

# The Molecular Aesthetics of Disease

## The Relationship of AIDS to the Scientific Imagination

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**Abstract:** This paper shows how the simulated molecular forms of HIV protease allow scientists to immerse themselves in the study of AIDS while simultaneously serving their aesthetic needs. To unravel the aesthetic nature of the computationally rendered representation of HIV protease, an analysis of the aesthetic function and properties of molecules is undertaken, with particular emphasis on the properties of tension, elegance, and sublimity.

**Keywords:** *HIV protease, aesthetic functionalism, elegance, beauty, sublime.*

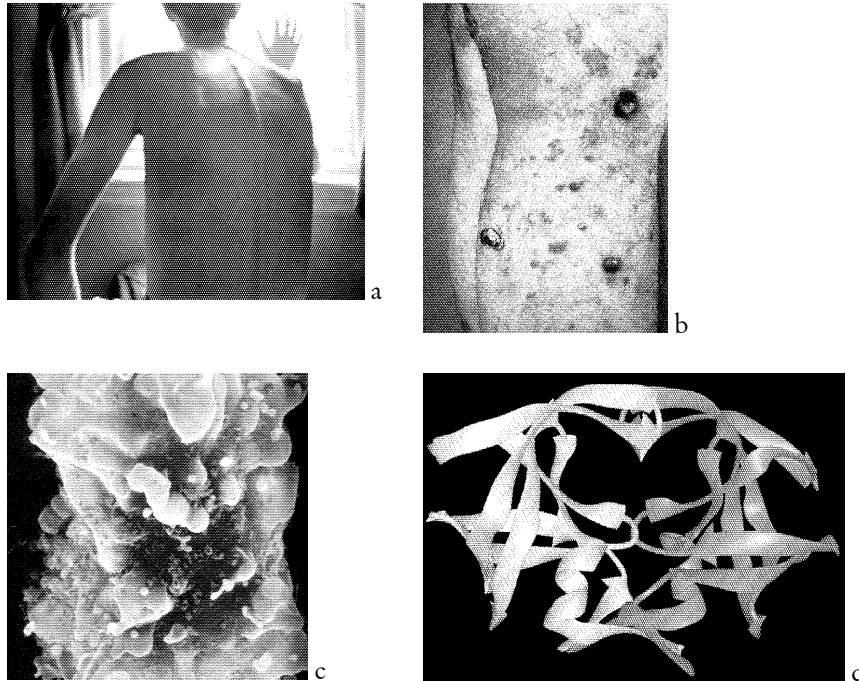
### 1. Introduction

AIDS, perhaps more than any other disease of this century, is a socially and visually marked disease. Laden with cultural implications, it has attracted the attention of social critics who labor to unearth its buried discourse.<sup>1</sup> Socially, AIDS reveals the inadequacies of biomedical science, provides a locus for disease moralists, can be carried invisibly and spread without consent, and stigmatizes particular sexual and racial communities – legitimizing prejudice. Images of AIDS link the diseased body to the deviant body and provide a mechanism for distancing the possibility of AIDS in our own lives. In the media this distancing is accomplished through the cultural lens of self-infliction, where people with AIDS are often portrayed as marginalized and isolated gay men, dark-skinned drug users, and emaciated prostitutes. Such images “construct distinctions between normal and perverse, legal and criminal, innocent and culpable, healthy and diseased” (Nelkin *et al.* 1991, p. 9), and feed our collective desire to stop AIDS from spreading into the mainstream psyche. Although AIDS has a variety of potential visual manifestations, including enlarged lymph nodes, wasting, and, in its late stages, paralysis, and blindness, the stigma of AIDS is most potently expressed through images of skin infections and lesions. As William Miller writes, “diseases that

attack the skin in especially grotesque ways often come to be understood as allegories of the moral condition of the inside" (Miller 1997, p. 52). The particular association of AIDS with images of diseased skin is cemented in medical and media representations of the disease. In medicine, even a quick perusal through clinical textbooks on HIV infection reveals that, with the exception of sections on the dermatological manifestations of AIDS, there are few photographs of people with the disease.<sup>2</sup> This powerful connection between AIDS and grotesque skin disorders is captured by Douglas Crimp's description of a priest with "his hand on the KS-lesion-covered head of a PWA [person with AIDS]— administering last rights" set at the close of the *Sixty Minutes* expose 'AIDS Hits Home' (Crimp 1992, p. 120) and by Roger Bennett's illuminating paper on the 'Effects of Horrific Fear Appeals on Public Attitudes Towards AIDS' (Bennett, 1996). In this study Bennett explicitly examines the impact of public health advertisement on attitudinal changes towards AIDS while implicitly explicating the visual connection of AIDS to diseased skin. Bennett does this by exposing the study's participants to three different types of AIDS public health posters: a "non-emotional appeal poster" from the World Health Organization "of a man and woman walking together with hands held, above the caption AIDS kills: stick to one partner"; a "[m]id-fear" image of the "Grim Reaper figure used in the Australian anti-AIDS campaign of the early 1990s" comprised of "a line drawing of a sinister and rather frightening hooded skeleton holding a scythe, above the caption AIDS kills: Prevention is the only cure we've got"; and "the horrific high-fear" poster "comprised [of] four appalling pictures of physical symptoms characteristic of the later stages of AIDS: the upper part of a man's torso covered in sores (Kaposi's sarcoma); a man with a large chin tumor (nodal lymphoma); a swollen fungus infected tongue (candidiasis), and a large skin abscess" with the caption "AIDS kills: don't risk infection."

In biomedical science, in contrast to the disease's grotesque visual effects depicted in medical and media images, AIDS is encapsulated by images of the human immunodeficiency virus and computer renderings of the structure of HIV protease (Figure 1d). Thus, scientists are compelled not only by their desire to understand the pathological mechanisms of AIDS, but also by a fascination fostered by the aesthetics of their models of HIV and its molecular components.

Faced with the seeming conflict between the avowed aims of science and art, how do scientists account for their aesthetic response to this especially stigmatized disease? In this paper I address this question by examining how media (Fig. 1a), medical (Fig. 1b), and biomedical (Fig. 1c) images of AIDS are mediated through the scientific rendering of HIV protease (Fig. 1d) as an aesthetic object.



**Figure 1:** a) Typical media image of a person with AIDS (Nixon & Nixon 1991, p. 13). b) Torso with Kaposi's sarcoma (KS) lesions from a medical text (Friedman-Kien & Ostreicher 1984, p. 26) (Reproduced with permission of Masson Publishing USA, Inc.). c) Particles of viral HIV (blue) coming out of a white blood cell (pink) (Nowak 1995, p. 59) (Reproduced with permission of Boehringer Ingelheim Pharma KG, photo Lenart Nilsson / Albert Bonniers Forlag AB). d) Ribbon structure of HIV protease.<sup>3</sup>

The cultural distancing from AIDS created in the social realm by media images of isolated and disfigured subjects is ironically recreated by scientists in the aesthetic realm through representations of the virus. For scientists, media images of disease, death, and dying are distilled to yield an aesthetic discourse which is controlled and rarified (Young 1993; Bakhtin, 1981). A pertinent analysis of how scientific images elevate AIDS into the purified realm of aesthetics is Mirelle Rosello's study, 'Pictures of a Virus: Ideological Choices and the Representations of HIV' (Rosello 1998). Rosello analyzes the icon of the virus used in French magazines and on French television to signal that the topic is AIDS. Created for the public rather than scientists, this iconic HIV virus is represented as a colorful, spiky, self-contained unit that has little

resemblance to scanning microscope images of the actual virus. Describing typical animations of how HIV infects our cells, Rosello characterizes the images as exquisitely seductive, where “the sophisticated pattern of encounters between organisms is portrayed as a beautiful encounter between beautiful creatures” (Rosello 1998, p. 341). The icon ultimately absents the possibility of real infection for a real populace. In this same vein, Marcus Boon has analyzed *Scientific American’s* images of the mechanism of HIV infection (Boon 1996). Intended for a technically literate general public, these depictions of HIV are more scientific, as indicated by the ample use of annotations and labels, and more aesthetic, as indicated by their painterly airbrushed quality, than the French icons. Such illustrations are made explicitly aesthetic in the 1991 *Artforum* spread of ‘Life, Death, and Hope in Ångstroms: The HIV Cycle Versus BI-RG-587 Antiviral Compound’, where the intended audience is not scientists but artists and patrons of the arts (Tierney & Mangiardi 1991).

A fascinating twist on the iconization of the virus is the 2001 overview on AIDS in *Nature* which included an article entitled ‘Gulliver’s Travels in HIVland’ (Weiss 2001). Its publication in one of the premiere scientific journals, and therefore clearly intended for scientists, begins

I, Lemuel Gulliver, have observed wondrous phenomena in many lands. In this my latest account, I shall endeavor to convince you that we are embarked upon a doleful new adventure that is only now beginning to unfold. My story concerns a creature, even smaller than the Lilliputians, indeed so minute as to be invisible, named – after quarrelsome debate among a band of pundits in 1986 – the human immunodeficiency virus. (Weiss 1991, p. 963)

This mixing of science with a classic satiric travelogue literally exposes the cultural narrative of AIDS depicted in the accompanying figures. Amazingly, among the forty-six pages of highly illustrated articles, beginning with Gulliver’s ‘story’ of HIV and ending with a review of the ‘Challenges and Opportunities for Development of an AIDS Vaccine’ (Nabel 2001), there is not one image of a person, or a part of a person, with AIDS. As exemplified in this issue of *Nature*, biomedicine provides an array of disembodied images to erase the individuality of AIDS. Infused with close-ups of KS lesions, epidemiological schema, and viral icons, such images provide legitimacy to an ethereal medical discourse that relies on distance, difference, and control.

## 2. The Inscription of HIV Protease as Scientific Object

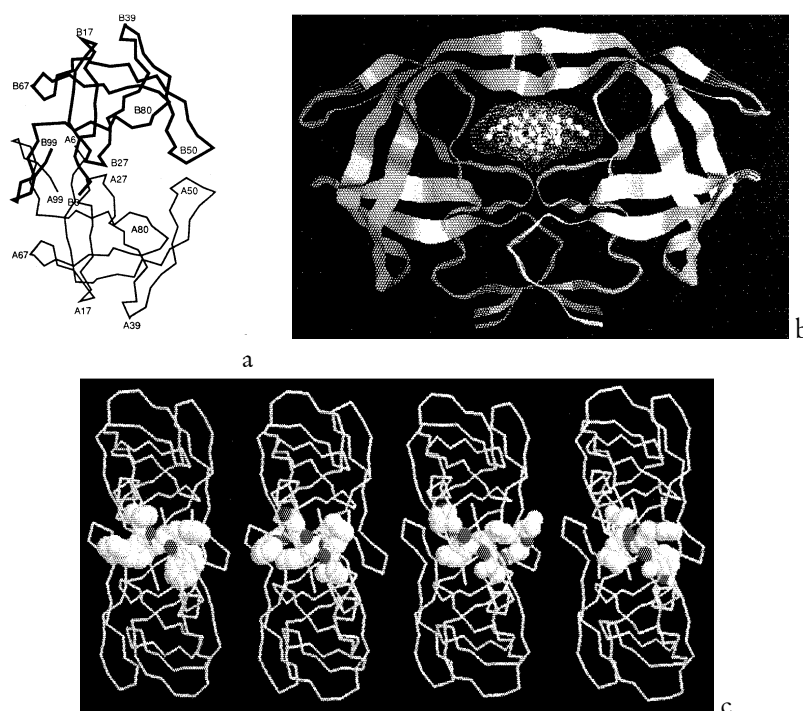
Delving deeper into the interior realms of scientific discourse, chemists, structural biologists, and biophysicists have taken this aesthetic transformation into the world of molecules through the structure of HIV protease.

An examination of the aesthetics of this molecular world relies on understanding that representations of HIV protease are constitutive and discrete scientific entities and not simply heuristics, models, or metaphors that merely illustrate the *real* object. Bruno Latour's canonical work *Laboratory Life*, which details how scientists constructed the peptide Thyrotropin Releasing Factor (TRF) as a neurochemical fact, can be readily applied to such representations in determining the status of molecular HIV protease as an object (Latour & Woolgar 1986).<sup>4</sup> Using Latour's signifiers for constructed scientific objects we find that (1) the molecular representation of HIV protease is scientifically productive, yielding research, journal articles, and biomedical uses (*i.e.*, it is a constitutive object); (2) there is a precise claim to the origin of its representation in time and space – that it was rendered by particular scientists on a particular date in a particular place; and (3) it is immutable to the accumulated techniques and uses applied to it since its inscription in the scientific literature (or, in scientific vernacular) 'was discovered'.

Unlike Latour's TRF peptide, however, which exists as an object to relatively few scientists, HIV protease has meaning to most molecular scientists. But what specifically is it that has meaning as an object? Is it the representations of HIV protease or is it HIV protease itself that has objective, iconic status? That the structural representation of HIV protease is a self-contained scientific entity is highlighted by its ready distinguishability from other similar structures (*i.e.*, other enzymatic representations). Indeed, among representations of enzymes, and even representations of other proteases, the molecular representation of HIV protease has obtained the elevated status of an instantaneously recognized cultural icon. In contrast, as a chemical substance, crystalline HIV protease is relatively indistinguishable from other crystalline solids.

To provide an understanding of how images of biomolecules are constructed as constitutive objects, it is instructive to outline the experimental procedures used to generate the three-dimensional structure we know as HIV protease. This procedure began in 1985 with the determination of the "complete nucleotide sequence of the AIDS virus" obtained from the "blood pooled from several American AIDS patients" (Ratner *et al.* 1985, p. 280). This work, performed by collaborators at the National Cancer Institute, Harvard School of Public Health, duPont, and Centocor, revealed that the HIV virus had 9,749 DNA base pairs and that its "overall structure [...] resembled that of other retroviruses" (Ratner *et al.* 1985, p. 280). In 1989 Paul L. Darke and co-workers at Merck Sharp and Dohme used recombinant DNA techniques to clone and express the protein HIV protease from *Escherichia coli*. Upon harvesting the *E. Coli* cell paste they isolated and characterized the protein as a 10-kiloDalton aspartic protease that is "likely to be structurally homologous with the well characterized family that includes pep-

sin and renin” (Darke *et al.* 1989, p. 2307). With the purified protein in hand scientists at Merck then used the “hanging drop vapor diffusion technique” at 4°C over four to seven days to form “tetragonal bipyramidal crystals approximately 0.25x0.25x0.50 mm in size” of HIV protease (McKeever *et al.* 1989, p. 1919). These crystals were then bombarded with X-rays to yield heavy atom diffraction patterns that were subsequently read and refined to yield atomic coordinates. Finally the atomic coordinates were computationally transformed into the first molecular representation of HIV protease (Fig. 2a) (Navia *et al.* 1989, p. 618). Thus, through the determination of the DNA sequence of the virus, isolation methods, computational refinement, and visualization, molecular HIV has become an object laden with cultural implications for the understanding and treatment of AIDS.



**Figure 2:** a) First published image of HIV protease (Navia *et al.* 1989, p. 618) (Reproduced with permission of Nature Publishing Group and Paula Fitzgerald). b) Gold and red ribbon structure of HIV protease with Glaxo Wellcome inhibitor in active site<sup>5</sup> (Reproduced with permission of Roger Sayle). c) Protein Data Bank June 2000 Molecule of the Month – HIV protease with four drugs (from left to right: Indinavir, Saquinavir, Ritonavir, and Nelfinavir) in the enzyme’s active site.<sup>6</sup>

Since the structure of HIV protease was elucidated, scientists have reproduced it in a variety of images for a plethora of studies. Two examples are Roger Sayle's RasMol image of HIV protease bound with the Glaxo Wellcome inhibitor (Fig. 2b)<sup>5</sup> and David S. Goodsell's image chosen for the June 2000 protein data bank molecule of the month (Fig. 2c).<sup>6</sup> These are only a few among the hundreds of structures of HIV protease found in the protein data bank (including genetic strains of the enzyme, enzyme-inhibitor complexes, and enzyme mutants), in scientific publications, and on the web, including proprietary databases maintained by pharmaceutical companies.<sup>7</sup> These structures are obviously scientifically illuminating, allowing for the determination of the enzyme's role in HIV viral maturation, its molecular mechanism, and most importantly, the development of HIV protease inhibitors for use in a drug cocktail for people with AIDS. Such visualized structures of HIV protease, and many other molecules, also evoke a strong aesthetic response from scientists. It is not uncommon to read about "the inherent beauty of biomolecules"<sup>8</sup> or to find descriptions of computer generated models which claim that "you will see beauty beyond any previous experience",<sup>9</sup> that we will be *awestruck* by the *ingenuity*, *perfection*, and *elegance* of these forms.

### 3. The Aesthetic Function and Properties of Molecules

Such exclamations are not merely a linguistic convention. For scientists these minimalist molecular representations actually express a visual and metaphysical aesthetics which accords with the larger aesthetic epistemology of twentieth-century science. This epistemology prioritizes the capacity of the human mind to subjectively contemplate ideas beyond those that are empirically evident. An equation such as  $E = h\nu$ , which symbolically represents the relationship between the energy and frequency of light, and Heisenberg's Uncertainty Principle ( $\Delta p \Delta x \geq h/2\pi$ ), which encapsulates the enigma that we cannot know the precise position and momentum of a particle simultaneously, epitomize this metaphysical aesthetics. Prioritization of the abstract, along with the streamlined character of equations which express large ideas in minimalist forms, has led to our heightened perception of the aesthetic nature of quantum mechanics as captured by Heisenberg when he wrote:

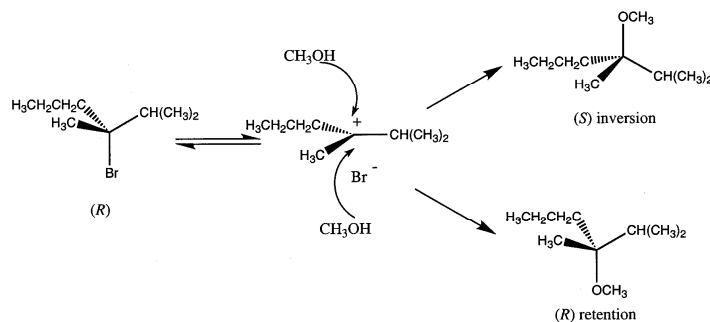
If nature leads us to mathematical forms of great simplicity and beauty – by forms I am referring to coherent systems of hypotheses, axioms *etc.* – to forms that no one has previously encountered, we cannot help thinking that they are *true*, that they reveal a genuine feature of nature. (Heisenberg 1971, p. 68)

This twentieth-century aesthetic prioritization of conceptually abstract mathematical models appears to be at odds with the chemist's *naive* depictions of molecules. Developed during the nineteenth century, molecular representations, as characterized by Berzelius' algebraic symbols and van't Hoff's three-dimensional line drawings, ostensibly provided a purely empirical view of chemical reactivity and were ideally viewed as convenient heuristics to illustrate and catalogue reactions and molecules. Created during a century when chemists were still hotly debating the existence of atoms and prior to the discovery of the electron, there was no consensus among chemists about what these structures actually represented. Explanations for the observed valency (*i.e.*, the "atom-fixing power", Russell 1971, p. 83) of the atoms within these structures were quite varied and included, among others, theories based on electrochemical interactions, gravitational forces, and the dynamic motions of the ultimate particles of matter (Nye 1993).

We now know that none of these explanations were ultimately correct, yet chemists continue to use these nineteenth-century molecular representations to postulate and communicate chemical information. The temporal robustness of these representations can be attributed to the inherent ingenuity of their form which, like a glass that can hold wine, water, or sand, may accept a plethora of theoretical contents. For chemists today these representations embody the empirically successful theories of a collective disciplinary past and provide an adaptive container for modern chemical concepts. For molecular scientists this has meant that the visual and conventional molecular structures of the nineteenth century have been imbued with the mathematical framework of chemistry developed during the early twentieth century through the paradigm of the covalent and ionic bond. Thus, rather than a bond that is a "tie which enable[s] an element [...] to attach itself to one or more atoms of other elements" with "no hypothesis as to the nature of the connection" (Russell 1971, p. 90), chemists now envision bonds as a space of high electron density probability (*i.e.*, a molecular orbital) between two atomic nuclei. Through this melding of twentieth-century theory and nineteenth-century structure, molecular representations have shifted from empirically useful pictorial heuristics to models with precise and predictive theoretical value. There are a number of aesthetic implications of this shift. Like Heisenberg's "mathematical forms of great simplicity and beauty" modern molecular structures encode the abstractions of Schrödinger's wave mechanics into the simplified and concise visual forms of bonds and orbitals. An example of the conceptual richness embedded in molecular forms is the scheme for an  $S_N1$  reaction presented in Figure 3. As shown here the chiral alkyl halide *R*-3-bromo-2, 3-dimethylhexane ionizes in methanol to form a planer, hypothetical, intermediate carbocation (*i.e.*, a place of low electron probability or empty orbital) which is subsequently attacked by methanol's oxygen



lone-pair electrons to form a racemic mixture of products. For chemists this reaction scheme's structures are laden with both the experimental realities of optical activity and the theoretical underpinnings of modern organic chemistry, including the dynamic nature of the reaction and the relationship between orbital theory and stereochemistry.

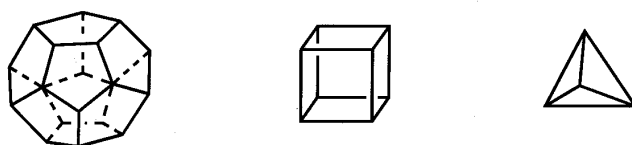


**Figure 3:** Mechanism for the S<sub>N</sub>1 reaction of chiral alkyl halide *R*-3-bromo-2,3-dimethylhexane.

The conceptual superimposition of electrons onto the bonds of the static molecular structures of the nineteenth century has also shifted the use of molecular representations from empirically convenient depictions and pedagogical tools into constitutive elements for doing chemistry. As Roald Hoffmann has written, the visual representations of molecules have a way of “sneaking into our subconscious [where] these schematic diagrams merge with the real world and motivate transformations that chemists effect in the laboratory” (Hoffmann 1991, p. 308). One implication of Hoffmann’s observation is that modern chemists often gear experiments toward the production of molecules with intriguing valence bond structures, where the production of an aesthetic molecular form is privileged over its practical chemical value. This is exemplified by the Platonic hydrocarbons tetrahedrane, cubane, and dodecahedrane (Fig. 4) (Maier 1988, p. 310). Fueling the chemist’s imagination these “chemical transliterations of Plato’s universe” are, in the words of organic chemist Leo Paquette, “structurally unusual,” have properties that “are not predictive with certainty *a priori* from current theories of bonding,” and exude “aesthetically delightful topologies” (Paquette 1982, p. 4495).

The conceptual superimposition of the electron onto the bond also allows chemists to imagine the dynamics of chemical transformations (*i.e.*, the mechanisms) which have not yet been developed, rather than simply classify those that already exist. As for static structures like the Platonic hydrocar-

bonds, the electron bond imbues mechanisms with constitutive power. For modern chemists it has become commonplace that the synthesis of a particular molecule serves merely as a vehicle for the use of an aesthetically intriguing mechanism. Organic chemists commonly use the practice of retrosynthetic analysis to imagine a path from the starting materials to the final product of a synthesis by thinking backward (*i.e.*, from product to starting material). Step-by-step, skilled chemists apply synthetic methods and mechanistic analogues to molecular representations to conceptualize a successful synthetic strategy in reverse. Often such syntheses build towards a key mechanistic step rather than focusing on the cost efficient production of the end product.

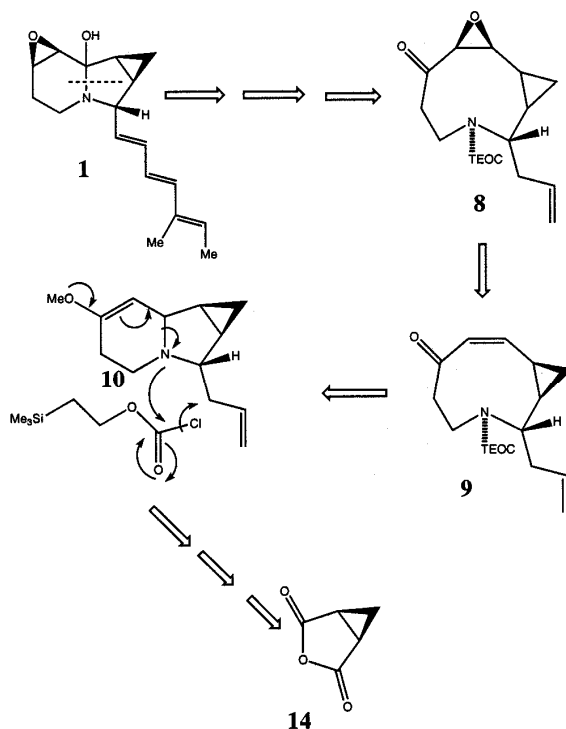


**Figure 4:** The Platonic hydrocarbons dodecahedrane (left), cubane (middle), and tetrahedrane (right).

Samuel Danishefsky's retrosynthetic analysis for the synthesis of the antibiotic indolizomycin exemplifies this point (Fig. 5). The focus of this synthesis, which involved over thirty synthetic transformations, was the transformation from compound **10** to compound **9**, where it was hoped that "10 could serve as a viable substrate for an interesting vinylogous McCluskey fragmentation" (Nicolaou & Sorensen 1996, p. 474).

According to Roald Hoffmann "the honesty and intensity of the aesthetic response of chemists, when they allow themselves to express it, must be taken positively, as a clue to an unformulated good, as spiritual evidence, a signpost to record, to empathize, to make connections with other aesthetic experiences" (Hoffmann 1991, p. 301). Here, Hoffmann hints at a more analytical approach to establish parameters for an aesthetics of structural chemistry. Following his lead, I have chosen to employ the concepts of aesthetic functionalism (not *artistic* functionalism) and the formalist terminology of art critics like Roger Fry, who articulated the interrelationship of aesthetic properties and aesthetic function in works such as Matisse's *The Conversation* when he wrote that "the perfect rightness of the relations" in the painting inspires a mood of "serenity and repose" (Fry 1996, p. 115). Philosophically, aesthetic functionalists claim that one function of art is to have aesthetic properties, and that these aesthetic properties "supervene on non-aesthetic properties" (Zangwill 2001, p. 125). Thus, in Fry's description of Matisse's

work the aesthetic property of serenity is a result of the embedment of a green, brown, red, and black rectangle in a blue background and placed next to a curved woman's body. Simultaneously, Matisse's painting can also have non-aesthetic functions, such as representing the nature of conversation, or even serving as the doorstep for a careless art collector.



**Figure 5:** Danishefsky's retrosynthetic analysis for the synthesis of indolizomycin (Nicolaou & Soresen 1996, p. 473) (Reproduced with permission of WILEY-VCH Verlag GmbH & Co).

From the world of chemistry the Platonic hydrocarbon cubane again serves as an apt example. In this context we can ask, what is the function of cubane and/or the representation of cubane? Experimentally, the chemical cubane has the non-aesthetic functions of being a potential explosive, a synthetic target, and a transparent solid with particular physical properties. In contrast, the *representation* of cubane has, in part, the function of expressing the aesthetic properties of tension (restraint/strain) and harmony through the non-aesthetic properties of distorted bond angles and  $O_h$  symmetry. This aesthetic property of tension in art was captured by Piet Mondrian when he wrote

that his desire was to annihilate the “static equilibrium” in his painting “through the continuous oppositions among means of expression” by presenting reality through “the equilibrium of form and color” (Waddington 1969, p. 39). Mondrian’s desire was “to represent the dichotomies of the universe in eternal tension” by the “balancing of horizontal and vertical stokes.”<sup>10</sup> For the chemist this same sense of tension is found in the representation of stable structures with significant strain such as the Platonic solids – molecules that are tightly wound and ready to spring into forms with lower energy states.

An enhanced aesthetic response is provided by an understanding of the theoretical relations embedded in visualized molecular structures. Mark Rothko’s paintings serve as an apt example of this phenomenon in modern art. Those who look at Rothko’s color field paintings in a museum might view them as imposing and (perhaps) meditative non-representational swatches of color. For many, however, understanding Rothko’s work as a purposeful expression of spirituality within the context of the abstract expressionist movement heightens their own aesthetic response when viewing his paintings. This same principle applies to molecular appreciation with the advantage that chemists throughout the world are trained in the same implicit molecular aesthetics: they share the same *taste* when determining what is aesthetically pleasing, neutral, or displeasing, where taste is defined as “the ability to identify aesthetic success, to distinguish good from bad design” (Zemach 2001, p. 53) within the world of molecular representations.

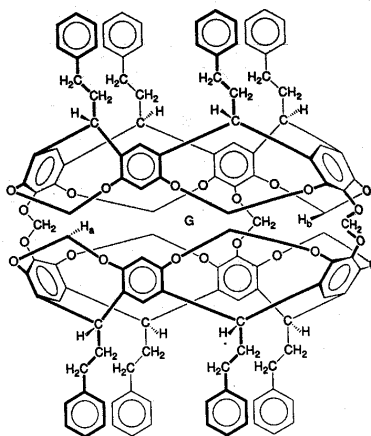
Aesthetic functionalism also claims that “a work (of art) must have its origins in the intention to make a thing with certain aesthetic properties in virtue of certain non-aesthetic properties” (Zangwill 2001, p. 137). In chemistry this might imply that the successful synthesis of a compound grants its aesthetic function; however, as for the Platonic hydrocarbons the aesthetic properties of some molecules lie not only in their form but also in the *goal* of making what is represented even before the synthesis is carried out, and in the synthetic schema used to fashion them. Thus tetrahedrane, which has never been synthesized, is an aesthetic object with particular aesthetic properties by virtue of the intent of chemists to synthesize the harmonious and restrained structure drawn on the page.

#### 4. Molecular Elegance, Sublimity, and HIV Protease

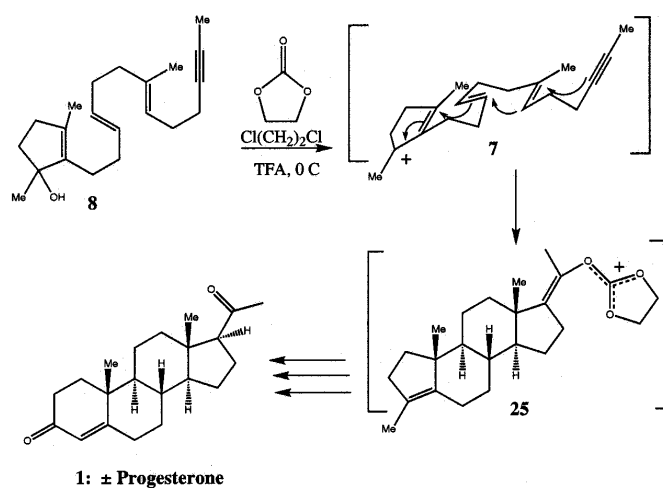
The following list summarizes the properties I have found relevant to understanding the intrinsic aesthetic nature of molecules: *tension*, *ephemerality*, *playfulness*, *novelty*, and *elegance*. This is not to say that other aesthetic prop-

erties or other critical approaches to the works are not equally valid. I have chosen these because chemists themselves use formalist terminology in their aesthetic proclamations about molecules, and it is the force of this response which often appears to aesthetically motivate a chemist toward one molecular system over another. For example, almost any chemist would claim to be more aesthetically compelled by the representation of the “Mount Everest of Alicyclic Chemistry” (Paquette 1982, p. 4503), dodecahedrane, than to its open chain, plain-Jane analogue, eicosane. In the following I will focus on elegance, as this is the term most used by scientists to express their aesthetic appreciation of a particular scientific structure, be it mathematical or biomolecular.

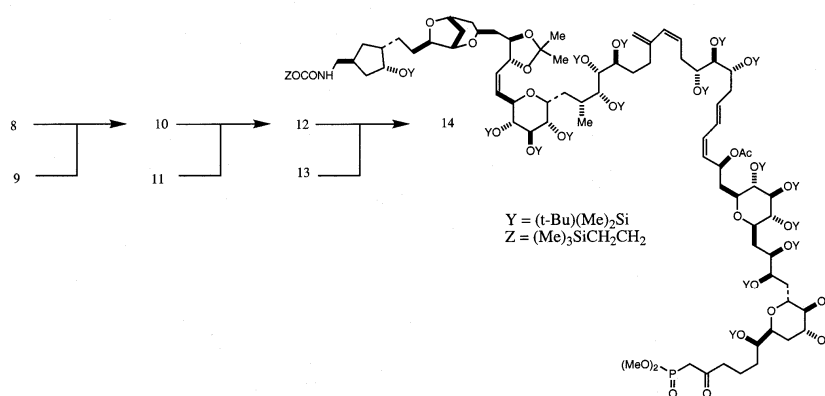
What is scientific elegance? A concise dictionary entry defines it as “ingenious simplicity, convenience, and effectiveness”,<sup>11</sup> but a closer examination reveals that elegance is unstable in scientific discourse, at times formally beautiful, and at others psychically sublime. For scientists, elegance is situational; its meaning depends on the intent of the specific scientific community using it and the context they use it in. In the context of this paper, therefore, the more appropriate question is: what is molecular and biomolecular elegance? To answer this question I provide Donald Cram’s synthesis of “cyclobutadiene lodged in the cavity” of a hemicarcerand (Cram 1991) and W. S. Johnson’s synthesis of progesterone (Nicolaou & Sorensen 1996, p. 91) as examples (Figs. 6 & 7).



**Figure 6:** In Cram’s experiment cyclobutadiene (G) is ‘tamed’ inside the hemicarcerand (Cram 1991, p. 1024) (Reproduced with permission of WILEY-VCH Verlag GmbH & Co).



**Figure 7:** A portion of Johnson's scheme for the synthesis of progesterone (Nicolaou & Sorensen 1996, p. 91) (Reproduced with permission of WILEY-VCH Verlag GmbH & Co).



**Figure 8:** A portion of Kishi's scheme for the synthesis of Palytoxin where compounds 8-13 are reacted in sequence to yield a key palytoxin precursor (14) (Armstrong *et al.* 1989, p. 7527) (Reproduced with permission from *J. Am. Chem. Soc.* 1989, 111, 7525-7530. Copyright 1989 American Chemical Society).

While these systems might, or might not, fulfill the dictionary definition of scientific elegance, they do exemplify a more situationally precise parameter of scientific elegance. Specifically, these systems foreground design at the expense of labor. We are presented with a final product, or in the case of Johnson's synthesis of progesterone, a culminating process, that mystifies the work involved in creating the molecule. In the first case the fragile and fleeting structure of cyclobutadiene, which Cram delightfully called "the Mona Lisa of organic chemistry" (Cram 1991, p. 1024), has been tamed at room temperature through an ingeniously crafted incarceration experiment. The elegance of Johnson's synthesis is best revealed in comparison to Yoshito Kishi's synthesis of palytoxin which I would classify as impressive and laborious but not elegant (Fig. 8) (Nicolaou & Sorensen 1996, pp. 720-728). In Johnson's synthesis we are momentarily poised at the place in the mechanism (Fig. 7, intermediate 7) where the precursor is magically transformed into the final product.

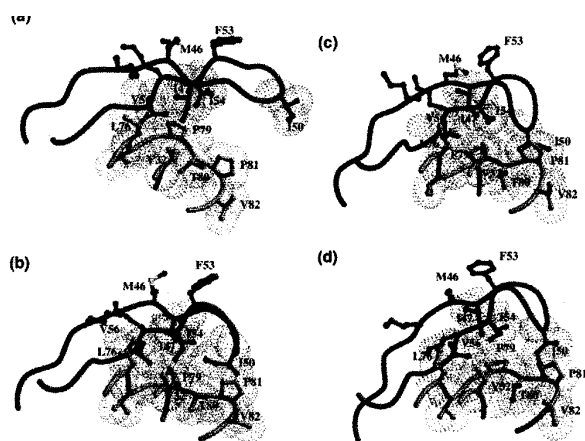
Linked by the sensation of disruption – a moment of awe expressed in astonishment – these illustrations of molecular elegance capture the transient sensation of sublimity. This sense of sublimity is expressed in Jeremy Gilbert-Rolfe's description of the techno-sublime as characterized by "simultaneity and invisibility rather than process and moving parts, the electronic as opposed to the mechanical" (Gilbert-Rolfe, 1999, p. 80). In Johnson's synthesis of progesterone the molecular structures encode their elegance as an instantaneous dynamic transformation of an intermediate into a complex product. In this case the existence of the product in nature is of little consequence to the chemist's aesthetic impulse. In contrast, the elegance in renderings of biomolecules *is* their relationship to the natural world. These structural representations of 'living' molecules provide a sense of awe at our ability to comprehend the enormity and complexity of nature defined by the Kantian sublime. As described by Kant, the sublime

[...] displays nothing purposive in nature itself, but only in that possible use of our intuitions of it by which there is produced in us a feeling of a purposiveness quite independent of nature. We must seek a ground external to ourselves for the beautiful of nature, but seek it for the sublime merely in ourselves and in our attitude of thought, which introduces sublimity into the representation of nature. (Kant, 1951, p. 84)

In short, the sublime is located not in nature but in the mind's capacity to experience its own might. For scientists, AIDS represents the complexity of nature through its orchestration of millions of atoms in a microscopic viral entity, and on a physiological level by its unpredictable mutation and potential for unchecked viral proliferation. Scientists are drawn to this complexity, while at the same time they seek aesthetically elegant solutions to their scientific problems that reflect the intellectual prowess of their own minds. Since

the 1990s they have reconciled these seeming contradictions through the aesthetics of HIV protease.

In the late 1980s it was found that a protease enzyme was necessary for HIV viral maturation. As described earlier, this discovery quickly led to the isolation and crystallization of HIV. Upon crystallization, HIV protease revealed nature's creation of an enzymatic machine comprised of two monomers related through an axis of symmetry. This structure is not just beautiful for its symmetry, but sublime, allowing scientists to understand and potentially conquer nature through the relationship of its form and function. The enchantment of a protein like HIV protease, as revealed by its crystal structure, is its remarkable ability to fold precisely into a molecule which performs a specific enzymatic task, and in the scientist's ability to understand and exploit its enzymatic action by carefully examining and simulating its structure. Since its unveiling, the crystal structure of HIV protease has been used as a starting point for hundreds of experimental and computational studies. In particular, studies of the 'flap opening' of the enzyme encapsulate the ingenuity of nature's design and human insight.<sup>12</sup> Starting from a crystal structure, the 10-nanosecond simulation shown in Figure 9 captures HIV protease in the act of curling back the tip of its glycine rich  $\beta$ -hairpin loop into a hydrophobic pocket to expose its active site.



**Figure 9:** Images from a molecular dynamics simulation of the flap opening of HIV protease starting with the crystal structure (a) and ending after 10 ns of simulation (d). The flap (purple) appears to curl back exposing the active site (blue) (Scott & Schiffer 2000, p. 1261) (Reproduced from Scott & Schiffer 2000 with permission from Elsevier).



These supercomputer ‘snapshots’ of HIV molecular dynamics illuminate a mechanism for how HIV protease interacts with its natural substrate, explain the drug resistance now being found in AIDS patients, and provide suggestions for potential new AIDS therapies, illustrating the sublime aesthetic power of molecular representation to subsume the terror of HIV.

## 5. Conclusion

As we saw earlier in the case of cubane (Fig. 4), we can use the perspective of aesthetic functionalism to elucidate the aesthetics of HIV protease. Specifically, we can ask how HIV protease’s aesthetic properties supervene on its non-aesthetic properties so that it may express its aesthetic function. Like all molecular objects, biochemical HIV protease has significant non-aesthetic functions. These include its role as an enzyme that hydrolyzes polyproteins into proteins for viral assembly and its manifestation as an isolatable crystalline material with particular experimental properties. The representation of HIV protease also has non-aesthetic functions, including its use as a template for the design of HIV protease inhibitors. At the same time, however, such representations have the function of expressing HIV protease’s aesthetic properties through its non-aesthetic properties of symmetry and hydrophobicity, which in turn result from the formal constraints embedded in its primary amino acid sequence.

It could be argued that the specific way in which HIV protease is visualized yields its aesthetic properties. For example, it could be assumed that what makes Roger Sayle’s image of HIV protease (Fig. 2b) aesthetically compelling is its artistic presentation of red and gold ribbons; however, such arguments do not account for the fact that HIV protease is more aesthetically potent than other enzymes no matter how it is visually rendered. All students of biochemistry learn the interrelationship of the primary, secondary, tertiary, and quaternary structures of proteins; that the building up of amino acids in a precise order yields a particular super-structure to these macromolecules through a mechanism that has yet to be elucidated. At times this mysterious collusion of intra and intermolecular forces yields aesthetically indeterminate globular structures, while at others they produce structures of high symmetry, like HIV protease, that scientists label as beautiful. Formally, it is the sequence of amino acids from N-terminus to C-terminus, and the juxtaposition of the enzyme’s secondary structures, which yields HIV protease’s aesthetic property of balanced beauty, while its sublimity lies in the relationship of this symmetrically dynamic form to its function – where, like the transporting oratory described by Longinus, its sublimity flashes “forth at

the right moment [and] scatters everything before it like a thunderbolt” (Longinus 1971, p. 77). For molecular scientists, HIV protease transforms disorder into order by refracting its exquisite form into a scientific object with a concise molecular structure that can be catalogued, refined, and transmuted; a medicinal object that can be pharmacologically exploited; and, a cultural object that absents the human form and psychologically mollifies the chaos of the disease represented by the person with AIDS.

## Notes

- <sup>1</sup> See among others: Treichler 1988, 1992 & 1999, Waldby 1996, Gilman 1988 & 1995, Leap 1990, Brandt 1991, Nelkin *et al.* 1991, Goldstein 1991, Sontag 1989, and Williamson 1989.
- <sup>2</sup> See among others Buckley & Gluckman 2002 and Schoub 1999.
- <sup>3</sup> This image was created for me in 1997 by E. Meng at the University of California San Francisco Computer Graphic Laboratory using MidasPlus.
- <sup>4</sup> See also Williamson 1989, Vasseleu 1991, Treichler 1992, and Waldby 1996.
- <sup>5</sup> See <http://www.umass.edu/microbio/rasmol/sayle1.htm>
- <sup>6</sup> See [http://www.rcsb.org/pdb/molecules/pdb6\\_2.html](http://www.rcsb.org/pdb/molecules/pdb6_2.html), David S. Goodsell, The Scripps Research Institute, Author and Illustrator of the ‘PDB Molecule of the Month’. See also: PDB ID: 1HSG (Chen *et al.*, 1994), PDB ID: 1HXB (Krohn *et al.* 1991), PDB ID: 1HXW, (Kempf *et al.* 1995) & PDB ID: 1OHR, (Kaldor *et al.* 1997).
- <sup>7</sup> See [http://www.rcsb.org/pdb/molecules/pdb6\\_1.html](http://www.rcsb.org/pdb/molecules/pdb6_1.html).
- <sup>8</sup> See Edger Meyer’s abstract ‘An Old Look at New Structures’ from the 1999 SouthWest Macromolecular Symposium. (<http://cmdnmr.tamu.edu/meyerlab/mlab/swms/pages/meyer.html>).
- <sup>9</sup> See the description of the “teaching aids for macromolecular structure” (TAMS) within Eric Martz and Eric Francoeur’s ‘History of Visualization of Biological Macromolecules’, website <http://www.umass.edu/microbio/rasmol/history.htm>.
- <sup>10</sup> See [http://www.guggenheimcollection.org/site/artist\\_work\\_md\\_1125.html](http://www.guggenheimcollection.org/site/artist_work_md_1125.html).
- <sup>11</sup> Oxford English Dictionary Online, Oxford University Press, 2003.
- <sup>12</sup> For example see Ishima *et al.*, 1999.

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