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Total Synthesis, Inside Out
Dr Martin J. Lear, Department of Chemistry

In concert with those mentioned in the references, we have been actively engaged in both the total and analogue synthesis of enediyne natural products. Not only are these products of Nature complex, but they are unstable. In the laboratory, this has translated into a constant fight against the inherent decomposition processes and, as such, has stretched the bounds of contemporary organic synthesis and the skills of the researcher at the bench. Yet, it is this instability that intrigues us the most. It is this instability that gives these enediyne natural products their most remarkable mechanism of action as antitumour antibiotics.

Emphasis herein is on new methods that have been derived from the challenging demands of several total synthesis programmes. Transition and implementation of these discoveries into new research directions will be described latterly. It is hoped that the synergy between total synthesis and new methodology will be conveyed: one does not exist without the other.

Concise routes to fully-fledged, bicyclic nine-membered epoxyenediyynes: At the heart of the matter are the reactive bicyclic cores of the natural enediynes. These nine-membered cores undergo spontaneous cycloaromatizations at ambient temperatures to generate para-benzyne biradicals, which invoke cytotoxic behaviours that are typically classified by the strand-cleavage of DNA or RNA and the degradation of cellular proteins.

Highly optimised and reliable approaches to the unstable bicyclic reactive cores of natural nine-membered enediyynes in fully-functionalised form have been achieved. On the one hand, a challenging series of isotopomers of enediyne models, specifically designed to bear $^{13}$C-labels at the supposed radical-forming 3- and 6-positions, were synthesised. These models allowed for the recording of solid spectroscopic evidence for the spontaneous Masamune-Bergman cyclisation, which for the first time demonstrated the differential reactivity of the C3 and C6 radical positions.

On the other hand, the first synthesis and thiol-triggered activation and DNA-cleavage profiles of N1999-A2 and its stereoisomers were realised, which demonstrated that the C11-naphthoate is the principal controlling element, both chemically and biologically.

New and general $\alpha$-selective glycosylation protocols for 2-deoxysugars, specifically developed for L-mycarose and L-kedarosamine: For the total synthesis of the kedarcidin chromophore, glycosylation protocols for 2-deoxysugars, L-mycarose and L-kedarosamine, needed to be developed in a direct, mild, and $\alpha$-selective manner. Besides concise synthetic procedures to 2-deoxy-pyranosides, specific developments include: (1) the general use of polystyrene-supported DBU to synthesise unstable Schmidt donors, (2) the general use of silver(I) salts to...
efficiently activate 2-deoxy sugars, and (3) the α-glycosylation of ansamacrolide and aglycon frameworks of the kedarcidin chromophore in high selectivities and yields.4,5

Forging unstable multicyclic frameworks of the kedarcidin chromophore: Several advanced approaches to the synthesis of the kedarcidin chromophore have been accomplished. Besides new and efficient gram-scale syntheses of the diyne and cyclopentene components, the inversion of the C4-stereocenter and use of C13-OMOM protection, resulted in an efficient synthesis of the multicyclic ansamacrolide framework of the kedarcidin chromophore. This tactical change allowed for the Sonogashira coupling step to proceed in 89 % yield (cf. 45 % before) with complete atropselectivity and for the β-C8 mesylate to be sterically allowed within the transannular cavity of the carbon-framework of the kedarcidin chromophore aglycon.6 This work has allowed for the successful development of anionic, cerium-acetylide procedures to form unstable, nine-membered diyne cores within pre-existing ansamacrolide-naphthoamide frameworks.

Methodology, total synthesis, and medicinal chemistry are thus integral to our research. Ongoing projects are highlighted below.

New Methods to Empower Sulfur as a Reaction Trigger: In a total synthesis setting, we are pursuing new methods and reagents that are extremely mild, yet powerful enough to effect desired transformations in increasingly more complex molecular structures. As an off-shoot on novel sugar chemistry results,4 for example, we recognise the “empowering” nature of Ag(I) salts to act as chemoselective, cationic “reaction-triggers” of heteroaryl sulfides and are developing exceptionally mild, yet potent, conditions to advance protective group chemistry.

Synthesis and Biology of a Novel Anti-tumour, Anti-malarial: Bielschowskysin is a structurally novel diterpene natural product of marine origin, which displays remarkable biological activity against P. falciparum and in vitro cytotoxicity against both lung and renal cancer. Aims here are to develop novel antimalarial agents and to investigate the differing modes of biological activity through total and analogue synthesis.

Non-peptidic, Anti-Virals to Fight SARS: A concerted effort needs to be made amongst the scientific community to develop an effective therapeutic treatment and diagnosis of SARS. It is thus our long-term aim to identify novel therapeutic approaches and synthesise non-peptidyl-based, anti-SARS agents based on the burgeoning X-Ray and biological data in the anti-viral field. A detailed pharmacophoric profile of
high-binding, structural scaffolds are to be performed as a prerequisite to designing flexible and expedient syntheses of optimal structures. An example lead compound is Sabadinine.

References


Abstract

Recent studies have mapped out the structural properties of single polysaccharide and gelatin systems at high levels of solids, and in mixture with increasing levels of sugar. Thermomechanical analysis demonstrated that the viscoelasticity of these systems is a good example of the application of the ‘synthetic polymer approach’ to biomaterials leading to the concept of the network glass transition temperature. Results offer a new insight into the structure and mechanical properties of preparations with direct use in food and pharmaceutical products.

Introduction

The glass transition temperature ($T_g$) is often measured calorimetrically as a change in heat capacity. It is also determined rheologically from the temperature dependence of the storage ($G'$) and loss ($G''$) moduli on shear as the temperature where the storage modulus starts to fall rapidly with increasing heating, the temperature where the loss modulus or the ratio of the loss modulus to the storage modulus (tan δ) reaches a maximum, and the temperature where the storage and loss moduli coincide. These four criteria will give different values for the mechanical $T_{g'}$.\(^1\)

A fundamental definition of the glass transition temperature can be advanced by considering that the appearance of the transition region in the viscoelastic spectrum is due to the extended and submolecular Rouse modes. These correspond to configurational rearrangements of parts of the polymeric chain between adjacent junction zones, which mainly dissipate energy thus augmenting the viscous element of the mechanical response. A connection can be made between the coupling model of the sub-Rouse motions and the free volume theory since the aforementioned modes are responsible for the diminishing free volume. The latter declines to mechanistically inconsequential levels at the end of the glass transition region being about 3% of the total volume of the molecule. Materials at temperatures far above the vitrification point, i.e. at the onset of the glass transition region or in the rubbery plateau, have much higher free volumes; in excess of 30% instead of 3%. Both theories support the concept of an apparent energy of activation required for the occurrence of local segmental motions in the solid-like environment of the glassy state, thus introducing the $T_g$ as a point of physical significance at the threshold of two distinct molecular processes.

The Network Glass Transition Temperature

Recently, we demonstrated that the Williams, Landel and Ferry (WLF) equation which was contrived to follow the effect of temperature on viscoelastic functions of amorphous synthetic polymers could also be utilized in biomaterials.\(^2\) The WLF equation provides a convincing fit of the shift factors derived in the glass transition region for single biopolymer or sugar/biopolymer blends thus generating predictions of $T_g$ in good agreement with experimental values. However, the WLF equation is unable to follow progress in viscoelasticity in the glassy state, which is better described by a modification of the equation of Arrhenius thus yielding...
a constant energy of activation.

It was found that small additions of a network forming biopolymer (0.5 - 2%) to a sugar preparation alter dramatically the rubber-to-glass transition as determined using this free volume/WLF approach. The acceleration of vitrification properties in the presence of polysaccharide shows that there is a considerable gap in the development of shear modulus values between sugar preparations, and their mixture with polysaccharide at level of solids between 60 and 93%. In contrast, calorimetry work from the literature argues that with or without biopolymer, vitrification is dominated by the sugar spectrum.

Our results point out that addition of gelatin fractions of increased molecular weight, pectin of increased degree of esterification, deacylated gellan with added sodium and k-carrageenan with added potassium, i.e. characteristics which enhance gelation, accelerate the mechanical manifestation of vitrification. This is not the case for agarose and k-carrageenan samples with a sugar content in excess of 93% where there is no significant difference between rheology and calorimetry. It appears that increasing removal of water from the polysaccharide network reduces the capacity for development of intermolecular associations, to such an extent, that at extremely high levels of solids (> 93%) formation of a three-dimensional structure is abandoned. Similarly, addition of non-gelling polysaccharides such as guar or locust bean gum has little effect on the conventional (calorimetry) and rheological trend of vitrification phenomena.

Note on Potential Applications and Future Trends

One of the incentives to do research on high solid systems is replacing gelatin in food and pharmaceutical applications. Gelatin is considered to be the archetype of a biological rubber and forms gels or glasses of brilliant clarity. Addition of high levels of sugar to polysaccharides transforms them into clear gels of considerable elasticity and yield properties extend to similar levels with those of the protein. In addition, normal requirements for product development do not exceed one percent of polysaccharide in the formulation, which can represent substantial savings over gelatin which is typically used at 5 to 15%. Although the small deformation rheology of high sugar gelatin systems can show a similar type of response to polysaccharide systems, there are important structural differences between the two classes of biopolymer.

This is illustrated by the TEM micrographs shown in Figure 1. The micrograph on the top shows an aqueous gellan gel in the presence of added calcium ions. A polymer network of fibrillar thickness up to 40 nm is obtained which should comprise tens of double helical strands per filament. In contrast, addition of high levels of sugar result in reduced aggregation of the polysaccharide network. While the polymer forms a continuous phase that supports the mixture in the form of a cohesive gel, dense fibrillar structures are not visible (middle micrograph). Similar results have been obtained for the remaining...
gelling polysaccharides of industrial importance.

Gelatin appears to respond differently to gelling polysaccharides in a high solids environment with sugar promoting chain association rather than inhibiting it. Thus, there are demixed gelatin and sugar rich domains of considerable size in the bottom micrograph of Figure 1, as opposed to the homogenous polysaccharide assemblies at high levels of co-solute. The heterogeneity in the protein/sugar mixture is also evident rheologically in the small deformation properties, which show a broader transition zone. This behaviour may have implications for the replacement of gelatin with small additions of gelling polysaccharide in high sugar biomaterials.

Conclusions

It has been put forward that for many polysaccharides as the solids concentration increases to levels encountered in food and pharmaceutical applications chain–chain association is reduced. As a consequence, the strain at break rises and approaches values found for ‘rubbery’ gelatin gels. The viscoelasticity of high sugar polysaccharides parallels that of amorphous synthetic polymers thus affording analysis with ideals developed for synthetics. Glassy behavior is observed at low temperatures and/or high solid contents. The glass transition temperature measured by calorimetry remains unaltered by the presence of low levels of polysaccharide suggesting that the mobility of the sugar is unaffected by the presence of the polysaccharide. However, the mechanical profile of the rubber-to-glass transition is strongly influenced by the polysaccharide particularly if it is network forming. We propose that it is possible to represent the magnitude of this polysaccharide contribution to rheology by a ‘network T$_g$’, the greater the extent to which this differs form the calorimetric $T_g$, the larger the influence of the polymer on the rheology.6

What happens in high solid biopolymer or sugar/biopolymer environments has only lately been considered in earnest by the research community. Yet, this is of great importance for the food industry and has other applications, for example, flavour or antioxidant encapsulation and preservation of bioactive molecules in glassy carbohydrate matrices related to drug delivery. It is our view, the fundamental approach discussed in the present paper has a role in generating a better understanding of current applications and developing new uses.

References


Polyelectrolyte brushes consist of charged polymer chains (polyelectrolytes) attached to a substrate. They have vast technological potential due to providing control of, e.g., gelation, lubrication, and flow behavior, so have found wide-spread applications from the stabilization of colloidal suspensions in cosmetics and food products to encapsulation and delivery of bioactive agents to living cells. Furthermore, polyelectrolyte brushes are thought to be a model system of the external envelope of certain microorganism and, hence, progress in this area also has implications for related fields such as cell recognition.

These systems can be prepared by anchoring the polyelectrolyte chains at an interface or, more interestingly, through the principle of self-assembly of diblock copolymers. Polyelectrolyte diblock copolymers comprise two linearly attached polymer chains - in this case, a polyelectrolyte, which is hydrophilic, and a neutral, hydrophobic polymer. In aqueous solution, the copolymers arrange themselves into micelles so that the hydrophobic attachments are shielded from the water. These nanometer-sized micelles thus comprise a neutral core of self-assembled neutral chains (typically about 100), surrounded by a polyelectrolyte coronal brush.

These copolymer micelles provide an excellent model system for investigating how spherical polyelectrolyte brushes behave, provided that their neutral cores are stable at ambient temperature. In practice, this can be realized by using a diblock copolymer with a high glass temperature of the core forming segments (for example, sodium poly(acrylate-block-styrene)). Because the coronal brush is ionic, the micelles readily disperse in water or aqueous salt solution. The polyelectrolyte dissociates into small counterions and the negatively charged polymer chains stretch out into the aqueous environment. Since technological formulations and biological environments usually contain other small ions, a significant aspect is the effect of adding salt. The addition of salt...
results in screening of the electrostatic repulsion between the charged segments in the coronal layer, which is expected to make it behave like a coiled, neutral brush.

The key approach in understanding of the functioning of the polyelectrolyte brush under various conditions is to look at the micelle structure, going from the core outwards, in terms of polymer and small ion density. My research team has measured these density profiles with small angle neutron and X-ray scattering and applying solute and solvent contrast variation techniques to highlight or blank the various components in the complex mixture of copolymer, salt and water.

**Individual micelles**

For highly charged brushes and no salt added - so with minimal screening - we found that the corona chains are almost fully stretched and that the density profile of the counterions follows that of the corona forming polymer segments (1,2). The brush was also observed to be rather robust against the addition of salt; quite a lot of salt is necessary to induce a significant contraction of the brush (3). These results show that stretching of the polyelectrolyte brush is primarily controlled by the counterions trapped in the coronal layer, which draw in water osmotically, rather than the electrostatic repulsion between the charged segments.

**High concentration**

We then extended our experiments to micelle concentrations high enough to cause the coronal brushes to shrink or interpenetrate. This is significant, because many of the technological applications are derived from the fluid properties of dense micelle systems, and yet not much is known about how the brushes behave.

We did small angle neutron and X-ray scattering experiments on a model system of spherical micelles up to concentrations where the polyelectrolyte brushes have to shrink and/or interpenetrate in order to accommodate the micelles in the increasingly crowded volume (4,5). We focused on the contraction of the brush before overlap, possible interpenetration at high packing fraction, and the relation with charge and electrostatic screening. We measured the sizes of the core and corona, which gave the overall spread of the micelles; we then measured the distance of closest approach between the micelles packed as hard spheres in the solution. The difference between these values gave the degree of interpenetration of the brushes.

The results showed that the polyelectrolyte brushes do shrink as the micelles are squeezed together. However, at high charge and minimal screening conditions - when the polyelectrolyte chains remain almost fully stretched - they start to interpenetrate above a certain concentration. Flow measurements showed that the viscosity increases by a thousand times resulting in a physical gel. We conclude, therefore, that tuning the properties of the brush is of paramount importance in developing formulations with the right fluid properties.

**Research team:** A.V. Korobko and W. Jesse (Leiden University), A. Lapp (CEA/CNRS Saclay), S.U. Egelhaaf (University of Duesseldorf), and J.R.C. van der Maarel (National University of Singapore).

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Quantum Geometry
Prof Lian Bong Hor, Department of Mathematics

This article’s title was coined by physicists in the late eighties to describe what was then an emerging subject in theoretical physics. The last twenty some years have arguably been the most exciting time in theoretical physics since the discoveries of quantum mechanics and Einstein’s theory of gravity, which quantum geometry or string theory ostensibly unifies. This article is a (perhaps unconscionably) brief account of this unifying theoretical framework, from the viewpoint of a mathematician who has enjoyed the good fortune of being a part of the exciting development of this framework. For a more extensive account, I would highly recommend reading (3), and (6) for the more ambitious readers.

Quantum corrections to classical physics. In the Newtonian framework, all laws of physics are deterministic in that the “physical state” of a system at a given time can, in principle, be fully determined by its initial condition – the physical state at an earlier time. By “physical state”, one technically means the full set of parameters (position, velocity, etc) that one uses to describe a system. Thus knowing the position and velocity of the earth relative to the sun at 12 o’clock, for example, we can predict with arbitrary accuracies the earth’s position and velocity at 1 o’clock, by taking into account the gravitational pull from the sun and any other nearby planets. In the framework of quantum mechanics, however, such determinacy is no longer available. In fact, under the laws of quantum physics, the parameters that characterize a physical state can no longer be determined with arbitrary accuracies. Instead, only their averages are physically meaningful. Fortunately, the corrections to our description of the macroscopic world, such as our planetary system, due to quantum effects are so insignificant that they can be safely ignored. But the quantum corrections become impossible to ignore in the microscopic world. For example, in the case of an electron orbiting around the nucleus in, say, a hydrogen atom, the quantum corrections would render the Newtonian description of the orbits virtually meaningless.

When the large meets the small. Einstein’s general theory of relativity is a theory of the dynamics of spacetime geometry, applicable at large scales. It is capable of accurately describing how matter interacts with and distorts the spacetime fabric surrounding it, such as in our solar system or in galactic systems in our universe. Wouldn’t it follow that quantum corrections arising in any gravitational phenomenon can be safely ignored? It would be so if the universe were nice and smooth everywhere, and the distortion to its geometry by matter is insignificant at a microscopic scale. Unfortunately, relativity itself predicts that there would be places, called singularities, where the local geometry is so warped that ordinary laws of physics can no longer be reliably applied. It is expected that quantum effects, whatever they might be, will become significant here and that those effects might even “repair” relativity’s inability to describe spacetime singularities.

Paradigm shift. String theory is one attempt to unify quantum theory and gravity. It is a theory that begins with a fundamental shift in our perception of matter itself: all matter is made up of little tiny vibrating loops; while the loops are identical, their different modes of vibrations result in different manifestations of their physical behavior representing different species of particles – such as quarks and electrons – that we are more accustomed to. There are many types of string theories. For a long time, physicists have been trying to compute some of the physical
quantities – masses, couplings, number of particle generations, etc – that these theories should predict. In the framework of the so-called type IIA closed string theory, one especially intriguing, but important, quantity is the Yukawa coupling. It measures the strength of interaction of three particular types of string states in a scattering process that takes place in a 10 (yes 10!) dimensional spacetime. Six of those 10 dimensions are known to be tightly curled up to a tiny geometrical object known as a Calabi-Yau (CY) manifold. The coupling is known to depend on both the shape and the size of the CY. The shape dependence is classical and it’s computation is relatively easy. The size dependence is a quantum effect and computing it would later turn out to be related to a long-standing mathematical problem about CY manifolds. But at first, no one knew what the form of this dependence was, let alone computing it exactly, that is until 1989.

Worldsheet instanton sum. That year, Candelas et al (2), found a way to compute the Yukawa coupling for a particular CY by using a conjectural relation between its physics and that of another string model known as a type IIB theory. They also proposed an ansatz, known as a worldsheet instanton sum, as follows:

\[ \text{Yukawa} = 5 + \sum_{d=1}^{\infty} \frac{n_d d^3 q^d}{1 - q^d} \]

giving the full quantum correction to the Yukawa coupling of a CY. Here \( q \) is a small complex number parametrizing the size of the CY, and the \( n_d \) can be interpreted as the numbers which count surfaces of certain kinds residing in the CY, which are something known to be exceedingly difficult to compute directly in mathematics. Thus their conjectural formula amounts to giving a prediction of all of these numbers! For example, one has \( n_1 = 2875, n_2 = 609, 250, n_3 = 317, 206, 375 \). The mathematical proof of the conjectural formula above had remained elusive for many years despite several attempts. It was finally proved in 1997 (4) jointly by K. Liu (UCLA), S.T. Yau (Harvard) and this author.

The proof makes use of a substantial amount of modern technical tools in differential and algebraic geometry. The formula above turns out to be a prototype of surface counting formulas (1). A number of generalizations are also discussed in my subsequent joint papers (see (5) for example.)

What’s next? The formula of Candelas et al and its many generalizations have given us a glimpse of how certain structures of spacetime geometry (the special surfaces contributing to Yukawa in the example above) can result in quantum corrections to a physical quantity. This may be a hint that similar kinds of quantum corrections may be necessary to render harmless those spacetime singularities that are inherent in relativity. Understanding such a mechanism both physically and mathematically is one of the central problems in quantum gravity, and much work remains to be done.

References


Research influenced by Statistical Practice
Prof Bruce Brown, Department of Statistics and Applied Probability

Without any doubt, the strongest influences on my research have been the enjoyment with working with friends and colleagues, and the great pleasure of applying Statistics to real-life problems as part of statistical consulting work. The latter applies particularly to more recent years. The benefits which practice brings to theoretical understanding are hard to exaggerate. Almost every statistical consulting problem I met has been valuable and enjoyable.

My PhD and early research was in Probability Theory: stopping times on martingales and martingale central limit theorems. This was a long time ago, before the explosion of interest in martingale applications in epidemiology, survival analysis, finance, etc. I had excellent PhD supervisors at Purdue, Professors Chow Yuan Sinh and Henry Teicher, to whom I owe a lasting debt of gratitude.

Enjoyable though this work was, the realities of commencing an academic career in the relative isolation of Australia, in the late 60s, forced me to the conclusion that my research had to have useful practical application. This was no hardship, having always enjoyed Statistics, especially during a brief one year employment as a Statistician with CSIRO in Sydney immediately after my honours year, before committing myself to graduate work and an academic career. Looking back, the enjoyment of this experience was an indication of what lay ahead.

Along with beginning to do statistical consulting work within Universities, I was led to a lifelong interest in Non-parametric and Robust Statistics. Professor Tom Hettmansperger of Penn State, a world leader in non-parametrics, has been an enduring personal friend and collaborator, and his influence has been profound. Over the years we have worked on bivariate rank measures and methods, redescending influence functions, normal probability plots, isotonic regression, and circularity in rank methods.

I moved to Tasmania for lifestyle reasons in the early 80s, and there discovered the true meaning of isolation. This had the effect, seen in hindsight to be very beneficial, of forcing an outreach for different types of work and contacts. One was collaborating with workers from CSIRO’s Marine Division in Hobart to work on animal abundance estimation methods in connection with aerial line transect surveys for investigating stocks of Southern Bluefish Tuna. Another was the setting up of a private company Industrial Resolutions Pty Ltd, doing commercial optimization work, largely for Tasmanian Paper Mills, in providing software for solving very large versions of the classical trim loss problem in Linear Programming.

These experiences were the beginning of a very serious interest in consulting work, which developed further after moving in 1999 to the University of South Australia in Adelaide. There, I founded and ran the Statistical Consulting & Research Service, which provided university-wide statistical assistance for research purposes. Most of the work was in the areas of Social Science, Health Sciences, Business and Marketing. All of this work was enjoyable, but what was quite

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astonishing was the degree to which it provided fresh perspectives and fresh problems for my own research in Non-parametric Statistics and associated areas. These days, many academics have a good working knowledge of Statistics, so it was quite common for the real needs of clients to be on the edge, or even outside, the domain of knowledge of standard methods. This work led me to investigate new aspects of rank correlation measures, and uncover a new distribution for discrete choice, stemming from a Marketing context.

Another development during this time was the beginning of an acquaintance with NUS, through a series of visits initiated by colleagues here, along with work in the Statistics of Financial Diffusion Processes, and applications of rank methods in BioStatistics.

Explaining the inherent interest in individual consulting problems can take time, because many such problems have their own detailed background infrastructure, which can be complex. But some of the stimulation of real-life statistical problems may be conveyed by the two graphs below, where it possible to see how the underlying story unfolded. Both these examples arose from cases of legal action, where the background was very serious, and the stakes were high.

My main area of research interest has been the theory and application of robust, nonparametric and distribution-free Statistics. A feature of these methods is that they rely on minimal or no assumptions about underlying distributions which generate data. This area has a long history of application in Social Science, especially Psychology, where observational distributions may be quite different from the normal. But, the area has become more widely applied, in many diverse parts of Science and Commerce, over the last thirty years. At the same time the theory has become more systematically understood. Thus, as Statistics expands into more fields of contemporary relevance (biostatistics, epidemiology, medical statistics, image analysis, bioinformatics, and genetics) so does Non-parametric Statistics find wider areas of application.

Within the Department of Statistics & Applied Probability there is a broad range of modern research interests, and promising avenues for interesting collaborations and worthwhile research projects, where non-parametrics has a valuable role to play. In time I hope to discuss Statistics with colleagues in other Departments as well, and from all points of view, I look forward to my time at NUS with a great deal of pleasure.
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