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Structure Elucidation Should End With a Confidence Statement, Not a Drawing: A Cross-Modal Evidence Ledger for Constitutional, Relative, and Absolute Assignment

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ABSTRACT

Structure elucidation is commonly reported as a definitive molecular drawing even when the evidential basis for connectivity, relative configuration, and absolute configuration is uneven. This reporting convention compresses heterogeneous analytical support, model dependence, unresolved alternatives, and method-specific uncertainty into a single visual endpoint. This article develops an original analytical evidence model in which structure elucidation terminates instead in a level-specific confidence statement supported by a cross-modal structure-evidence ledger. The model separates constitutional assignment, relative configuration, and absolute configuration; records the analytical provenance of support and contradiction; distinguishes measured evidence from calculated or predicted evidence; and preserves uncertainty arising from conformational flexibility, candidate-set incompleteness, reference-database coverage, and model-domain limitations. Cross-modal agreement is treated as informative only when the contributing modalities address the same structural claim without being assumed independent by default. The proposed ledger therefore avoids a universal numerical structure-confidence score. Method-specific probabilities may be reported when their calibration and domain justify them, but broader confidence is expressed as a transparent, claim-level synthesis of evidence, alternatives, and unresolved gaps. The model is intended for both new structure assignments and retrospective structural revisions, where it can expose which parts of an assignment remain secure and which require re-evaluation. Its principal limitation is that it organizes evidence rather than validating a universal hierarchy of methods; prospective calibration, inter-rater testing, and external chemical-space evaluation are still required.

Keywords: Structure elucidation, NMR, Stereochemistry, Absolute configuration, Uncertainty, Cross-modal evidence

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Introduction

A molecular structure is not a single analytical claim. It is a bundle of propositions about elemental composition, atom connectivity, regiochemistry, stereochemical relationships, conformation, and, where relevant, absolute configuration. Yet publication practice usually collapses these propositions into one polished drawing. Computer-assisted structure elucidation (CASE) already established a different logic: spectra can be converted into constraints, candidate structures can be generated, and alternatives can be tested against the available evidence rather than accepted because a single drawing appears chemically plausible [1]. Contemporary natural-product workflows extend computer assistance across dereplication, structure elucidation, and prioritization, further increasing the number and diversity of intermediate analytical outputs that may contribute to a final assignment

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[2]. The central reporting problem is therefore no longer merely whether software participated, but which structural proposition each evidence stream actually supports.

Recent analytical models sharpen that problem. Multitask machine learning can extract substantial structural information from routine one-dimensional NMR spectra and rank plausible molecular candidates within defined chemical and data domains [3]. Separately, DP5 demonstrated that uncertainty in a proposed structure can be expressed probabilistically under a specific computational-NMR framework rather than hidden behind a binary correct/incorrect judgment [4]. These advances are important, but neither implies that all structural evidence can be converted into one universally calibrated number. A model score, a calculated chemical-shift match, a coupling constant, an electron-diffraction solution, and a chiroptical spectrum do not necessarily answer the same structural question or carry independent information.

This article therefore proposes a cross-modal structure-evidence ledger that makes the target of each evidential claim explicit. The model separates constitutional assignment, relative configuration, and absolute configuration; records supportive, contradictory, missing, and model-dependent evidence; and ends with a confidence statement for each relevant level rather than a single unqualified structure label. The proposal is analytical rather than normative: it does not claim that one modality is universally superior, that a fixed hierarchy fits every molecule, or that confidence categories are already calibrated across chemical space. Instead, it treats a structure as a set of linked claims whose evidential histories can differ. A constitution may be strongly constrained while an absolute configuration remains provisional; conversely, an absolute stereochemical observation cannot rescue an incorrect molecular graph. The framework therefore asks not only whether evidence supports "the structure," but what proposition was tested, against which alternatives, under what analytical assumptions, and with what unresolved conflict. Its purpose is to make the reasoning behind a final structure auditable and to prevent visual finality from being mistaken for evidential uniformity. This is especially important when later investigators must decide whether to accept a reported structure, reinterpret only one stereochemical element, or reopen the constitution itself.

Why a final structure can conceal unequal certainty

A complete drawing can conceal that different portions of the assignment were established to different depths. In reactive natural products, even chemical identity itself may be unstable. Chemoreactive 2,5-diketopiperazines isolated from a *Penicillium* species required structural revision alongside analysis of facile transformation pathways, showing that interconversion and sample chemistry can complicate retrospective interpretation of an apparently discrete molecular identity [5]. The relevant uncertainty is not simply "bad NMR"; it may arise because the material being measured is chemically contingent.

Published revision also demonstrates that visual completeness does not guarantee evidential completeness. Reinvestigation of metabolites from *Talaromyces stipitatus* led to revision of talaromycesone A, illustrating how a structure that has entered the literature can remain vulnerable when later analytical evidence favors a different explanation [6]. The point is not that published structures are generally unreliable, but that the drawing itself does not disclose which propositions were strongly constrained and which were inferred more tentatively.

Stereochemistry makes this asymmetry especially visible. Muanlactam required DP4+-based reassignment followed by total synthesis, showing that a constitutional framework may remain useful while the stereochemical interpretation changes [7]. Flexible natural products create a related difficulty because conformational freedom can alter observables used for stereochemical discrimination; the sanyensin study illustrates the value of integrating multiple analytical approaches when flexibility complicates stereochemical identification [8]. These cases support a proposed distinction between confidence in constitution and confidence in stereochemical assignment. They do not establish a universal ordering in which constitution is always more certain. Unequal certainty can arise from missing observations, candidate-set incompleteness, conformational multiplicity, chemical change during measurement, or the fact that a method is informative for one structural dimension but nearly silent for another. The useful question is therefore not whether the whole drawing is "confirmed," but where uncertainty resides and what evidence would resolve it. The final report should state which layer is secure, which remains conditional, and which alternatives were actually tested. In that sense, structural revision is not merely a record of error; it is evidence that structural claims can fail locally, at different levels, without every earlier observation becoming worthless.

Layers of structural assignment

The proposed model begins by separating the structural questions that evidence is being asked to answer. Constitutional assignment concerns which atoms are connected to which and includes regiochemical choices that alter the molecular graph. Automated inversion of routine NMR data can generate and rank structural candidates from spectral constraints, demonstrating that constitutional inference is increasingly amenable to computational assistance [9]. Cross-modal retrieval from ^13C NMR further shows that identification performance depends on the composition of the reference library: narrowing the candidate universe can improve retrieval, but the resulting rank remains conditional on what the library contains [10]. A retrieved candidate is therefore evidence for constitution, not proof that all alternatives have been excluded.

Relative configuration asks how stereogenic elements are related without necessarily establishing their absolute handedness. Residual dipolar couplings provide solution-state three-dimensional constraints capable of discriminating candidate stereostructures [11]. J-DP4 similarly integrates scalar-coupling information with chemical-shift-based probability, demonstrating that couplings and shifts contribute nonidentical stereochemical information [12]. These methods justify recording relative configuration as a distinct evidential layer rather than allowing a constitutional assignment to imply stereochemical completion.

Absolute configuration introduces an additional claim: which enantiomeric arrangement corresponds to the sample. Experimental chiroptical comparison by vibrational circular dichroism and diffraction-based analysis by MicroED provide distinct stereo-sensitive routes for testing such assignments when their respective sample and method requirements are satisfied [13, 14]. Neither method is universally applicable, and neither should be treated as interchangeable with relative-configuration evidence.

The resulting classification is summarized in **Table 1**. It is proposed as a reporting architecture, not as a fixed hierarchy of analytical superiority.

Table 1. Proposed classification of structural assignment layers and the evidence questions they require

Assignment layer	Core question	Evidence role	Typical unresolved problem	Confidence statement should disclose
Constitution	Is the molecular graph and regiochemistry adequately constrained?	Connectivity-sensitive spectra, candidate generation, retrieval, chemical logic	Alternative graphs remain compatible; candidate absent from library	Candidate space tested, decisive constraints, residual constitutional alternatives
Relative configuration	Are stereogenic elements related correctly within the proposed constitution?	Couplings, spatial NMR constraints, stereochemical calculations, comparison among diastereomers	Conformer ambiguity or weak discrimination among stereoisomers	Stereochemical alternatives considered, conformational assumptions, discriminating observations
Absolute configuration	Is the handedness of the assigned stereostructure established?	Chiroptical evidence, diffraction, or other absolute-stereochemistry-sensitive analysis	Enantiomer unresolved; method/sample suitability limited	Direct versus inferential basis, model dependence, remaining enantiomeric ambiguity
Cross-layer consistency	Do the separately supported layers coexist in one chemically coherent assignment?	Reconciliation across modalities and structural hypotheses	One layer conflicts with another or depends on the same underlying model	Contradictions, dependencies, and which layer limits the final claim

Cross-modal evidence and contradiction

Once the structural layers are separated, evidence must be reconciled without pretending that all modalities are commensurate. Quantum-chemical NMR calculations are powerful precisely because they convert proposed structures into predicted observables that can be compared with experiment, but their results depend on conformational sampling, electronic-structure method, solvent treatment, and other protocol choices [15]. Agreement between calculated and experimental shifts is therefore model-conditioned support. It is not a second experimental measurement.

Automation does not remove this dependence. DP4-AI demonstrates that NMR processing, computation, and probabilistic candidate evaluation can be integrated into an automated workflow [16]. ML-J-DP4 similarly combines quantum-mechanical and machine-learning elements to accelerate stereochemical discrimination using

chemical shifts and coupling information [17]. Such systems can make comparison more systematic, yet their outputs still depend on candidate definition, representation, and the validity of the underlying approximations. In the proposed ledger, automation changes provenance and efficiency; it does not erase epistemic conditions.

The same discipline is needed when a method addresses absolute configuration. A ^19F NMR-guided machine-learning approach can predict absolute configuration for carboxylic acids within its defined derivatization and analytical domain [18]. That result supports domain-specific predictive evidence, not a general claim that machine learning can determine absolute configuration for arbitrary molecules. Confidence language must therefore travel with the assay and chemical-space boundary that made the prediction meaningful.

Cross-modal concordance is most valuable when modalities contribute genuinely complementary information. A unified benchmark for deep-learning NMR chemical-shift prediction shows how apparent performance can change with dataset construction and evaluation domain, cautioning against treating model agreement as intrinsically transferable [19]. By contrast, combining ^1H NMR and infrared spectroscopy can improve automated structure verification because the two modalities encode different molecular features [20]. The proposed ledger consequently records both concordance and dependence. Agreement strengthens a structural claim when the evidence streams are relevant and sufficiently distinct; contradiction triggers reinspection of candidates, measurements, calculations, or sample identity. Missing evidence is recorded separately and is never converted into contradiction.

This distinction matters because a contradiction is an active diagnostic event: it may indicate the wrong candidate, a misassigned signal, an inadequate conformational ensemble, a calculation failure, sample heterogeneity, or a mismatch between reference conditions and the measured material. The ledger should preserve that conflict rather than averaging it away. Conversely, concordance between two outputs derived from the same candidate set or computational assumptions should not be counted as two independent confirmations. Cross-modal synthesis is therefore an exercise in evidential reconciliation, not vote counting.

A structure-evidence ledger

A confidence statement requires more than a list of techniques. It requires an explicit account of what each observation bears on, how the observation was generated, which alternatives were tested, and what could still defeat the assignment. This need is clear in computational NMR. Critical evaluation of DP4+ has shown that apparently decisive probabilities can be distorted by candidate omission, inappropriate conformational treatment, or incorrect computational practice [21]. The proposed structure-evidence ledger therefore treats a probability, similarity score, or rank as a method output with stated assumptions, not as a transferable measure of chemical truth.

Modern models add further reasons to preserve provenance. NMRMind maps multidimensional NMR information into structural predictions, demonstrating that learned representations can extract relationships that are cumbersome to encode manually [22]. Such an output is evidentially useful, but it remains distinct from the experimental spectrum from which it was inferred. The ledger consequently separates measured observations, processed features, calculated observables, model-generated candidates, and interpretive judgments. This prevents a downstream prediction from being silently recounted as an independent upstream observation.

Recent automated systems reinforce this distinction. NMR-Solver combines large-scale spectral matching with physics-guided fragment optimization, whereas SECS integrates multimodal spectral information with structure search and contextualized confidence or ranking outputs [23, 24]. Their value lies partly in making candidate comparison more systematic, not in establishing a universal definition of confidence. A flexible multispectral model likewise shows that the available modality set can vary across problems [25]. Accordingly, “not measured,” “uninformative,” “contradictory,” and “supportive” are separate ledger states.

The proposed ledger has four functions: claim decomposition, evidence provenance, contradiction handling, and confidence synthesis. Each structural claim is linked to the evidence that directly interrogates it; dependencies among evidence streams are noted; alternatives remain visible until excluded; and unresolved conflicts are carried forward rather than averaged away. A further ledger field concerns evidential dependence. Two outputs should not receive the rhetorical force of two confirmations merely because they are displayed separately. If both depend on the same assigned peaks, conformer ensemble, training distribution, or candidate list, their concordance is partly inherited. Conversely, a disagreement between genuinely different observables can be disproportionately informative because it identifies a claim that has not survived cross-examination. The ledger therefore records the

reason evidence streams are considered complementary and identifies the structural layer at which a conflict occurs. This makes the confidence statement reconstructable rather than impressionistic.
Table 2 converts that logic into a comparative analytical matrix.

Table 2. Proposed structure-evidence ledger states for cross-modal structural reasoning

Ledger state	Analytical meaning	Required record	Interpretation rule
Direct support	Observation discriminates the focal structural claim	Modality, observable, candidate comparison	Strengthens only the claim actually tested
Conditional support	Support depends materially on model, conformer, library, or assay domain	Dependency and applicability condition	Cannot be promoted to unconditional confirmation
Contradiction	Observation is inconsistent with the favored assignment	Conflicting datum and plausible causes	Triggers reinspection rather than averaging
Missing evidence	Relevant experiment or modality was not acquired	Missing item and reason if known	Must not be treated as negative evidence
Dependent concordance	Multiple outputs share data, model, candidates, or assumptions	Shared dependency	Agreement is not counted as independent replication
Residual alternative	Plausible competing structure remains compatible	Alternative and unresolved discriminator	Confidence remains bounded until adjudicated

The complete architecture is summarized in **Figure 1.** It is intentionally non-numerical: the figure shows where evidence is accumulated, where contradiction returns the analysis to earlier claims, and where a final confidence statement remains bounded by reporting and validation requirements.

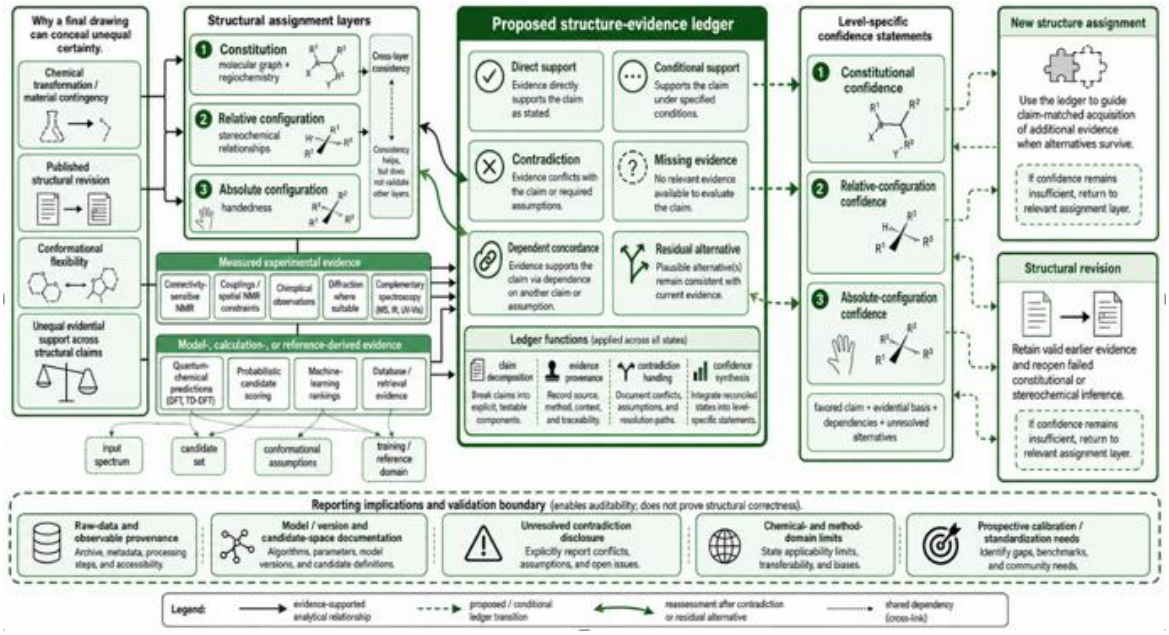

Figure 1. From structural drawing to claim-level confidence: a proposed cross-modal evidence-ledger architecture

Confidence statements for different levels of assignment
A confidence statement should communicate both the strength and the scope of the inference. Reviews of machine learning in NMR emphasize that performance depends on task definition, data quality, representation, and validation design [26]. For structure elucidation, this means that "high confidence" is uninformative unless the reader knows whether it refers to a molecular graph, a relative stereochemical relationship, an absolute configuration, or merely a model's ranking among supplied candidates.
The proposed model therefore uses level-specific statements rather than a single global verdict. A constitutional statement should identify whether competing graphs were explicitly considered and which observations discriminate them. A relative-configuration statement should identify the stereochemical alternatives and the

conformational or coupling assumptions that matter. An absolute-configuration statement should specify whether the assignment rests on direct stereo-sensitive measurement, model-assisted interpretation, chemical correlation, or another bounded route. Where a calibrated method-specific probability exists, it may be reported as that method's output; it should not be converted into a universal cross-modal probability.

Level-specific reporting also avoids a misleading weakest-link rule. An unresolved absolute configuration should limit claims about absolute configuration, but it need not erase strong evidence for constitution. Equally, secure absolute stereochemical evidence cannot compensate for a molecular graph that was never adequately discriminated. The confidence statement should therefore preserve both the strongest established layer and the layer that remains limiting. This produces a more informative endpoint than either a single global label or a practice of downgrading the entire structure to the least certain component.

Confidence also depends on re-auditability. High-precision coupling constants and access to raw NMR data preserve structural information that can be lost when observations are rounded, summarized, or detached from the underlying spectrum [27]. The proposed confidence statement therefore includes not only the favored assignment but also its evidential basis, unresolved alternatives, and major dependencies. This is deliberately more demanding than labels such as "confirmed" or "tentative," yet less presumptive than an invented numerical scale.

The model does not require identical language for every compound. If constitution is secure but absolute configuration is unresolved, the statement should say exactly that. If one stereochemical conclusion is supported by several outputs derived from the same calculations, dependence should be disclosed. If an orthogonal experiment contradicts an otherwise strong computational consensus, the contradiction should remain visible until resolved. Confidence is thus treated as a property of a specified structural claim under specified evidence, not as an intrinsic property of the drawing.

Use in new structures and structural revisions

For a newly isolated compound, the ledger begins before the final structure is fixed. Early database matching can efficiently identify known or closely related natural products, as demonstrated by ^13C NMR- and HSQC-based dereplication platforms such as ReCQC [28]. Such matching narrows the problem, but it does not establish that a truly novel constitution has been proven. The ledger therefore records whether a candidate arose through dereplication, de novo constraint satisfaction, computation, or another route, and then asks what independent evidence tests the resulting claim.

The same architecture is useful retrospectively. In a revision, the original assignment should not be treated as a single object that becomes wholly "wrong." Reanalysis may preserve the molecular formula and most connectivity while changing one regiochemical or stereochemical element; alternatively, chemical transformation may undermine assumptions about material identity. Chemoreactive diketopiperazines illustrate how transformation can complicate identity and revision [5]. Talaromycesone A shows that later analytical interpretation can alter an established structural assignment [6]. Muanlactam demonstrates stereochemical reassignment supported by computation and synthesis [7]. Sanyensin illustrates the distinct challenge posed by conformationally flexible natural products [8]. A revision ledger therefore identifies which evidence survives, which interpretation fails, and which new observation adjudicates the disputed layer.

Validation should also be matched to the unresolved claim. MicroED can be decisive when a suitable crystal addresses a crystallographic or absolute-stereochemical problem [14]. Multimodal verification using ^1H NMR and infrared spectroscopy addresses a different kind of candidate discrimination [20]. Adding more techniques indiscriminately is not the objective; acquiring evidence that interrogates the remaining uncertainty is. For prospective work, this logic can guide additional experiments without pretending to optimize them universally. The next analytical step is the one expected to discriminate the surviving alternatives at the uncertain layer, subject to sample availability and method suitability.

Table 3 summarizes the proposed decision logic for applying the ledger prospectively and retrospectively.

Table 3. Proposed decision logic for new assignments and structural revisions

Decision state	Primary question	Recommended ledger action	Stop condition
Candidate generation	What structures remain compatible?	Record origin and candidate space	Plausible set defined
Constitutional adjudication	Which graph best fits direct constraints?	Compare decisive connectivity evidence	Residual graph alternatives disclosed

Stereochemical adjudication	Which relative or absolute alternatives remain?	Add claim-matched stereo-sensitive evidence	Remaining ambiguity stated
Contradiction	Which observation conflicts, and why?	Recheck sample, assignment, model, and candidate assumptions	Conflict resolved or retained explicitly
Revision	Which earlier claim changed?	Preserve valid evidence; isolate failed inference	Revised layer and basis documented
Final reporting	What is supported now?	Issue separate confidence statements by level	Evidence, dependencies, and gaps auditable

Reporting implications

Reporting should preserve enough information for another analyst to reconstruct why the final assignment was favored. Large experimental resources such as NMRexp, which aggregates millions of experimental spectra, illustrate both the opportunity created by reusable spectral data and the importance of provenance, metadata, and quality control when those records are repurposed [29]. A structure drawing without its evidential context is difficult to audit computationally or manually.

The proposed minimum reporting package therefore has three parts. First, report the structural claim at the appropriate level rather than relying on an undifferentiated statement of "structure confirmation." Second, make the evidence chain inspectable: acquisition data or accessible raw records where practicable, processed observables used in reasoning, computational method and version information when relevant, and the candidate or reference space against which a conclusion was tested. Third, report unresolved alternatives and contradictions rather than removing them from the narrative once a preferred structure has been chosen.

Traceability should extend to negative and incomplete outcomes. An experiment that was attempted but produced non-discriminating data is analytically different from an experiment that was never performed, and both differ from a measurement that contradicts the proposed structure. Preserving those states can prevent later analysts from interpreting silence as support.

This proposal does not require every article to publish every intermediate calculation in the main text. Supplementary repositories and machine-readable records can carry much of the evidential burden, provided identifiers and provenance remain stable. The reporting objective is traceability, not maximal volume. High-precision NMR observables are useful only if their acquisition and interpretation can be reconstructed [27], and computational outputs are useful only if the model and input conditions remain identifiable.

Such reporting would also improve later revision. When a structure is challenged, investigators could determine whether disagreement originates in the raw measurement, signal assignment, candidate enumeration, conformational treatment, model prediction, or final interpretation. That distinction is analytically more informative than simply replacing one drawing with another. The ledger thus reframes reporting as preservation of the reasoning path that connects measured material to structural claim.

Limitations and standardization needs

The proposed model organizes uncertainty; it does not eliminate it. Flexible molecules, reactive or interconverting species, mixtures, low-information spectra, proton-deficient structures, and samples unsuitable for diffraction can remain difficult even when every ledger field is complete. The framework also cannot guarantee that the true structure was ever included in the candidate set.

Computational evidence introduces additional limits. Domain-specific absolute-configuration prediction should not be generalized outside the chemistry and assay in which it was evaluated [18]. Benchmark studies show that model performance can change with dataset composition and evaluation design [19], while critical assessment of DP4+ demonstrates how candidate and computational choices can distort apparent confidence [21]. Broader machine-learning experience in NMR likewise argues against treating model scores as method-independent measures [26].

A second limitation is that evidence categories themselves may require disciplinary calibration. Different laboratories can reasonably disagree about when a candidate alternative has been sufficiently excluded, how much conformational uncertainty is material, or whether two modalities are sufficiently independent to count as orthogonal support. Those judgments cannot be resolved by table design alone. Standardization work should therefore test whether independent analysts using the same underlying data produce comparable ledger entries and confidence language.

The framework also depends on adequate reporting. If raw spectra, candidate lists, discarded assignments, or computational settings are unavailable, retrospective completion of the ledger may be impossible. In such cases, the appropriate state is evidential incompleteness rather than reconstructed certainty.

Standardization should therefore begin with terminology and provenance before numerical calibration. Prospective blinded elucidation exercises, retrospective testing on independently adjudicated revisions, inter-rater studies of ledger interpretation, modality-ablation analyses, and external chemical-space evaluation are needed. If numerical cross-modal confidence is eventually proposed, calibration against adjudicated outcomes would be essential. Until then, the framework should be treated as a proposed reporting and reasoning model, not an implementation-ready standard.

Conclusion

Structure elucidation should not end when a chemically plausible drawing is selected. It should end when the evidential status of the structural claims embodied by that drawing has been made explicit. The model proposed here separates constitution, relative configuration, and absolute configuration because each can be supported, contradicted, or left unresolved by different analytical information. It then records provenance, dependence, contradiction, missing evidence, and residual alternatives in a cross-modal structure-evidence ledger before producing level-specific confidence statements.

This approach changes the endpoint of elucidation without claiming to replace expert judgment or establish a universal hierarchy of analytical methods. A probability produced by a defined model remains a model-specific result; cross-modal agreement remains conditional on the relevance and dependence of the contributing evidence; and an unresolved stereochemical claim is not repaired by confidence in constitution. Conversely, a later revision need not invalidate every earlier observation if the failed inference can be localized.

Its practical test is therefore simple: a reader should be able to identify what is known about the molecular graph, what is known about stereochemical relationships, what establishes or fails to establish handedness, and which observations could still change those conclusions. If the final drawing cannot answer those questions, the assignment is visually complete but evidentially underreported.

The principal contribution is therefore a proposed discipline of evidential bookkeeping: structural certainty should be attached to the claim actually tested and bounded by the evidence actually available. Its value will depend on prospective evaluation, reproducibility across analysts, and validation in chemical spaces and analytical settings beyond those represented by current methods. Until such work is completed, the ledger should be used as a transparent reasoning and reporting architecture rather than as a calibrated universal score.

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