A. Data Preprocess

Inspired by classic molecular distance geometry (Crippen et al., 1988), in our framework we also generate the conformations by taking the inter-atomic distances as the intermediate variables, which enables the invariant property to rotation and translation. In practice, the chemical bonds existing in the molecular graph are not sufficient to determine a conformation, and thus we follow existing works (Simm & Hernández-Lobato, 2020; Xu et al., 2021) to first expand the graphs by extending *auxiliary* edges. Specifically, the atoms that are 2 or 3 hops away are connected with *virtual bonds*, labeled differently from the real bonds in the vanilla molecule. These extra bonds contribute to reducing the degrees of freedom in the 3D coordinates and characterizing the unique graph, with the edges between 2-hop neighbors helping to fix the angles between atoms, and those between 3-hop neighbors fixing dihedral angles.

B. Training Algorithm

Algorithm 1 Training Algorithm of ConfVAE.

Input: objective reweighting coefficients α and λ; the inner loop optimization iterations T and learning rate η; alignment function $A(\cdot, \cdot)$; data samples $\{\mathcal{G}_t, \boldsymbol{R}_t^*\}$.

Initial: prior $p_\psi(z|\mathcal{G})$, decoder $p_\theta(\boldsymbol{R}|z, \mathcal{G})$ and its dynamics defined as g_θ, encoder $q_\phi(z|\boldsymbol{R}, \mathcal{G})$

  while θ, ϕ, ψ have not converged **do**

    $\mu, \sigma \leftarrow q_\phi(z|\mathcal{G}_t, \boldsymbol{R}_t^*)$

    $z \leftarrow \epsilon \odot \sigma + \mu$ {Reparameterization}

    $\mu_q, \sigma_q \leftarrow p_\psi(z|\mathcal{G}_t)$

    $\mathcal{L}_{prior} = \frac{1}{2}\log\frac{\sigma}{\sigma_q} - \frac{\sigma_q^2 + (\mu_q - \mu)^2}{2\sigma^2}$

    $\boldsymbol{d}^* \leftarrow \boldsymbol{R}_t^*$ {Calculate $\boldsymbol{d}$ from $\boldsymbol{R}^*$}

    $\boldsymbol{d}_0^* = D_\theta^{-1}(z, \mathcal{G}) = \boldsymbol{d}^* + \int_{t_1}^{t_0} g_\theta(\boldsymbol{d}^*(t), t, \mathcal{G}, z)\mathrm{d}t$

    $\mathcal{L}_{aux} = \log p(\boldsymbol{d}_0^*) - \int_{t_0}^{t_1}\mathrm{Tr}\left(\frac{\partial g_\theta}{\partial \boldsymbol{d}(t)}\right)\mathrm{d}t$

    Initialize $\boldsymbol{R}_0$, sample $\boldsymbol{d}(t_0) \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{I})$

    $\boldsymbol{d} = D_\theta(z, \mathcal{G}) = \boldsymbol{d}(t_0) + \int_{t_0}^{t_1} g_\theta(\boldsymbol{d}(t), t, \mathcal{G}, z)\mathrm{d}t$

    for $t = 1, 2, \cdots, T$ **do**

      $\boldsymbol{R}_{t+1} = \boldsymbol{R}_t - \eta\nabla H(\boldsymbol{R}_t, \boldsymbol{d})$ {Inner loop}

    end for

    $\boldsymbol{R} \leftarrow \boldsymbol{R}_T$

    $\mathcal{L}_{recon} = -\sum_{i=1}^{n}\sum_{j=1}^{3}(\boldsymbol{R}_{ij} - A(\boldsymbol{R}, \boldsymbol{R}^*)_{ij})^2$

    $\mathcal{L} = \mathcal{L}_{recon} + \lambda\mathcal{L}_{prior} + \alpha\mathcal{L}_{aux}$

    $\theta, \phi, \psi \leftarrow \mathrm{Adam}(\mathcal{L}; \theta, \phi, \psi)$

  end while

  return q_ϕ, p_θ, p_ψ

C. Additional Comparisons

C.1. Property Prediction

This task is first proposed in Simm & Hernández-Lobato (2020), which estimates the expected molecular properties for molecular graphs by a set of generated conformations. This task can further demonstrate the effectiveness and quality of generated samples, and is important for many real-world applications such as drug and material design.

Dataset. Following Simm & Hernández-Lobato (2020), we also employ the ISO17 dataset. More details about the dataset can be found in Sec. 4.3.

Evaluation metrics. For comparison, we calculate the ensemble properties of each molecular graph by averaging over a set of generated conformations. Specifically, we calculate the total electronic energy E_{elec}, the energy of HOMO ϵ_{HOMO} and the LUMO ϵ_{LUMO}, and the dipole moment μ, using the quantum chemical calculation package Psi4 (Smith et al., 2020). In practice, we generate 50 samples from different methods to estimate the property, and report median error of averaged properties to measure the accuracy of predicted properties. Similar to Simm & Hernández-Lobato (2020), we exclude CVGAE from this analysis due to its poor generated quality.

Results. The results are shown in Tab. 3. As shown in the table, ConfVAE outperforms all other generative models, and shows competitive results compared with RDKit. Close observation indicates that CGCF struggles with this task since the generated conformations suffer a extremely high variance. By contrast, our proposed method enjoys the best performance thanks to the high quality of generated samples.

Table 3. Median difference in averaged properties between ground-truth and generated conformations from different methods. Unit: E_{elec}(kJ/mol), ϵ_{HOMO}(eV), ϵ_{LUMO}(eV), μ(debye).

	E_{elec}	ϵ_{HOMO}	ϵ_{LUMO}	μ
RDKit	42.7	**0.08**	0.15	**0.29**
GraphDG	58.0	0.10	0.09	0.33
CGCF	208.2	0.80	1.11	0.46
ConfVAE	**40.2**	0.10	**0.08**	**0.29**

C.2. More Results of Coverage Score

In this section, we give more results about **Cov**erage score with different thresholds δ. The details about the COV score can be found in Sec. 4.2. Results are shown in Fig. 4. As shown in the figure, ConfVAE consistently achieves better performance than previous state-of-the-art models, which demonstrates our proposed method is capable to generate
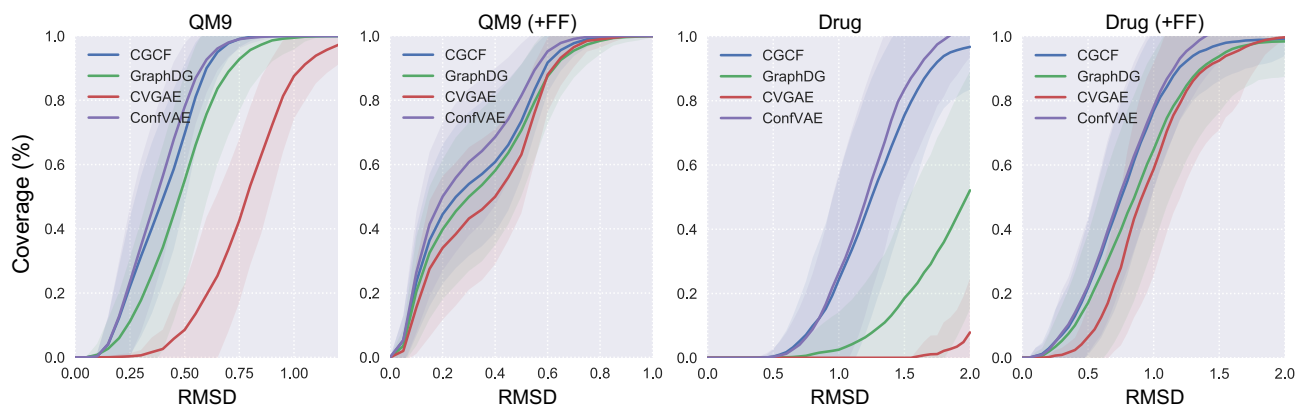
Figure 4. Curves of the **Cov**erage score with different thresholds δ on GEOM-QM9 (left two) and GEOM-Drugs (right two) datasets. The first and third curves evaluates the generated conformations from different generative models, while the other two are further optimized with the empirical force field.
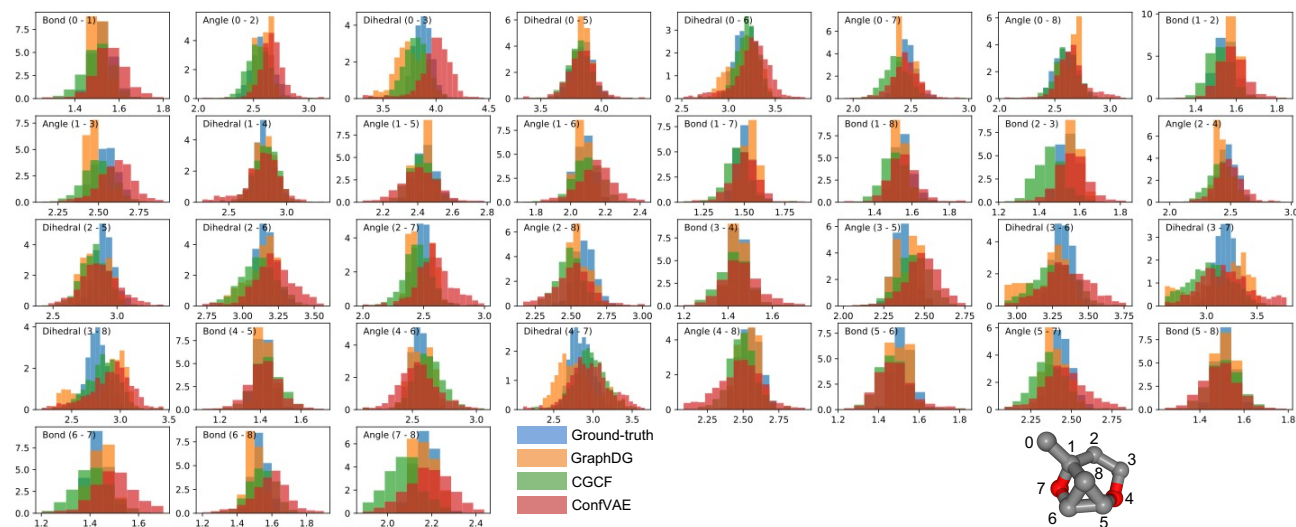

Figure 5. Marginal distributions $p(d_{uv}|\mathcal{G})$ of ground-truth and generated conformations from generative models. We study the edges between C and O atoms, and omit the H atoms for clarity. In each subplot, the annotation $(u - v)$ denotes the corresponding atoms connected by the chemical bond d_{uv}.

more realistic samples.

C.3. Visualization of Distributions

In Fig. 5, we investigate the accuracy of generated conformations by visualizing the marginal distributions $p(d_{uv}|\mathcal{G})$ for all pairwise distances between C and O atoms of a molecular graph in the ISO17 test set. As shown in the figure, though primarily designed for learning the 3D structures via an end-to-end framework, our method can still make a much better estimation of the distance distributions than the state-of-the-art model for molecular geometry modeling. As a representative element of the pairwise property between atoms, the inter-atomic distances demonstrate the capacity of our model to capture the inter-atomic interactions.