ConStruQt® by ChemAlive

High throughput quantum chemistry for molecular design

Quantum chemical accuracy (>10x improvement)

5,000 or more molecules per minute

Conformational, tautomeric and stereoisomeric analysis

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1 Introduction to ConstruQt

1.1 Motivation

ConstruQt is a member of the Qt series of web applications and APIs under development by ChemAlive SA (LLC). The Qt series delivers fully automated, hassle-free, web access to advanced quantum chemical (QC) calculations for small to medium-sized organic molecules. The tools are designed for high-throughput (HT) applications suited for analysis of large chemical libraries and for extracting trend and statistical data from collections of target compounds. The Qt series aims to displace classical mechanics and rules-based cheminformatics with quantitative predictive analytics based on modern physics and quantum chemistry. We operate under the principle - know your molecules better.

With automated and HT-QC, accurate chemical structures, molecular energies and electronic properties become available to all chemists creating a sea-change in predictability while accessing a big data regime for advanced analytics of self-consistent computed datasets. The Qt series delivers more accurate properties than classical mechanics (force field) approaches. The module ConstruQt specifically provides improved molecular structure prediction along with functionally accurate energetics and allows the sorting and prioritizing of chemical structures at a scale of thousands of molecules. From SMILES designation, one can scale structural analysis with a reliable tool having low latency, robust error management, quality control and data storage / look-up.

ConstruQt is available through an application programming interface (API) at api.chemalive.com.

1.2 Technical Description

ConstruQt is a molecular structure management tool that allows quantitative prioritization of chemical structures including tautomers, protomers, zwittomers, stereoisomers and conformers based on quantum chemical energetics. It connects web-based cheminformatics tools to advanced quantum chemistry routines, cloud infrastructure and the world's largest database of pre-computed initial guess quantum chemical data, called Qontext.

1.2.1 ConStruQt API Software/Infrastructure

The remote ConstruQt-API runs over HTTP using JSON-RPC. It connects to a backend (Scala) that manages API implementation, distributed computation scheduling and user accounts. Submitted jobs run on a 6000+ core Apache Spark computational cluster (Google Cloud Services) using spot computing nodes. Results are stored into an open PostgreSQL relational database on an RDS volume currently serving 200 M+ structures and 4 M+ molecules. The technology complex components are summarized in Figure 1 and show the various ways to access the core technology through API, Frontend, or local dockerized or compiled software.

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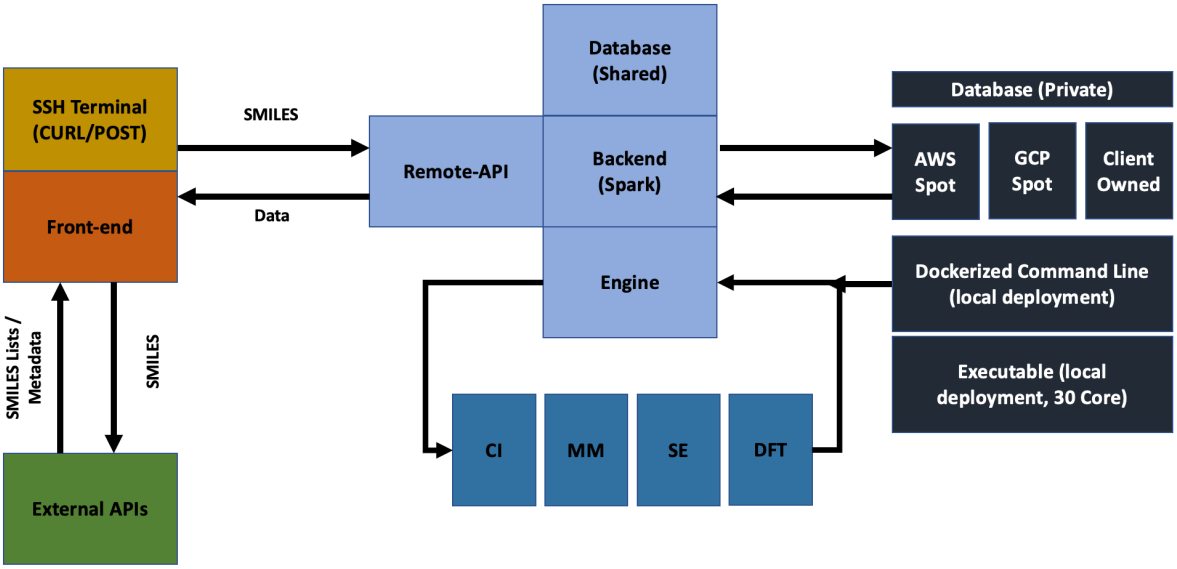


Figure 1. Technology complex for ConstruQt. Multiple access points allow flexibility in deployment.

At base, ConstruQt is a set of C++ stack (Qt) wrapper routines that employ Apache 3, ECL or ED3 license open-source software modules to perform core computational chemistry and cheminformatcs calculations. The application allows users to input list of SMILES that trigger a series of validation and set-up steps up at the cheminformatics (CI) level (relying on RDKit (version 2021.09.4) and Openbabel (2.4.9) libraries), guess 3D structures and filtering is then implemented with RDKIT (MM) and the Gromos (Kabsch-based) clustering. These structures (cluster representatives) are then passed to the PM6 semi-empirical level (using Cp2k version 9.1) of theory (QM). Structures are confirmed as minima through harmonic frequency analysis and thermal corrections provided. NWChem (version 6.8) can then provide post-Hartree-Foch *ab initio* computations (DFT).

1.2.2 ConstruQt Cluster

ConstruQt is deployed within an Apache Spark 3.2 context. It runs on both AWS and GCP spot computing nodes having 4, 8 or 16 vcpu configurations. When idling, the Cluster maintains a single worker node. Upon request the cluster will scale based on an average CPU usage threshold of 80%. A typical scaling behavior is shown in Figure 2, where the ramp up can take

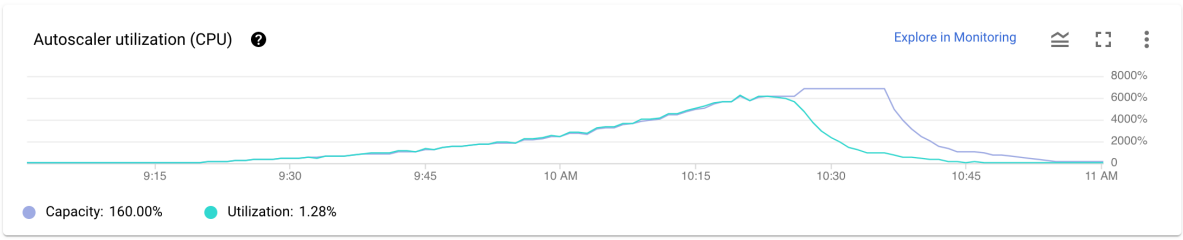
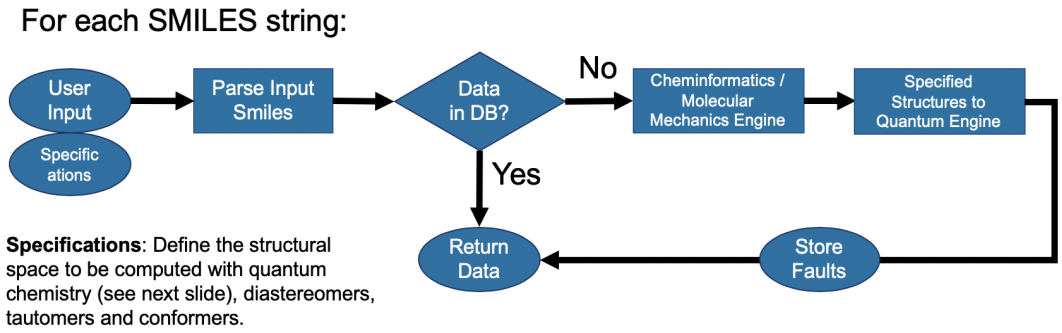


Figure 2. Scale-up and scale-in behavior on GCP based on a 500-molecule library submission running DFT single points.

some time. The use of resources is highly efficient with capacity matching usage for most of the scale-up period and scale-in occurring quickly once the jobs have been completed.

1.2.3 ConstruQt Core Algorithms

Directly from SMILES descriptions, ConstruQt manages the 2D and 3D structural description of new molecules, launches quantum chemical calculations, verifies their outcomes and stores the data. For molecules already existing in Qontext, the software returns the stored data. The top-level workflow is shown in Scheme 1.



Scheme 1. Top-level workflow of **Con**struQt Engine.

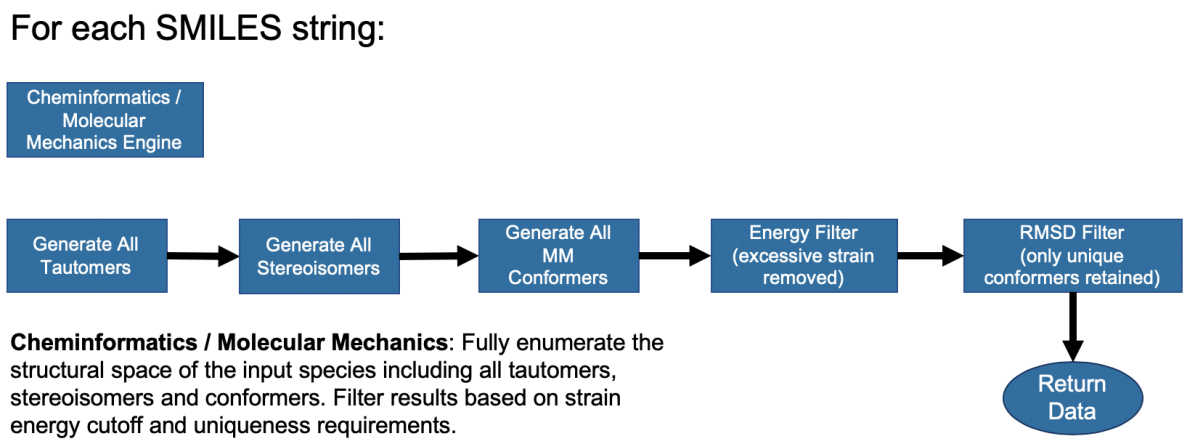
The input SMILES is processed by the Cheminformatics/Molecular Mechanics and Quantum Engines according to user specifications and quality controlled by each engine's algorithm (described below). Inputs are checked for redundancy with existing data in the ChemAlive database, Qontext.

1.2.3.1 ConstruQt Chemistry Routines

The ConstruQt default structure management routine (cheminformatics/mechanics) follows the following main steps:

(1) Conversion of input SMILES to canonical form, rejection of false inputs (e.g. salts or complexes, many metal containing molecules).
(2) Rejection of large macromolecules (current default limit is 200 characters).
(3) Enumeration of tautomeric, protomeric, zwittomeric SMILES and generation of InChI for comparison.
(4) Enumeration of stereoisomeric SMILES, removal of identical meso SMILES.
(5) Monte Carlo generation of conformations of each unique SMILES at the Universal Force Field (UFF) level using RDKIT's distance geometry method.
(6) Removal of very strained conformations, removal of identical conformations (Kabsch RMSD Distance).

These steps are represented in Scheme 2, below.

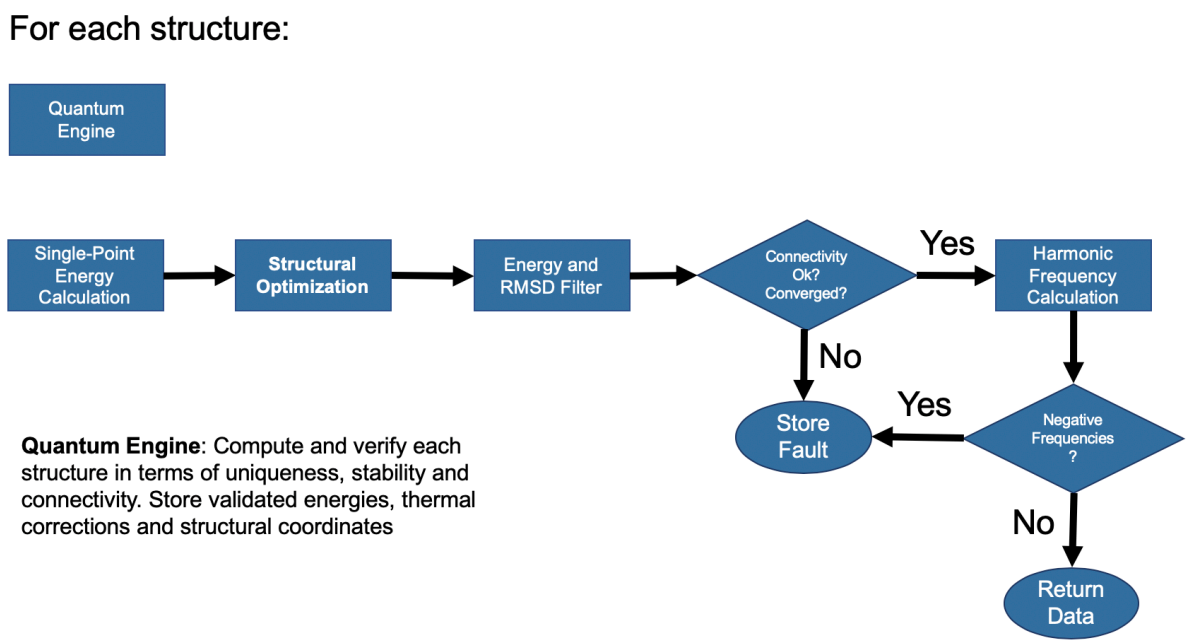


Scheme 2. Cheminformatics / Molecular Mechanics Engine workflow.

The **Con**struQt default Quantum Engine routine (quantum mechanics) follows the following main steps:

(1) Single-point calculation at the PM6 semi-empirical level on the input UFF structure.
(2) Structural optimization at the PM6 level.
(3) Removal of identical 3D structures.
(4) Validation that the molecular connectivity of the input structure is the same as the output structure.
(5) Harmonic frequency calculation at the PM6 level to obtain thermal corrections (zero-point energy, enthalpy, entropy).
(6) Validation that the obtained structure is a minimum on the potential energy surface.

The workflow is represented in Scheme 3, below.



Scheme 3. Quantum Engine workflow.

1.2.3.2 How ConstruQt Defines a Substance

The standard definition of a substance for a molecule is related to its empirically observable states in equilibrium, often in solution, where energetically accessible tautomers, distereomers (stereoisomers) and conformations comprise a substance. This definition is not compatible with computation as in order to compute a molecule, one must precisely define, which tautomer, which stereoisomers and which conformer. To further complicate the definition of substance, the protomeric state of a molecule is also a feature – protomers. Although the canonicalized SMILES format almost uniquely defines a molecule and its state, certain 'clashes' can occur in the ppm range where two different molecules may have the same SMILES string. To address this, the InChI format was developed, which has a much smaller clash rate, ppb. However, to accomplish this involves a nefarious trick. The InChI format lumps tautomers and protomers together using its own enumeration algorithm. As these types of structures are primarily responsible for the clash rate for SMILES, grouping them into a single InChI hides these clashes and causes a serious knock-on effect - InChI now defines for the user what a substance is based on a biased internal protocol designed to appeal to medicinal chemists. The InChI protocol does not work for more exotic structures, like zwitterions, or highly energetic protomeric states, that play a role in synthetic chemistry.

In order to build a comprehensive database of molecules that can be properly used for synthetic chemists and is unrestrained by conventional knowledge of what is, and what is not, an important enumerated substance structure, ChemAlive built a robust enumeration routine to completely define all states of an input molecule. While this routine maintains a few basic rules, it primarily relies on molecular energetics to discern important from unimportant structures. In addition, a substance, as defined for the Qontext database, is nothing more than the set of fully defined molecules generated by its own routine. This set can be enlarged when new input structures are found to generate previously existing molecules (substance merger). Thus, the ChemAlive approach removes all chemical 'intuition' and allows the full chemical space of a molecule to be explored and expanded, at will, into ever complex substance groups. The only remaining rules that effect tautomer (deprotonate / reprotonate) and protomer generation are as follow:

(1) We do not deprotonate sp3 carbons that are not 'allylic.'
(2) We do not deprotonate vinylic protons or protonate unsaturated positions.
(3) We do not deprotonate or protonate aromatic carbon atoms.

The API allows the user to specify the tautomer enumeration generations (tautomers of tautomers) with the default value of generationCounter being 0 (1 generation). This is usually enough to get a full list of tautomers.

1.2.3.3 How ConstruQt Manages Chirality

A molecule with a chiral center that is not defined is not computable. Unfortunately, databases are full of 'racemic' SMILES and chemists are often unconcerned with, or fail to define, stereochemistry. If ConstruQt encounters a chiral molecule that is not fully defined, but partially defined, it will attempt to maintain the defined chiral center during enumeration. Often enumeration will destroy the chirality so this is not guaranteed. If the input molecule has chiral centers not defined at all, ConstruQt will randomly assign them and return a guess structure. The allStereoisomers option will lead to full enumeration of all stereoisomers, with the limit of 10 centers. More than ten centers will lead to an explosion of calculations. In this case, resubmit your molecule with a fully defined stereochemistry.

1.2.3.4 How ConstruQt Clusters Molecules

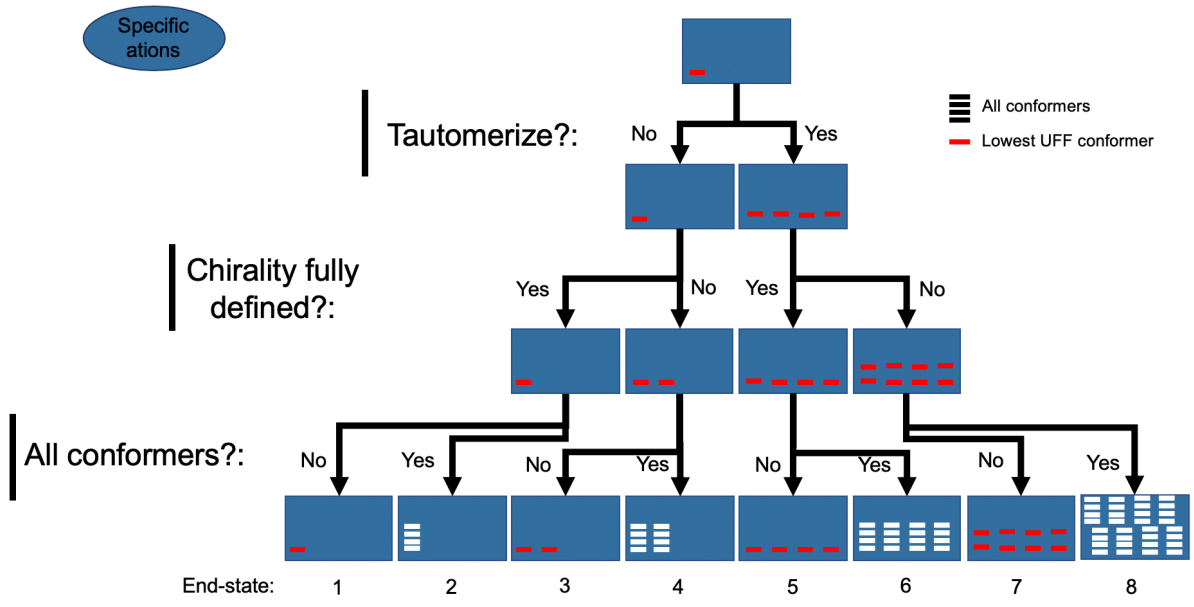
ConstruQt uses a clustering routine based on the GROMACS Gromos Kabsch clustering approach. The structures which are eventually computed with QM are not a full set of conformations but rather a set of representative structures that refer to clusters of conformations. The conformations themselves are generated with RDKit, where the target number of randomly generated conformers using the distance-geometry Monte Carlo method is 25 times the number of rotatable bonds in the molecule plus one. In this way the number of conformers generated and subsequently clustered is dependent on the flexibility of the molecule (i.e. anthracene will have always only one conformer). Once the conformer set is generated, the Gromos clustering algorithm is applied and redundant structures removed. In general, 30% of molecular mechanics conformations are spurious compared to semi-empirical conformations.

1.2.3.5 ConstruQt User Controls

Once these structures are enumerated/generated the options manage the set of structures that are passed on to the Quantum Engine (see API calls and Frontend Manual) according to user specifications. This allows the user to control the latency of the query and to select the most relevant information to process, which is necessary due to the slower speed of quantum chemical calculations. Eight End-states are accessible through two user-controlled toggles (allTautomers / allConformers) and an automatic stereoisomer check. The decision tree is as follows in Scheme 4.

The default behavior is to arrive at End-state 1 – a single structure calculated with quantum chemistry (red line). Only the user inputted molecule is computed. No tautomers are computed with QM. If the user has not fully specified all chirality in the molecule, undefined centers are guessed. If allStereoisomers is used as option, all stereoisomers (up to 10 centers) are enumerated. Finally, the lowest energy conformer, as determined by the universal force field (UFF), is selected for further quantum chemical calculation.

If the user specifies the on-state of the allConformer toggle End-state 2 will result, where all UFF conformers are passed to the Quantum Engine.



Scheme 4. User specification decision tree to arrive at End-states 1 - 8.

End-state 3 is the default behavior when the user has entered a SMILES string with an unspecified chiral center (allConformers and allTautomers are off). The lowest energy conformer for each according to UFF is returned.

End-state 4 is the result of the allConformer toggle switch on for a chirality unspecified molecule.

End-state 5 is the result of the on-state for the allTautomer toggle with off-state for the allConformer toggle with a fully specified (or achiral) input SMILES string. The tautomer options includes also the allProtomer and allZwittomer options, which further enumerate the set of microstructures.

End-state 6 results from both the allTautomer and allConformer toggle switched on for a fully specified stereoisomer (or achiral molecule).

End-state 7 is arrived at by the on-state for allTautomer toggle, off-state for the allConformer toggle and an unspecified chirality for input molecule.

End-state 8 results from an unspecified chiral molecule as input and the allTautomer and allConformer toggles switched.

In addition to these options, the user can specify allZwittomers and allProtomers to enumerate additional zwitterionic tautomers or to add +/- protomers to the substance, respectively.

Once all data is computed and stored it is possible to continue with further quantum chemical calculations using NWCHEM software that gives access to advanced electronic structure theory and properties. For bespoke follow-on routines contact info@chemalive.com.

2 ConstruQt-API Instructions

2.1 Access and Use of the API (Branding)

ConstruQt-API is currently operating in a restricted freemium configuration for tier 1 users. If you decide to deploy the API we expect that proper referrals are made to ChemAlive through a clickable company logo found here at www.chemalive.com with the subtext "For larger scale projects, more advanced calculations or bespoke projects please contact info@chemalive.com." The link should refer to the company main page, www.chemalive.com.

2.1.1 Obtaining an API Key

Access to the API is through a supplied APIkey. These keys are distributed on a case-by-case basis. Get in touch at info@chemalive.com for further information.

2.1.2 Restrictions

Currently the API is restricted to reading or submitting libraries of no more than 10,000 molecules. Submissions are restricted to molecules with less than 200 characters. For best results, organic molecules of 30-75 heavy atoms are recommended (think fragment libraries).

2.2 API Calls

2.2.1 API-Submit

API-Submit submits a set of molecules for computation. It expects two required parameters that control access and what is submitted. To define what data to compute there are five Boolean parameters. To make an API-Submit request of default routine data, one needs to send an HTTP request as follows:

* URL: https://api.chemalive.com

* Method: POST

* Headers: Content-Type: application/json-rpc

* Body:

```
{
"id":"0",
"method":"submit",
"params":{
"apiKey":"APIKEY",
"procedure": "NAME",
"substances": ["SMILES"],
"allTautomers": false,
"allConformers": false,
"allZwittomers": false,
"allProtomers": false,
"allStereoisomers": false,
"generationCounter": 0,
},
"jsonrpc":"2.0"
}
```

The APIKEY is a required parameter and will be provided upon request by contacting info@chemalive.com. In your e-mail you may already provide your own API key by generating it here: https://randomkeygen.com/

Which molecules are calculated is determined by the required "substances" parameter as a sequenced list of SMILES. Note that "substances" is plural (with an s) as it expects a list of SMILES using the JSON list format with '[]'. The list limit is 10,000 molecules, but we recommend simply looping the api request in a python or bash script as this will avoid timeouts.

To control what type of data is calculated for the input molecules there are five parameters: "allTautomers", "allConformers", "allZwittomers", "allProtomers" and "allStereoisomers." See section 1.2.1 for further description. All parameters default to 'false' if they are excluded from the query.

Here is how to perform this operation via a common CURL tool from a terminal:

```
curl -d '{"id": "0", "method": "submit", "params": {"apiKey": "APIKEY", "substances":["SMILES"],
"procedure": "UFF-PM6",  "allTautomers": true, "allConformers": true}, "jsonrpc": "2.0"} ' -H
"Content-Type: application/json-rpc" -X POST https://api.chemalive.com
```

This command is asking for PM6 calculations on UFF guess structures of all tautomers and all conformers of the molecule SMILES.

The API response will be a block text of JSON formatted data indicating the status of the query molecule: submitted, running, exists or failed like this:

```
{"jsonrpc":"2.0","result":["submitted"],"id":"0"}
```

The molecule has been submitted to the queue and is pending launch.

or,

{"jsonrpc":"2.0","result":["running"],"id":"0"}

The molecule is currently running on the cluster.

or,

{"jsonrpc":"2.0","result":["exists"],"id":"0"}

The molecule and the requested data have previously been calculated and is immediately available to be read.

or,

{"jsonrpc":"2.0","result":["failed"],"id":"0"}

The molecule has failed on submission or previously failed after submission by another user. A failure occurs for only three reasons.

1. The input SMILES is incorrect (contains bad characters) or out of scope (has a heavy metal).
2. A lateral frequency greater than -300 cm^-1 has been observed. - PM6 often can have large but chemically meaningless imaginaries up to this value. Larger than -300, they become more meaningful and so we do not return structures which are not minima.
3. The molecule has changed its connectivity during the PM6 optimization. In other words, the molecule put in is not what came out. The most common reason for this is tautomerization, although highly strained polycyclic ring systems often break as well.

Unfortunately, the API does not return specific error messages yet. If you would like to know what happened, simply e-mail info@chemalive.com.

As API-Submit queries the status of a molecule, it is recommended that the submit routine be always the initial point of entry for querying a molecule. If the molecule does not yet exist in the database it will be calculated, if it does, API-Read can be invoked to read the data (see below). A list of existing molecules for testing is provided in Table 1 below.

Table 1. Example molecules already in Qon**text** for testing of API-Read.

Name	SMILES
Nitroglycerin	C(C(CO[N+](=O)[O-])O[N+](=O)[O-])O[N+](=O)[O-]
Aspirin	CC(=O)OC1=CC=CC=C1C(=O)O
Serotonin	C1=CC2=C(C=C1O)C(=CN2)CCN
Nicotine	CN1CCCC1C2=CN=CC=C2
Clofenotane (DDT)	C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)(Cl)Cl)Cl
Camphor	CC1(C2CCC1(C(=O)C2)C)C
Glyphosphate	C(C(=O)O)NCP(=O)(O)O
Glycine	C(C(=O)O)N
Ascobic Acid (Vitamin	C(C(C1C(=C(C(=O)O1)O)O)O)O
Folic Acid	C1=CC(=CC=C1C(=O)NC(CCC(=O)O)C(=O)O)NCC2=CN=C3C(=N2)C(=O)N=C(N3)N
Lenalidomide	C1CC(=O)NC(=O)C1N2CC3=C(C2=O)C=CC=C3N
Penicillin	CC1(C(N2C(S1)C(C2=O)NC(=O)COC3=CC=CC=C3)C(=O)O)C
Morphine	CN1CCC23C4C1CC5=C2C(=C(C=C5)O)OC3C(C=C4)O
Progestin	CC1=CC2C(CCC3(C2CCC3(C(=O)C)OC(=O)C)C)C4(C1=CC(CC4)OC(=O)CCC5CCCC5)C

To use a CURL command for multiple queries using part of the list above like this:

curl -d '{"id": "0", "method": "submit", "params": {"apiKey": "APIKEY", "substances":["CC(=O)OC1=CC=CC=C1C(=O)O","C1=CC2=C(C=C1O)C(=CN2)CCN","CN1CCCC1C2=CN=CC=C2","C1=CC(=CC=C1C(C2=CC=C(C=C2)Cl)C(Cl)(Cl)Cl)Cl","CC1(C2CCC1(C(=O)C2)C)C","C(C(=O)O)NCP(=O)(O)O"], "interactive":false, "force": false, "allTautomers": false, "allConformers": false}, "jsonrpc": "2.0"}' -H "Content-Type: application/json-rpc" -X POST https://api.chemalive.com

The API response would be:

{"jsonrpc":"2.0","result":["exists","exists","exists","exists","exists","exists"],"id":"0"}

Default values are assumed when an optional parameter is missing.

2.2.2 API-Read

API-Read reads pre-existing information from the ChemAlive database, named Qon**text**. To make an API-Read request of default routine data, one needs to send an HTTP request as follows:

* URL: https://api.chemalive.com
* Method: POST
* Headers: Content-Type: application/json-rpc
* Body:

```
{
"id":"0",
"method":"read",
"params":{
"apiKey":"APIKEY",
"substances":["SMILES"],
        "procedure": "UFF-PM6",
        "sdf": false,
        "allTautomers": false,
        "allConformers": false,
        "allZwittomers": false,
        "allProtomers": false,
        "allStereoisomers": false
},
"jsonrpc":"2.0"
}
```

Where, again, the APIKEY will be provided upon request and where 'substances' is a list of molecules in SMILES format. The "procedure" value lets the user specify which procedure data is returned by JSON (see below). If this value is not included, then it will default to UFF-PM6. The current acceptable strings are in Table 2.

Here is how to perform this operation via a common CURL tool on Linux:

```
curl -d '{"id": "0", "method": "read", "params": {"apiKey": "APIKEY", "substances": ["SMILES"], "procedure": "UFF-PM6", "sdf": false}, "jsonrpc": "2.0"}' -H "Content-Type: application/json-rpc" -X POST https://api.chemalive.com
```

Do not begin queries to ConStruQt-API with a call to API-Read unless the molecules are known to exist, e.g. they are pre-computed or sample molecules (as in Table 1). To check a molecule's existence in the database use API-Submit (above).

The API-Read response will be a block text of JSON formatted data (discussed below). Post-processing of API-read JSON data can put the structural data in any desired format. Lookout for future API calls with support for other common formats. In the meantime, for SDF format choose 'true' for the "sdf" parameter, which returns the JSON block text but also a block text of the SD format of each computed structure for more facile reading of structural data into common web-based tools (e.g. JSMOL). If left out, sdf will default to 'false.'

2.2.3 Procedures

Procedure nomenclature follows the staging-method sequence for the calculation shown in Table 2, below. There are 9 stages [0-8] representing points at which data can be saved to the

Table 2. Procedures and Stages accessed by the 'procedure' option (procedures in red are not currently exposed via API, let us know if you want to use them).

Stage	Main Function	Available Methods	Procedure Names	Molecular Properties
0	Cheminformatics, enumerations, validations	Bespoke enumerations	CI	None
1	Molecular Mechanics, validation	UFF, MMFF	UFF, MMFF	3D structure, relative strain energy, structural descriptors
2	Clustering	GROMOS	--	None
3	Semi-empirical Optimization	PM6, AM1, RM1	--	None
4	Semi-Empirical Frequency Correction	PM6, AM1, RM1	UFF-PM6, MMFF-PM6	3D structure, energy, atomic charges, electronic descriptors, Infra Red spectra, HOMO and LUMO, dipole moment
5	Single-Point Ab Initio	B3LYP, PBE0,PBE96, BLYP,BHLYP,PW91,BECKEH ANDH, HF	UFF-PM6-B3LYP-SP, UFF-PM6-B3LYP-SP-D, UFF-PM6-B3LYP-SP-WATER, etc	energy, atomic charges, electronic descriptors, Infra Red spectra, HOMO and LUMO, dipole moment, NMR tensors, UV-Vis transitions
6	Optimization Ab Initio	ibid	UFF-PM6-B3LYP-OPT, UFF-PM6-B3LYP-OPT-D, UFF-PM6-B3LYP-OPT-WATER, etc	Refined 3D structure and ibid
7	Single Point after Optimization Ab Initio	ibid	UFF-PM6-B3LYP-OPT-SP, UFF-PM6-B3LYP-OPT-D-SP, UFF-PM6-B3LYP-OPT-WATER-SP, etc	Improved values of ibid
8	Optimization and Frequency CorrectionAb Initio	ibid	UFF-PM6-B3LYP-FREQ-SP, UFF-PM6-B3LYP-FREQ-D-SP, UFF-PM6-B3LYP-FREQ-WATER-SP, etc	Refined frequency correction

database or read prior to launching a new set of calculations (stage 2 and 3 are only accessible for development and testing). Thus, if one submits a calculation with "procedure": "CI" for example, only the cheminformatics enumerations will be executed, and the results saved to the database. This could be useful for assessing the total number of individual molecules that would need to be calculated at a higher level. If one submits "procedure": "UFF" for example, the universal force field 3D structural optimization using the RDkit distance geometry method will be executed providing first estimates of 3D structure. The default procedure is "UFF-PM6"

2.3 Interpreting the JSON

The API block text that is returned is in JSON format. The structure of this data and definitions of terms are provided in this section.

2.3.1 Structure of the JSON Output

What follows is a detailed description of the JSON output for a set of queries for Uracil. From a terminal, the following curl command is inputted:

```
curl -d '{"id": "0", "method": "read", "params": {"apiKey": " APIKEY", "substances":
["C1=CNC(=O)NC1=O"], "procedure": "UFF-PM6", "sdf": false}, "jsonrpc": "2.0"}' -H "Content-
Type: application/json-rpc" -X POST https://api.chemalive.com
```

The JSON response has been formatted from its block form using standard JSON tools as below. The response delivers the coordinates of the lowest energy UFF conformer of the input tautomer:

The Boltzman Section contains the Boltzmann weighted values of a number of molecular descriptors. If only one conformer is being computed, these numbers are the same as listed for that conformer.


```
[
  {
    "boltzmann": {
      "UFF": {
        "asphericity": 0.34694692967641244,
        "coreCoreRepulsionEnergy": 0.0,
        "coreHamiltonianEnergy": 0.0,
        "coulombEnergy": 0.0,
        "dipoleMagnitude": 4.68708345761393e-310,
        "eccentricity": 0.947338313241827,
        "electronicEnergy": 0.0,
        "exchangeCorrelationEnergy": 0.0,
        "fermi": 0.0,
        "heatOfFormation": 0.0,
        "hlGap": 0.0,
        "homo": 0.0,
        "inertialShapeFactor": 0.006121881877067221,
        "lumo": 0.0,
        "npr1": 0.32023447700728574,
        "npr2": 0.6797655232986453,
        "pmi1": 8.296435807957963,
        "pmi2": 235.7030680057386,
        "pmi3": 346.74172185426625,
        "radiusOfGyration": 1.7913424075580737,
        "spherocityIndex": 5.135720898246309e-10,
        "twoElectronIntegralEnergy": 0.0
      },
      "UFF-PM6": {
        "asphericity": 0.3431083051751754,
        "coreCoreRepulsionEnergy": 100301.69934983723,
        "coreHamiltonianEnergy": -56294.52974470875,
        "coulombEnergy": 0.0,
        "dipoleMagnitude": 4.586663218661433,
        "eccentricity": 0.946115517591424,
        "electronicEnergy": -134589.31287675884,
        "exchangeCorrelationEnergy": 0.0,
        "fermi": -0.203674,
        "heatOfFormation": -74.39090447306108,
        "hlGap": 0.350114,
        "homo": -0.378731,
        "inertialShapeFactor": 0.005779336773523455,
        "lumo": -0.028617,
        "npr1": 0.3238293182723143,
        "npr2": 0.6761707520591688,
        "pmi1": 8.750961284147017,
        "pmi2": 244.2972592309976,
        "pmi3": 361.295217941666,
        "radiusOfGyration": 1.8285492870213438,
        "spherocityIndex": 1.0519860249349452e-07,
        "twoElectronIntegralEnergy": -156589.5662641002
```

```
  }
},
"comment": "",
"id": 37968756947,
"inchi": "C4N2O2/7-3-1-2-5-4(8)6-3",
"nHeavyAtoms": 8,
"tautomers": [
 {
  "achiralSmiles": "O=c1cc[nH]c(=O)[nH]1",
  "charge": 0,
  "id": 262816635559,
  "molecularFormula": "C4H4N2O2",
  "molecules": [
   {
    "chiralSmiles": "O=c1cc[nH]c(=O)[nH]1",
    "conformerLinks": {
     "UFF-PM6": {
      "125398263543": [
       503644458492
      ]
     }
    },
    "conformers": {
     "UFF": [
      {
       "atoms": [
        {
         "element": "O",
         "partialCharge": 0.0,
         "valence": 0,
         "x": 2.5554,
         "y": -0.6053,
         "z": -0.116
        },
        {
         "element": "C",
         "partialCharge": 0.0,
         "valence": 0,
         "x": 1.3292,
         "y": -0.3213,
         "z": -0.0604
        },
        {
         "element": "C",
         "partialCharge": 0.0,
         "valence": 0,
         "x": 0.3781,
         "y": -1.3418,
         "z": -0.0333
        },
```


This Section contains basic molecular information

AchiralSmiles reference the tautomer whereas the chiralSmiles reference the Molecule. These may be equivalent if the molecule has no chiral centers

Atomic properties and coordinates
"atoms" section containing the coordinates for each conformer.
"partialCharge" is the atomic partial charge using the Mulliken formalism

```
{
 "element": "C",
 "partialCharge": 0.0,
 "valence": 0,
 "x": -0.9698,
 "y": -0.9932,
 "z": 0.0283
},
{
 "element": "N",
 "partialCharge": 0.0,
 "valence": 0,
 "x": -1.3328,
 "y": 0.3164,
 "z": 0.0605
},
{
 "element": "C",
 "partialCharge": 0.0,
 "valence": 0,
 "x": -0.3922,
 "y": 1.3006,
 "z": 0.0334
},
{
 "element": "O",
 "partialCharge": 0.0,
 "valence": 0,
 "x": -0.7458,
 "y": 2.51,
 "z": 0.0639
},
{
 "element": "N",
 "partialCharge": 0.0,
 "valence": 0,
 "x": 0.93,
 "y": 0.9796,
 "z": -0.0268
},
{
 "element": "H",
 "partialCharge": 0.0,
 "valence": 0,
 "x": 0.6751,
 "y": -2.383,
 "z": -0.0593
},
{
 "element": "H",
```

```
    "partialCharge": 0.0,
    "valence": 0,
    "x": -1.7269,
    "y": -1.7669,
    "z": 0.0504
   },
   {
    "element": "H",
    "partialCharge": 0.0,
    "valence": 0,
    "x": -2.3471,
    "y": 0.564,
    "z": 0.1066
   },
   {
    "element": "H",
    "partialCharge": 0.0,
    "valence": 0,
    "x": 1.6467,
    "y": 1.741,
    "z": -0.0473
   }
  ],
  "bonds": [
   {
    "firstAtom": 1,
    "secondAtom": 2,
    "stereo": 0,
    "type": 2
   },
   {
    "firstAtom": 2,
    "secondAtom": 3,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 2,
    "secondAtom": 8,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 3,
    "secondAtom": 4,
    "stereo": 0,
    "type": 2
   },
   {
    "firstAtom": 3,
```

```
    "secondAtom": 9,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 4,
    "secondAtom": 5,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 4,
    "secondAtom": 10,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 5,
    "secondAtom": 6,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 5,
    "secondAtom": 11,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 6,
    "secondAtom": 7,
    "stereo": 0,
    "type": 2
   },
   {
    "firstAtom": 6,
    "secondAtom": 8,
    "stereo": 0,
    "type": 1
   },
   {
    "firstAtom": 8,
    "secondAtom": 12,
    "stereo": 0,
    "type": 1
   }
  ],
  "chiral": false,
  "cpuTime": 0,
  "descriptor": {
```

```
      "asphericity": 0.34694692967641244,
      "boltzmannWeight": 1.0,
      "coreCoreRepulsionEnergy": 0.0,
      "coreHamiltonianEnergy": 0.0,
      "coulombEnergy": 0.0,
      "dipoleMagnitude": 4.68708345761393e-310,
      "eccentricity": 0.947338313241827,
      "electronicEnergy": 0.0,
      "exchangeCorrelationEnergy": 0.0,
      "fermi": 0.0,
      "heatOfFormation": 0.0,
      "hlGap": 0.0,
      "homoEnergy": 0.0,
      "id": 134100995222,
      "inertialShapeFactor": 0.006121881877067221,
      "lumoEnergy": 0.0,
      "npr1": 0.32023447700728574,
      "npr2": 0.6797655232986453,
      "pmi1": 8.296435807957963,
      "pmi2": 235.7030680057386,
      "pmi3": 346.74172185426625,
      "radiusOfGyration": 1.7913424075580737,
      "spherocityIndex": 5.135720898246309e-10,
      "twoElectronIntegralEnergy": 0.0
    },
    "energy": 11.128214837776504,
    "id": 503644458492,
    "irPeaks": [],
    "molecularOrbitals": [],
    "molecularTransitions": [],
    "nmrPeaks": []
  }
],
"UFF-PM6": [
  {
    "atoms": [
      {
        "element": "O",
        "partialCharge": -0.481888,
        "valence": 0,
        "x": 2.6004901002,
        "y": -0.5740069975,
        "z": -0.1168675839
      },
      {
        "element": "C",
        "partialCharge": 0.670271,
        "valence": 0,
        "x": 1.4062162483,
        "y": -0.3898354042,
```


The molecular descriptors of the conformer. Here you also have the Boltzmann weight. 1.0 because it is the only structure in the ansemble.

```
  "z": -0.0642611498
 },
 {
  "element": "C",
  "partialCharge": -0.504149,
  "valence": 0,
  "x": 0.3333069109,
  "y": -1.3773586174,
  "z": -0.0321638489
 },
 {
  "element": "C",
  "partialCharge": 0.182726,
  "valence": 0,
  "x": -0.9730715491,
  "y": -1.0258172067,
  "z": 0.0270988564
 },
 {
  "element": "N",
  "partialCharge": -0.461409,
  "valence": 0,
  "x": -1.3546235427,
  "y": 0.3195644944,
  "z": 0.0611270682
 },
 {
  "element": "C",
  "partialCharge": 0.682473,
  "valence": 0,
  "x": -0.3936247819,
  "y": 1.385653052,
  "z": 0.0351816427
 },
 {
  "element": "O",
  "partialCharge": -0.501083,
  "valence": 0,
  "x": -0.7658696257,
  "y": 2.5401485084,
  "z": 0.067215383
 },
 {
  "element": "N",
  "partialCharge": -0.579878,
  "valence": 0,
  "x": 0.9544727081,
  "y": 0.985540447,
  "z": -0.0272786336
 },
```

```
  {
   "element": "H",
   "partialCharge": 0.218588,
   "valence": 0,
   "x": 0.6566045893,
   "y": -2.419068777,
   "z": -0.0595660884
  },
  {
   "element": "H",
   "partialCharge": 0.160023,
   "valence": 0,
   "x": -1.7877181996,
   "y": -1.7616994076,
   "z": 0.0512903376
  },
  {
   "element": "H",
   "partialCharge": 0.301024,
   "valence": 0,
   "x": -2.3414456057,
   "y": 0.5853531025,
   "z": 0.1057981024
  },
  {
   "element": "H",
   "partialCharge": 0.313303,
   "valence": 0,
   "x": 1.6651876145,
   "y": 1.7318461013,
   "z": -0.0475723612
  }
 ],
 "bonds": [
  {
   "firstAtom": 1,
   "secondAtom": 2,
   "stereo": 0,
   "type": 2
  },
  {
   "firstAtom": 2,
   "secondAtom": 3,
   "stereo": 0,
   "type": 1
  },
  {
   "firstAtom": 2,
   "secondAtom": 8,
   "stereo": 0,
```

```
  "type": 1
},
{
  "firstAtom": 3,
  "secondAtom": 4,
  "stereo": 0,
  "type": 2
},
{
  "firstAtom": 3,
  "secondAtom": 9,
  "stereo": 0,
  "type": 1
},
{
  "firstAtom": 4,
  "secondAtom": 5,
  "stereo": 0,
  "type": 1
},
{
  "firstAtom": 4,
  "secondAtom": 10,
  "stereo": 0,
  "type": 1
},
{
  "firstAtom": 5,
  "secondAtom": 6,
  "stereo": 0,
  "type": 1
},
{
  "firstAtom": 5,
  "secondAtom": 11,
  "stereo": 0,
  "type": 1
},
{
  "firstAtom": 6,
  "secondAtom": 7,
  "stereo": 0,
  "type": 2
},
{
  "firstAtom": 6,
  "secondAtom": 8,
  "stereo": 0,
  "type": 1
},
```

```
  {
   "firstAtom": 8,
   "secondAtom": 12,
   "stereo": 0,
   "type": 1
  }
],
"chiral": false,
"cpuTime": 7566,
"descriptor": {
 "asphericity": 0.3431083051751754,
 "boltzmannWeight": 1.0,
 "coreCoreRepulsionEnergy": 100301.69934983723,
 "coreHamiltonianEnergy": -56294.52974470875,
 "coulombEnergy": 0.0,
 "dipoleMagnitude": 4.586663218661433,
 "eccentricity": 0.946115517591424,
 "electronicEnergy": -134589.31287675884,
 "exchangeCorrelationEnergy": 0.0,
 "fermi": -0.203674,
 "heatOfFormation": -74.39090447306108,
 "hlGap": 0.350114,
 "homoEnergy": -0.378731,
 "id": 1002387253302,
 "inertialShapeFactor": 0.005779336773523455,
 "lumoEnergy": -0.028617,
 "npr1": 0.3238293182723143,
 "npr2": 0.6761707520591688,
 "pmi1": 8.750961284147017,
 "pmi2": 244.2972592309976,
 "pmi3": 361.295217941666,
 "radiusOfGyration": 1.8285492870213438,
 "spherocityIndex": 1.0519860249349452e-07,
 "twoElectronIntegralEnergy": -156589.5662641002
},
"energy": -34286.94565921555,
"enthalpy": 61.610482175447395,
"gibbsEnergy": 42.4767632403888,
"id": 125398263543,
"irPeaks": [
 {
  "frequency": -511.457011,
  "intensity": 5539.270726
 },
 {
  "frequency": 239.248968,
  "intensity": 3050.216553
 },
 {
  "frequency": 375.180573,
```


The energies and thermal corrections of the conformer

The infrared peak position and intensity. You can see this molecule has a large lateral frequency, but it is under the threshold

```
 "intensity": 66.306694
},
{
 "frequency": 498.532526,
 "intensity": 5.865505
},
{
 "frequency": 604.851432,
 "intensity": 11.713545
},
{
 "frequency": 666.592013,
 "intensity": 37.290694
},
{
 "frequency": 790.598032,
 "intensity": 355.291355
},
{
 "frequency": 840.057839,
 "intensity": 47.23064
},
{
 "frequency": 945.526727,
 "intensity": 30.035422
},
{
 "frequency": 1032.725795,
 "intensity": 98.305883
},
{
 "frequency": 1056.067213,
 "intensity": 177.747283
},
{
 "frequency": 1105.732621,
 "intensity": 94.318631
},
{
 "frequency": 1134.338616,
 "intensity": 49.840692
},
{
 "frequency": 1159.600564,
 "intensity": 317.314437
},
{
 "frequency": 1241.963947,
 "intensity": 141.071879
},
```

```
{
 "frequency": 1269.928071,
 "intensity": 121.547409
},
{
 "frequency": 1358.303971,
 "intensity": 168.165078
},
{
 "frequency": 1430.310225,
 "intensity": 110.689322
},
{
 "frequency": 1528.156692,
 "intensity": 55.04118
},
{
 "frequency": 1546.73328,
 "intensity": 130.004632
},
{
 "frequency": 1585.334233,
 "intensity": 125.307241
},
{
 "frequency": 1657.178086,
 "intensity": 115.642054
},
{
 "frequency": 1677.832559,
 "intensity": 351.220876
},
{
 "frequency": 1886.642903,
 "intensity": 640.884772
},
{
 "frequency": 1970.848673,
 "intensity": 4893.303204
},
{
 "frequency": 2040.726703,
 "intensity": 865.278414
},
{
 "frequency": 2746.698528,
 "intensity": 90.101821
},
{
 "frequency": 2791.130766,
```

```
    "intensity": 242.482957
   },
   {
    "frequency": 2837.581705,
    "intensity": 177.877889
   },
   {
    "frequency": 2868.636646,
    "intensity": 210.622228
   }
  ],
  "molecularDipole": [
   3.93014166,
   2.36107479,
   -0.12958337
  ],
  "molecularOrbitals": [
   {
    "gaussianCube": "",
    "id": 64739441304,
    "orbEnergy": 0.207397,
    "orbIndex": 36,
    "orbOccupancy": 0.0,
    "orbType": "alphabeta"
   },
   {
    "gaussianCube": "",
    "id": 715473978927,
    "orbEnergy": 0.198691,
    "orbIndex": 35,
    "orbOccupancy": 0.0,
    "orbType": "alphabeta"
   },
   {
    "gaussianCube": "",
    "id": 99117467754,
    "orbEnergy": 0.188397,
    "orbIndex": 34,
    "orbOccupancy": 0.0,
    "orbType": "alphabeta"
   },
   {
    "gaussianCube": "",
    "id": 383601495068,
    "orbEnergy": 0.165097,
    "orbIndex": 33,
    "orbOccupancy": 0.0,
    "orbType": "alphabeta"
   },
   {
```


Molecular dipole and molecular orbitals, with type, energy and occupancy. It is possible to request a gaussian cube file be returned using a procedure with "ORB" in its name.

```
  "gaussianCube": "",
  "id": 557252240643,
  "orbEnergy": 0.156846,
  "orbIndex": 32,
  "orbOccupancy": 0.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 891857229959,
  "orbEnergy": 0.150918,
  "orbIndex": 31,
  "orbOccupancy": 0.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 274324231843,
  "orbEnergy": 0.13066,
  "orbIndex": 30,
  "orbOccupancy": 0.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 507593627399,
  "orbEnergy": 0.127135,
  "orbIndex": 29,
  "orbOccupancy": 0.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 15255334353,
  "orbEnergy": 0.116075,
  "orbIndex": 28,
  "orbOccupancy": 0.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 259030580477,
  "orbEnergy": 0.102698,
  "orbIndex": 27,
  "orbOccupancy": 0.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 195244022544,
```

```
 "orbEnergy": 0.054329,
 "orbIndex": 26,
 "orbOccupancy": 0.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 185865795533,
 "orbEnergy": 0.03493,
 "orbIndex": 25,
 "orbOccupancy": 0.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 1029975813641,
 "orbEnergy": 0.008741,
 "orbIndex": 24,
 "orbOccupancy": 0.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 175040958979,
 "orbEnergy": 0.001647,
 "orbIndex": 23,
 "orbOccupancy": 0.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 827267040032,
 "orbEnergy": -0.028617,
 "orbIndex": 22,
 "orbOccupancy": 0.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 434289103942,
 "orbEnergy": -0.378731,
 "orbIndex": 21,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 424508762202,
 "orbEnergy": -0.410352,
 "orbIndex": 20,
```

```
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 202294813228,
 "orbEnergy": -0.414443,
 "orbIndex": 19,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 383130390128,
 "orbEnergy": -0.443646,
 "orbIndex": 18,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 1709252659,
 "orbEnergy": -0.495845,
 "orbIndex": 17,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 852306719300,
 "orbEnergy": -0.538917,
 "orbIndex": 16,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 994535715610,
 "orbEnergy": -0.54416,
 "orbIndex": 15,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 874220343867,
 "orbEnergy": -0.555392,
 "orbIndex": 14,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
```

```
},
{
 "gaussianCube": "",
 "id": 409089246576,
 "orbEnergy": -0.58063,
 "orbIndex": 13,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 814952480280,
 "orbEnergy": -0.620835,
 "orbIndex": 12,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 928531913337,
 "orbEnergy": -0.624401,
 "orbIndex": 11,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 967411458709,
 "orbEnergy": -0.659722,
 "orbIndex": 10,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 1054488326612,
 "orbEnergy": -0.705961,
 "orbIndex": 9,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
 "gaussianCube": "",
 "id": 189003047071,
 "orbEnergy": -0.745789,
 "orbIndex": 8,
 "orbOccupancy": 2.0,
 "orbType": "alphabeta"
},
{
```

```
  "gaussianCube": "",
  "id": 832989266206,
  "orbEnergy": -0.859844,
  "orbIndex": 7,
  "orbOccupancy": 2.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 355774697026,
  "orbEnergy": -0.89553,
  "orbIndex": 6,
  "orbOccupancy": 2.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 44785202289,
  "orbEnergy": -1.017341,
  "orbIndex": 5,
  "orbOccupancy": 2.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 667108700508,
  "orbEnergy": -1.145205,
  "orbIndex": 4,
  "orbOccupancy": 2.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 1030532980734,
  "orbEnergy": -1.185906,
  "orbIndex": 3,
  "orbOccupancy": 2.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 673146002961,
  "orbEnergy": -1.20616,
  "orbIndex": 2,
  "orbOccupancy": 2.0,
  "orbType": "alphabeta"
},
{
  "gaussianCube": "",
  "id": 623486531648,
```

```
            "orbEnergy": -1.267901,
            "orbIndex": 1,
            "orbOccupancy": 2.0,
            "orbType": "alphabeta"
           }
          ],
          "molecularTransitions": [],
          "nmrPeaks": [],
          "sourceEnergy": -34267.3457957308,
          "zeroPointEnergy": 58.452028831557
         }
        ]
       },
       "id": 934780510075,
       "stable": true
      }
     ],
     "nAtoms": 12,
     "nHs": 4,
     "nRadicals": 0,
     "nRotationBonds": 0,
     "type": "tautomer",
     "weight": 112.027277368
    }
   ]
  }
]
```


Certain procedures will allow the computation of NMR or UV-vis spectra. Get in touch.

Three conformers are listed. If allTautomers and allConformers are both set to 'true' the JSON output will include the super set. If a molecule with chiral ambiguity is inputted, then the stereoisomers will be generated. Here is a random example to try:

```
curl -d '{"id": "0", "method": "read", "params": {"apiKey": "APIKEY", "substances": ["CCCC(C)CC"],
"procedure": "UFF-PM6", "sdf": false, "allConformers": true}, "jsonrpc": "2.0"}' -H "Content-Type:
application/json-rpc" -X POST https://api.chemalive.com
```

The JSON output now contains two SMILES, CCC[C@@H](CC)C and CCC[C@H](CC)C. If either of these is used instead for the CURL then only that stereoisomer will be returned.

2.3.2 Analysis Example: Uracil

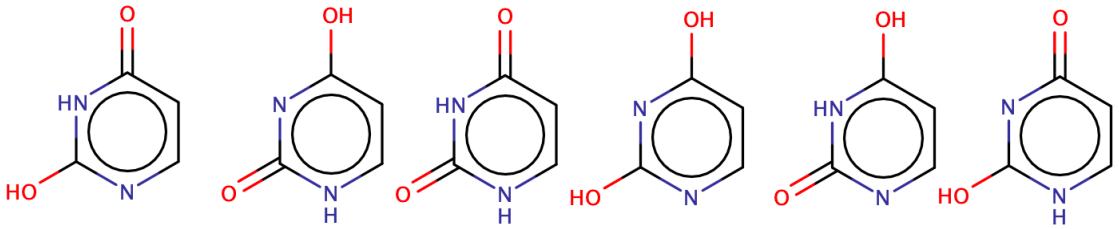
So, what do we do with all this data? **Con**struQt-API is the only game in town for automated accurate energetic assessment of tautomers and conformers on the web. We will analyze Uracil.

2.3.2.1 Uracil Tautomers

In the example above (with allTautomers), Uracil will produce 6 "chiralSmiles" listed now in Table 3, below.

Table 3. Tautomeric data extracted from the JSON

chiralSmiles	energy	gbibbsEnergy	energy + gibbsEnergy = Free-energy	Rele*tiove Free- Energy*
Oc1nccc(=O)[nH]1	-34273.36296	32.29779069	-34241.06517	12.61
Oc1cc[nH]c(=O)n1	-34272.22744	32.5279814	-34239.69946	13.98
O=c1cc[nH]c(=O)[nH]1	-34286.91865	33.23979291	-34253.67886	0.00
Oc1ccnc(n1)O	-34261.91822	31.56413815	-34230.35408	23.32
Oc1ccnc(=O)[nH]1	-34269.14405	31.71863757	-34237.42541	16.25
Oc1nc(=O)cc[nH]1	-34261.74206	31.90388754	-34229.83818	23.84



Note that Uracil does not have any chiral centers and thus, there are also 6 achiralSmiles that are identical. To extract all unique structures enumerated we look for chiralSmiles (irrespective of the existence of chirality). Each of these unique structures has undergone full conformationally analysis with the lowest structure according to UFF used to pass on to the PM6 stage. The "energy" and gibbsEnergy" values listed above are taken for the conformer with a more negative (more stable) energy value when more than one exists. To obtain the free-energy, which is corrected for entropy effects, we simply add the "energy" to "gibbsEnergy" as in column 4. To make more sense of the data we normalize against the most negative resulting value to get the Relative Free-energy in column 5. The zero value is the most stable tautomer, O=c1cc[nH]c(=O)[nH]1, according to quantum mechanical gas-phase estimates using the semi-empirical PM6 method taking into account all enumerated tautomers and conformational structures. The most stable tautomer is the structure most likely to exist in a practical setting. From the magnitude of the difference we can conclude that this tautomer would represent nearly 100% of the molecules. The large kcal/mol differences (next structure is 12.61 kcal/mol higher) are well above the kT value at room temperature and thus these other structures essentially do not exist under the model conditions. Of course, this could change in a solvent, or when embedded in a protein. Further solvent calculations are possible using density functional theory.

2.3.2.2 Uracil Conformers

Now let's take a look at the conformations. The first tautomer in Table 1 is Oc1nccc(=O)[nH]1. It has two conformations shown in Figure 1.

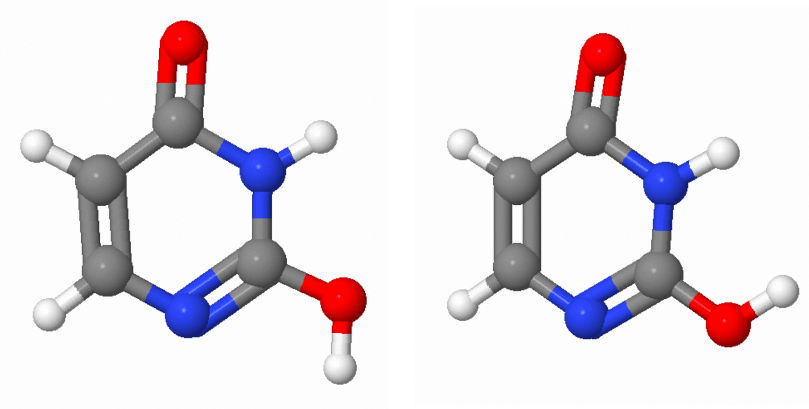


Figure 1. Relative Free-energies of the two conformers of the first tautomer of Uracil.

As uracil is conformationally simple, there are only two reasonable conformers for this tautomer, OH ‘down’ (left, 0.0 kcal/mol) and OH ‘up’ (right, 6.5 kcal/mol). OH ‘up’ is significantly less stable than OH ‘down’ mostly due to the 1,3-H---H unfavorable interaction versus the 1,3-H---N: favorable interaction. Now you know. Also, now you see why conformational analysis can be important. If we had chosen the OH ‘up’ conformer to represent this tautomer, we would have predicted that this tautomer was the fourth highest in energy in the set instead of the second. (12.61 + 6.5).

3 Terms of Service

3.1 Access to Our APIs and web applications

Subject to the restrictions below, we grant you a non-exclusive, worldwide, non-transferable (subject to the section titled "Assignment"), limited license to access our APIs and web applications and documentation (all together called SERVICES) only as necessary to develop, test and support an integration of your application (an "**Application**" or "**App**") with the Services or to perform calculations with our front-end SaaS web application. You may charge for your Application; however, you may not sell, rent, lease, sublicense, redistribute, or syndicate access to any of our Services.

3.2 Rules

Your license to access our Services is limited and subject to compliance with the Brand Guidelines above in section 2.1 where use of our APIs should refer to and link to our company website. Use of our web application for research should be properly referenced in any publications by referring to our main page www.chemalive.com. Further, you will not: (A) access our Services in violation of any law or regulation; (B) access our Services in any manner that (i) compromises, breaks or circumvents any of our technical processes or security measures associated with the Services, (ii) poses a security vulnerability to customers or users of the Services, or (iii) tests the vulnerability of our systems or networks; (C) access our APIs, web applications or documentation in order to replicate or compete with the Services; (D) attempt to reverse engineer or otherwise derive source code, trade secrets, or know-how of our APIs or Services; or (E) attempt to use our Services in a manner that exceeds rate limits, or constitutes excessive or abusive usage.

3.3 Transparency and Reporting

If you offer your Application for use by others outside your organization, you must maintain a user agreement and privacy policy for your Application, which is prominently identified or located where users download or access your Application. Your privacy policy must meet applicable legal standards and describe the collection, use, storage and sharing of data in clear, understandable and accurate terms. You must promptly notify us in writing via email to info@chemalive.com of any breaches of your user agreement or privacy policy that impact or may impact customers or users of the Services.

3.4 Privacy Policy

Our Services (including ConstruQt) connect to a single tenancy database fully owned and operated by ChemAlive. Molecules submitted by a user may be linked to that user to allow easy navigation of passed submissions, but this linkage is not publicly available. ChemAlive will collect and use data relating to the use and performance of our Services and will store all chemical data. We strongly suggest that no user submit intellectual property sensitive molecules to our Services as their structure will be integrated within our database. If the submission of sensitive molecules should become necessary, please contact info@chemalive.com and we will arrange for a private database and engage in a side contract. WE WAIVE ALL RESPONSIBILITY FOR BREACHES OF INTELLECTUAL PROPERTY SECURITY that may occur from the use of our Services – consider it as connected to an open database.

3.5 Right to Suspend Access and Audit

If we believe that there is a violation of the Contract that can simply be remedied by your modification or update of your Application, we will, in most cases, ask you to take direct action rather than intervene. In such instance, we may use your name, address and other contact details to contact you or provide this contact information to any third party that reasonably, in ChemAlive's sole determination, claims that you do not possess all of the necessary intellectual property rights. In some instances, we may directly step in and take what we determine to be appropriate action if you are not responsive, or if we believe there is a credible risk of harm to us, the Services, our customers or users or any third parties. ChemAlive also reserves a right to audit your application to ensure it does not violate our terms and policies. You agree that you will cooperate with inquiries related to such an audit and provide us with proof that your application complies with our terms and policies.

3.6 Ownership and Property Rights

You retain your ownership rights in your Application and we own and will continue to own our Services, including all related intellectual property rights therein. All of our rights not expressly granted by the Contract are hereby retained.

The more suggestions made, the better our Services become. If you send us any feedback or suggestions regarding our Services, there is a chance we will use it, so you grant us an unlimited, irrevocable, perpetual, sublicensable, transferable, royalty-free license to use any such feedback or suggestions for any purpose without any obligation or compensation to you. If we choose not to implement the suggestion, please don’t take it personally. We appreciate it, nonetheless.

3.7 Termination

You may terminate the Contract by discontinuing use of our Services. We may terminate the Contract with or without cause, and without notice to you. Upon termination of the Contract,

all rights and licenses granted to you will terminate immediately. You understand that any Services that are not made generally available but that are otherwise made available to you are the confidential information of ChemAlive. Upon termination of the Contract, you will promptly destroy copies of any documentation and any other ChemAlive information in your possession or control that was received under the Contract.

3.8 Representations; Disclaimer of Warranties

You represent and warrant that you have validly entered into the Contract and have the legal power to do so.

EXCEPT AS EXPRESSLY PROVIDED FOR HEREIN, THE APIS, DOCUMENTATION AND SERVICES AND ALL RELATED COMPONENTS AND INFORMATION ARE PROVIDED BY US ON AN "AS IS" AND "AS AVAILABLE" BASIS WITHOUT ANY WARRANTIES OF ANY KIND, AND WE EXPRESSLY DISCLAIM ANY AND ALL WARRANTIES, WHETHER EXPRESS OR IMPLIED, INCLUDING THE IMPLIED WARRANTIES OF MERCHANTABILITY, TITLE, FITNESS FOR A PARTICULAR PURPOSE, AND NON-INFRINGEMENT. YOU ACKNOWLEDGE THAT WE DO NOT WARRANT THAT THE APIS WILL BE UNINTERRUPTED, TIMELY, SECURE, OR ERROR-FREE.

3.9 Limitations of Liability

IN NO EVENT WILL OUR LIABILITY ARISING OUT OF OR RELATED TO THE CONTRACT (WHETHER IN CONTRACT OR TORT OR UNDER ANY OTHER THEORY OF LIABILITY) EXCEED CHF 100.

IN NO EVENT WILL WE HAVE ANY LIABILITY TO YOU OR TO ANY THIRD PARTY FOR ANY LOST PROFITS OR REVENUES OR FOR ANY INDIRECT, SPECIAL, INCIDENTAL, CONSEQUENTIAL, COVER OR PUNITIVE DAMAGES HOWEVER CAUSED, WHETHER IN CONTRACT, TORT OR UNDER ANY OTHER THEORY OF LIABILITY, AND WHETHER OR NOT YOU OR THE THIRD PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THE FOREGOING DISCLAIMER WILL NOT APPLY TO THE EXTENT PROHIBITED BY APPLICABLE LAW.

The limitations under this "Limitation of Liability" section apply with respect to all legal theories, whether in contract, tort or otherwise, and to the extent permitted by law. The provisions of this "Limitation of Liability" section allocate the risks under the Contract between the parties, and the parties have relied on these limitations in determining whether to enter into the Contract.

3.10 Application of Consumer Law

Our Services are intended for use by businesses and organizations and not for consumer purposes. To the maximum extent permitted by law, you hereby acknowledge and agree that consumer laws do not apply. If however any consumer laws (e.g., in Australia, the Competition and Consumer Act 2010 (Cth)) do apply and cannot otherwise be lawfully excluded, nothing in these Terms will restrict, exclude or modify any statutory warranties, guarantees, rights or remedies you have, and our liability is limited (at our option) to the replacement or repair of the Services.

3.11 Your Indemnification of Us

You will defend us from and against any and all third party claims, actions, suits, proceedings, and demands arising from or related to your violation of the Contract or your violation of your user agreement or privacy policy (a "**Claim Against Us**"), and will indemnify the ChemAlive Indemnified Parties for all reasonable attorney's fees incurred and damages and other costs finally awarded against a ChemAlive Indemnified Party in connection with or as a result of, and for amounts paid by a ChemAlive Indemnified Party under a settlement you approve of in connection with, a Claim Against Us. We must provide you with prompt written notice of any Claim Against Us and allow you the right to assume the exclusive defense and control, and cooperate with any reasonable requests assisting your defense and settlement of such matter. This section states your sole liability with respect to, and the ChemAlive Indemnified Parties' exclusive remedy against you for, any Claim Against Us.

3.12 Limitations on Indemnifications

Notwithstanding anything contained in the preceding section, (a) we will always be free to choose our own counsel if we pay for the cost of such counsel; and (b) no settlement may be entered into by you, without our express written consent (such consent not to be unreasonably withheld), if: (i) the third party asserting the claim is a government agency, (ii) the settlement arguably involves the making of admissions, (iii) the settlement does not include a full release of liability, or (iv) the settlement includes terms other than a full release of liability and the payment of money.

3.13 Survival

The sections titled "Our Rights to Suspend Access and Audit," "Ownership & Proprietary Rights," "Termination," "Representations; Disclaimer of Warranties," "Limitation of Liability," "Your Indemnification of Us," "Limitations on Indemnifications," and "Survival," as well as all of the provisions under the general heading "General Provisions," will survive any termination or expiration of the Contract.

3.14 General Provisions

(1) You grant us the right to use your company name and logo as a reference for marketing or promotional purposes on our website and in other public or private communications with our existing or potential customers, subject to your standard trademark usage guidelines as provided to us from time-to-time.

(2) Neither we nor you will be liable by reason of any failure or delay in the performance of its obligations on account of events beyond the reasonable control of a party, which may include denial-of-service attacks, a failure by a third party hosting provider or utility provider, strikes, shortages, riots, fires, acts of God, war, terrorism, and governmental action.

(3) The parties are independent contractors. The Contract does not create a partnership, franchise, joint venture, agency, fiduciary or employment relationship between the parties. There are no third-party beneficiaries to the Contract.

(4) Except as otherwise set forth herein, all notices under the Contract will be by email. Notices will be deemed to have been duly given the day after they are sent.

(5) ChemAlive is still evolving, and so we need the flexibility to occasionally make changes to our APIs, including backwards incompatible changes. We will try to give notice of these changes through email and updates to this document. Also, parts of our API are undocumented, including certain methods, events, and properties. Given that these undocumented aspects of our APIs may change at any time, you should not rely on their behaviors.

3.15 Modification to the Contract

As our business evolves, we may change these Terms and the other components of the Contract. If we make a material change to the Contract, we will provide you with reasonable notice prior to the change taking effect, either by emailing the email address associated with your account or by messaging you through the Services. You can review the most current version of the Terms at any time by downloading this document and by visiting the most current versions of the other pages that are referenced in the Contract. The materially revised Contract will become effective on the date set forth in our notice, and all other changes will become effective upon posting of the change. If you access our APIs after the effective date, that access will constitute your acceptance of any revised terms and conditions.

3.16 Waiver

No failure or delay by either party in exercising any right under the Contract will constitute a waiver of that right. No waiver under the Contract will be effective unless made in writing and signed by an authorized representative of the party being deemed to have granted the waiver.

3.17 Severability

The Contract will be enforced to the fullest extent permitted under applicable law. If any provision of the Contract is held by a court of competent jurisdiction to be contrary to law, the provision will be modified by the court and interpreted so as best to accomplish the objectives of the original provision to the fullest extent permitted by law, and the remaining provisions of the Contract will remain in effect.

3.18 Assignment

Neither party may assign or delegate any of its rights or obligations hereunder, whether by operation of law or otherwise, without the prior written consent of the other party (not to be unreasonably withheld). Notwithstanding the foregoing, either party may assign the Contract in its entirety, without consent of the other party, to a corporate affiliate or in connection with a merger, acquisition, corporate reorganization, or sale of all or substantially all of its assets. Any purported assignment in violation of this section is void. A party's sole remedy for any purported assignment by the other party in breach of this section will be, at the non-assigning party's election, termination of the Contract upon written notice to the assigning party. Subject to the foregoing, the Contract will bind and inure to the benefit of the parties, their respective successors and permitted assigns.

3.19 Entire Agreement

The Contract, including these Terms constitutes the entire agreement between the parties and supersedes all prior and contemporaneous agreements, proposals or representations, written or oral, concerning its subject matter.

4 Appendix

4.1 Web Links

URL for our front-end web applications: https://api.chemalive.com

Corporate URL: www.chemalive.com

To download this document: https://www.chemalive.com/construqt-docs/

To contact us: info@chemalive.com