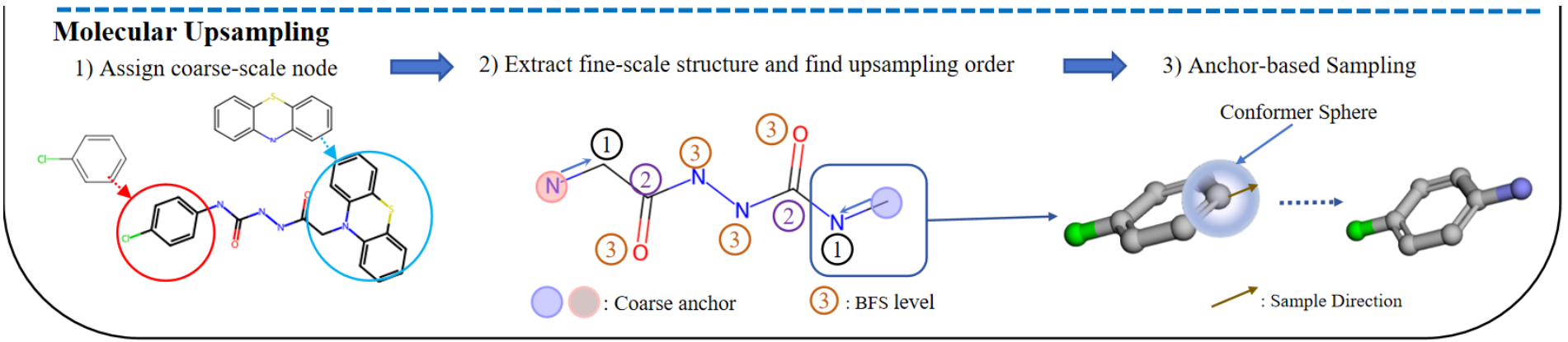


Figure: Molecular Upsampling Design

Full Pipeline

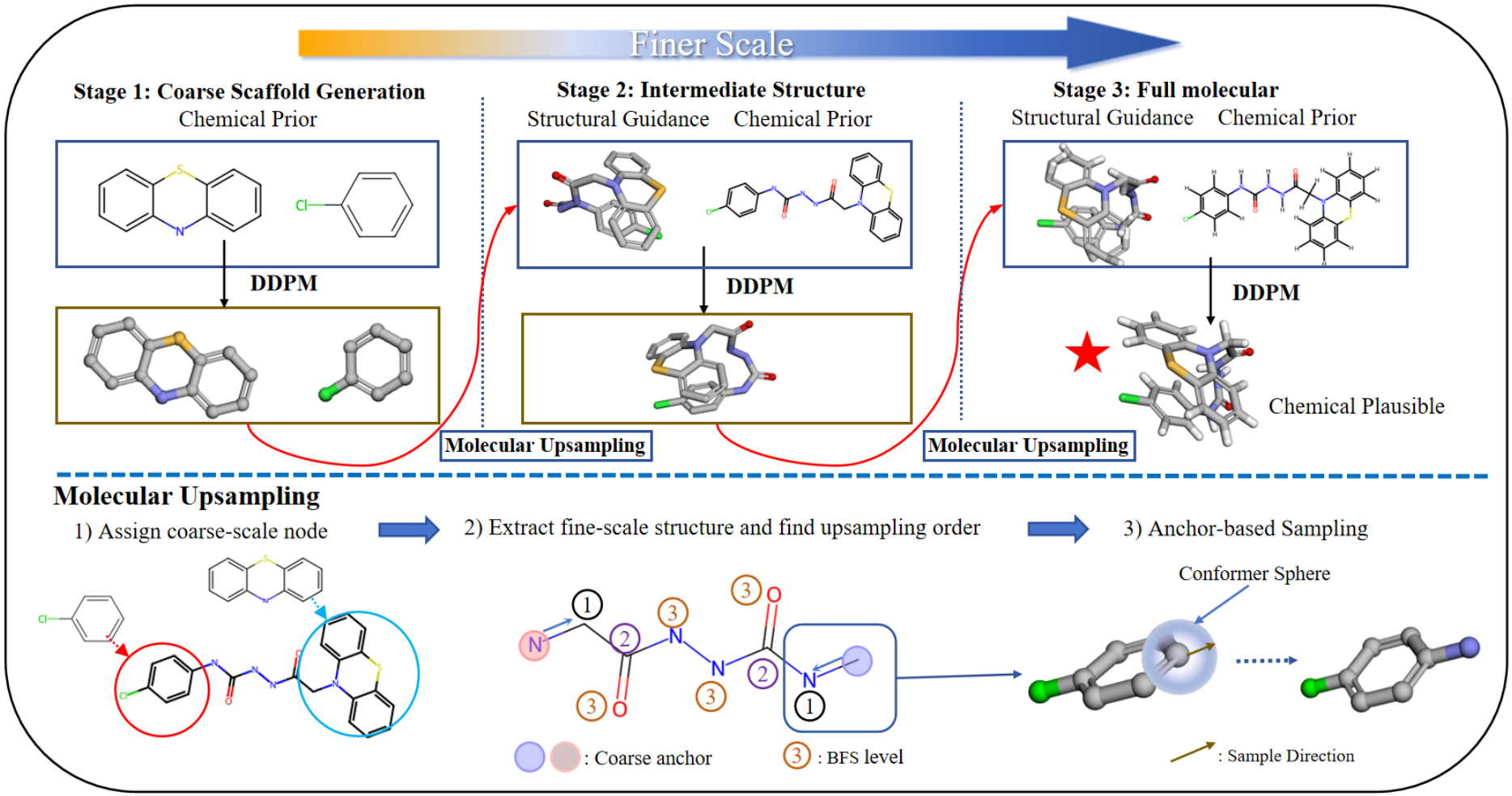


Figure: MSGEN Framework

Experiments

Setting

1. **Datasets.** We conduct our experiments on the GEOM dataset, which contains GEOM-QM9 and GEOM-Drugs.
2. **Evaluation.** We adopted the widely used Coverage (COV) and Average Minimum (AMR) metrics.
3. **Framework Setting.** Our main experiment adopts a 2-stage framework, where each molecule is divided into heavy-atom backbones and hydrogen atoms. We also contain a 3-stage generation process to demonstrate the scalability of our framework.

Geometric Evaluation

Table: Geometric evaluation on GEOM-Drugs using different baselines ($\delta = 1.25\mathring{A}$)

Models	COV-R(%) ↑		MAT-R($\mathring{A}$) ↓		COV-P(%) ↑		MAT-P($\mathring{A}$) ↓	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
RDkit	45.74	31.75	1.5376	1.4004	54.79	59.48	1.3341	1.1996
GraphDG	8.27	0.00	1.9722	1.9845	2.08	0.00	2.4340	2.4100
CGCF	53.96	57.06	1.2487	1.2247	21.68	13.72	1.8671	1.8066
ConfVAE	55.20	59.43	1.2380	1.1417	22.96	14.05	1.8287	1.8159
GeoMol	67.16	71.71	1.0875	1.0586	-	-	-	-
ConfGF	62.15	70.93	1.1629	1.1596	23.42	15.52	1.7219	1.6863
GeoDiff	87.86	97.00	0.8686	0.8545	60.17	62.21	1.1871	1.1412
GeoDiff+MSGEN	**90.41**	**98.16**	**0.8424**	**0.8248**	**66.26**	**70.65**	**1.1217**	**1.0682**

Chemical Evaluation

This task estimates the molecular *ensemble properties* over a set of generated conformers. This can provide a direct assessment of the quality of generated samples.

Method	$\bar{E}$	E_{min}	$\overline{\triangle\epsilon}$	$\triangle\epsilon_{min}$	$\triangle\epsilon_{max}$
RDkit	0.9233	0.6585	0.3698	0.8021	0.2359
GraphDG	9.1027	0.8882	1.7973	4.1743	0.4776
CGCF	28.9661	2.8410	2.8356	10.6361	0.5954
ConFVAE	8.2080	0.6100	1.6080	3.9111	0.2429
ConFGF	2.7886	0.1765	0.4688	2.1843	**0.1433**
GeoDiff	0.2597	0.1551	0.3091	0.7033	0.1909
GeoDiff+MSGEN	**0.1795**	**0.1019**	**0.2035**	**0.5898**	0.1755

Table: MAE of different physical properties between generated and ground truth ensemble properties in eV.

Framework Generalizability

To validate the generalizability of our framework in enhancing structural awareness, we integrate our framework with different generative models.

Backbone	Variant	$\delta(\AA)$	COV-R(%) ↑		MAT-R(Å) ↓		COV-P(%) ↑		MAT-P(Å) ↓	
			Mean	Median	Mean	Median	Mean	Median	Mean	Median
GeoDiff	baseline	1.25	87.86	97.00	0.8686	0.8545	60.17	62.21	1.1871	1.1412
	+MSGEN (2-stage)		90.41	98.16	0.8424	**0.8248**	66.26	70.65	1.1217	1.0682
	+MSGEN (3-stage)		**91.05**	**98.33**	**0.8410**	0.8265	**66.87**	**71.40**	**1.1147**	**1.0579**
ET-Flow	baseline	0.75	74.47	81.06	0.5514	0.5288	55.21	54.22	0.7855	0.7341
	+MSGEN (2-stage)		80.50	88.71	0.4579	0.4394	64.67	68.34	0.7342	0.6783
	+MSGEN (3-stage)		**81.91**	**89.24**	**0.4363**	**0.4280**	**66.12**	**69.51**	**0.7159**	**0.6573**
Conf-GF	baseline	1.25	62.15	70.93	1.1629	1.1596	23.42	15.52	1.7219	1.6863
	+MSGEN(2-stage)		**65.51**	**73.31**	**1.1415**	**1.1328**	**27.72**	**20.21**	**1.6986**	**1.6765**
EBD	baseline	1.25	**92.10**	98.40	0.8292	0.8391	65.97	67.95	1.1300	1.1026
	+MSGEN(2-stage)		91.92	**98.48**	**0.8257**	**0.8198**	**68.10**	**72.25**	**1.1013**	**1.0680**

Table: Geometric evaluation of applying MSGEN across different baselines on GEOM-Drugs

Takeaways

1. Hierarchical generation introduces inductive bias aligned with molecular structure.
2. Topology-aware coarse modeling simplifies complex 3D generation.
3. Structured refinement bridges geometry and chemistry.
4. Hierarchical generative modeling opens new opportunities for AI in Science.