chromatography on silica gel (hexane/diethyl ether 10/1) to give 65.4 mg of (*S*)-alcohol **2** (86% yield, 60% *ee*).

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[7] The enantioselectivity was determined by ^{1}H NMR analysis of the (*S*)-MTPA ester (MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid). The absolute configuration was assigned by the specific rotation: (*S*)-**2** (50% *ee*) $[\alpha]_D^{23} = +28.9$ ($c = 0.97$ in EtOH); value of $[\alpha]_D^{18} = +55.9$ ($c = 1.40$ in EtOH) in the literature: G. Berti, F. Bottani, P. L. Ferrarini, B. Macchia, *J. Org. Chem.* **1965**, *30*, 4091–4096.
[8] When *s*BuLi/(−)-sparteine was used instead of *t*BuLi/**3**, (*S*)-**2** was obtained in 36% yield and with 24% *ee*, and **1** was recovered in 66% yield.
[9] When the reaction temperature was lowered to −110 °C, 71% *ee* was observed with 37% chemical yield.
[10] T. F. Bates, M. T. Clarke, R. D. Thomas, *J. Am. Chem. Soc.* **1988**, *110*, 5109–5112.
[11] Treatment of **1** with *t*BuLi alone in diethyl ether under the same conditions did not gave any trace of **2**. In sharp contrast, the reaction in THF gave **2** in 70% yield.
[12] For the chemistry of RLi/R′OLi complexes, see P. Caubetre, *Chem. Rev.* **1993**, *93*, 2317–2334.
[13] We found that the separately premixed *t*BuLi/lithium alkoxide of **2** is not reactive enough to induce the rearrangement.
[14] The rearrangement of **4** and **6b** with 10 mol% of **3** resulted in 53% *ee* (56%) and 54% *ee* (35%), respectively.
[15] The enantiomeric excesses were determined by ^{1}H NMR analysis of the (*S*)-MTPA esters. The absolute configurations of the major enantiomers obtained from **4** and **5** were not determined. The (*R*) configuration of **7a** was assigned by conversion into the known (*R*)-methyl α-benzylmandelate: $[\alpha]_D^{23} = -13.5$ ($c = 1.20$ in $CHCl_3$) (65% *ee*); value of $[\alpha]_D^{26} = -32.4$ ($c = 3.4$ in $CHCl_3$) in the literature: H. R. Sullivan, J. R. Beck, A. Pohland, *J. Org. Chem.* **1963**, *28*, 2381–2385.

The Design of Leadlike Combinatorial Libraries

Simon J. Teague,* Andrew M. Davis, Paul D. Leeson, and Tudor Oprea

Combinatorial chemistry is now widely applied in the drug-discovery process, for both the identification and optimization of lead compounds (chemical starting points). Initially the key factors in the design of libraries intended for finding lead compounds were considered to be library size and diversity.[1] More recently consideration has been given to designing libraries in which the members have druglike physicochemical properties.[2] Druglike properties are most commonly defined using the "rules of 5": M_r is smaller than 500, the calculated logarithm of the octanol–water partition coefficient (clg *P*) is less than 5, there are less than five hydrogen-bond donor atoms, and the sum of the number of nitrogen and oxygen atoms is less than 10.[3] These guidelines have achieved widespread acceptance as defining the limiting properties of most orally active drugs which are able to be absorbed by passive mechanisms. However, it should be borne in mind that these are empirical rules derived by examination of the properties of existing drugs. Herein we propose that the properties required of library compounds intended to provide leads suitable for further optimization may be rather different.

Our analysis starts from consideration of the common sources of leads for drug discovery (Figure 1). These have been divided broadly into three types. The first are leadlike,

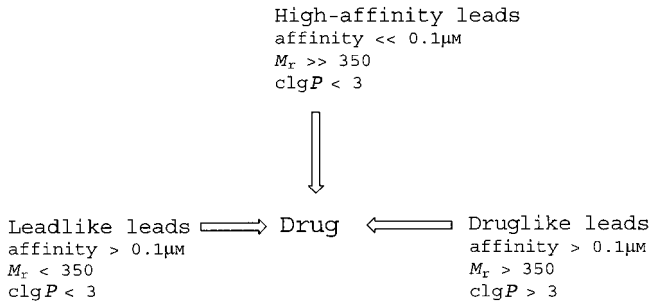

Figure 1. Classification of leads by binding affinity. Lower potency leads are subdivided into leadlike and druglike by reference to their M_r and clg *P* values.

low-affinity (>0.1 μM)[4] compounds which have low molecular weight and clg *P*, typified by some endogenous molecules, for example histamine and GABA. These have been converted into drugs, through the optimization of potency and pharmacokinetic profile, by increasing molecular weight and lipophilicity (Table 1, entries 1–8). The second major source of leads is typified by high affinity and molecular weight. It

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Table 1. Examples of low-affinity leads which have been converted into drugs.[a]

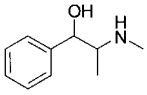
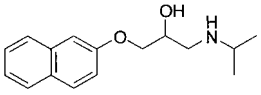
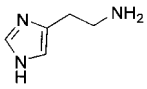
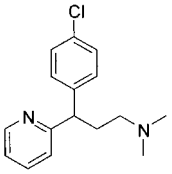
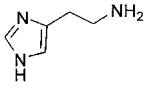
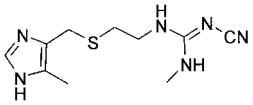
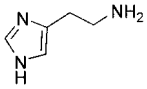
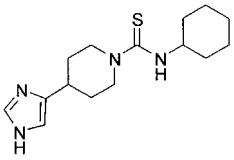
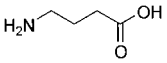
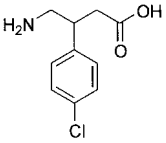
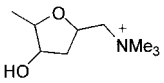
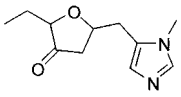
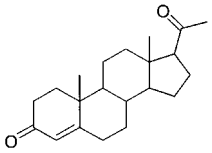
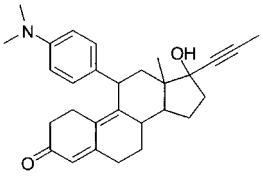
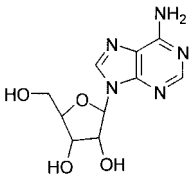
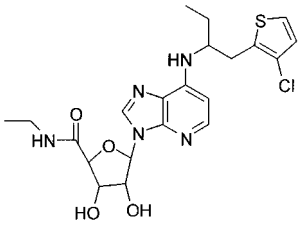
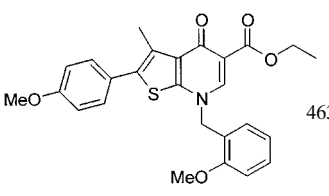
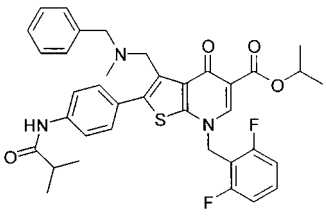
Entry	Receptor	Lead[b]			Drug			ΔM_r	Δclg P	Ref.
			M_r	clg P		M_r	clg Pd			
1	β1	 norepinephrine	165	1.05	 propranolol	259	3.1	94	2.05	[8]
2	H1	 histamine	111	– 0.84	 chlorpheniramine	274	3.39	163	4.23	[9]
3	H2	 histamine	111	– 0.84	 cimetidine	252	0.36	141	1.2	[10]
4	H3	 histamine	111	– 0.84	 thioperamide	292	1.73	181	2.57	[11]
5	GABA	 GABA	103	– 0.64	 baclofen	213	1.56	110	2.2	[12]
6	muscarinic	 muscarine	147	–[c]	 pilocarpine	208	– 0.1	61	–[c]	[13]
7	steroid	 progesterone	314	4.04	 mifepristone	429	4.91	115	0.87	[14]
8	adenosine	 adenosine	267	– 1.26	 RPR-100,579	477	3.05	210	4.31	[15]
9[d]	LHRH		463	5.09	 T-98475	657	7.04	194	1.95	[16]

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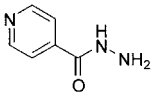
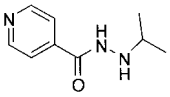
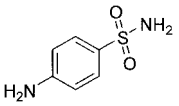
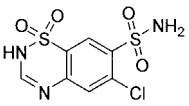
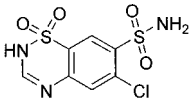
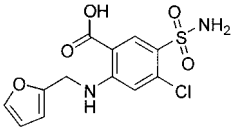
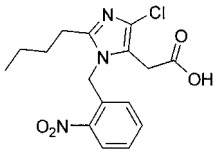
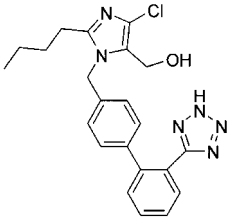
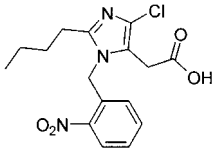
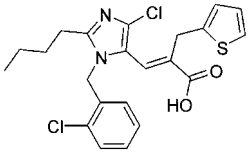
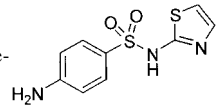
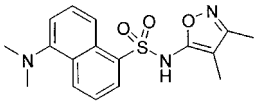
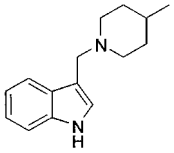
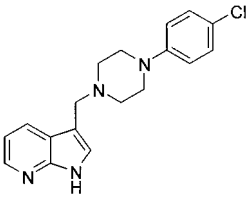
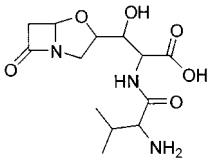
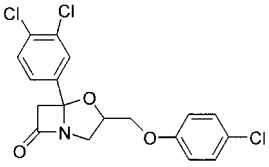
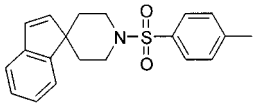
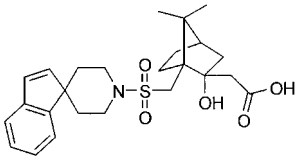
Table 1. (Continued)

Entry	Receptor	Lead[b]			Drug			ΔM_r	Δclg P	Ref.
			M_r	clg P		M_r	clg Pd			
10	MAO	 isoniazid	137	– 0.89	 iproniazide	179	0.55	42	1.44	[17]
11	Cl channel	 sulfanilamide	172	– 0.72	 chlorothiazide	295	– 0.03	123	0.69	[18]
12	Cl channel	 chlorothiazide	295	– 0.03	 furosemide	330	2.92	35	2.95	[19]
13	Ang II	 Takeda lead	351	3.18	 losartan	422	3.5	71	0.32	[20]
14	Ang II	 Takeda lead	351	3.18	 eprosartan	448	6.75	97	3.57	[21]
15	endothelin	 sulfathiazole	255	0.33	 BMS-182874	345	3.72	90	3.39	[22]
16	dopamine		229	3.52	 L-745,870	326	4.08	97	0.56	[23]
17	AGT	 clavamycin D	315	– 2.3	 SDZ PGU 693	411	3.78	96	6.08	[24]
18	oxytocin		339	4.83	 L-366,509	459	3.03	120	– 1.8	[25]

[a] An increase in M_r (ΔM_r) of 100–200 and in clg P (Δclg P) of 0.5–4 is typically observed. [b] Unless indicated otherwise, the leads are leadlike (see Figure 1). [c] clg P is not definable for a permanently charged compound. [d] The lead is druglike (see Figure 1).

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encompasses many peptidic materials and certain potent natural products. This type of lead has provided a number of drugs, for example indinavir from HIV protease substrate[5] and trimethoprim from dihydrofolate.[6] Here the issue is usually one of retaining sufficient potency whilst improving pharmacokinetic profile. This is often achieved by reducing molecular weight and increasing lipophilicity. However, the increasing dependency upon screening historical compound collections and combinatorial libraries in order to obtain leads often results in a third type of lead. These have low affinity and druglike molecular weight (350–500) and lipophilicity (3–5). This is borne out by examination of the results obtained from our own high-throughput screens. The distribution of IC_{50} values for approximately 3000 compounds identified in 10^6 high-throughput screens at AstraZeneca R&D Charnwood is plotted in Figure 2 together with the corresponding distribution of M_r and clg P values.

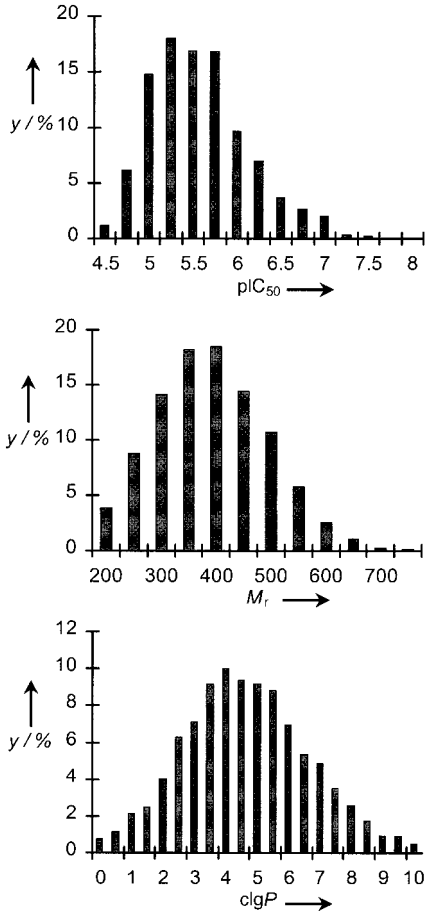

Figure 2. Distributions of pIC_{50} values (top) for approximately 3000 compounds identified in 10^6 high-throughput screening tests and the corresponding distributions of M_r (middle) and clg P values (bottom). The ordinate (y) represents percentages of the total sample set in each abscissa bin.

We find that potent ligands ($IC_{50} < 0.1$ μM) are rarely found directly from screening druglike libraries. To achieve high potency, a specific, tight fit between the ligand and the receptor binding pocket is needed, requiring the correct placement of hydrogen bonds as well as charged and hydrophobic groups. The data suggests that the probability of this occurring is small ($< 1{:}10^6$). The usual result is the discovery of a number of ligands with IC_{50} values of 1–10 μM (83% with >1 μM) with M_r values of 350–450 (54% with >350) and clg P of 3–4.5 (75% with >3). Optimization of these molecules with druglike properties and leadlike affinity is difficult. Precedent from small, polar leads (Table 1, entries 1–8) suggests that an increase in M_r of 1–200 and in clg P of 0.5–4 often results, as a consequence of affinity enhancement, during the optimization of a low-potency lead into a drug. However, both of these changes are likely to move a druglike lead out from under the envelope of druglike property distributions into regions where poor bioavailability would be predicted (Table 1, entry 9).

Druglike leads probably achieve μM affinity using many poorly optimised interactions. This is demonstrated by using Andrews' equation.[7] Although this analysis is only a crude estimation of binding affinity, large positive and negative deviations of potency from that predicted by Andrews' analysis are indicative of the complimentarity of the drug–receptor interaction. As the original paper states, "the primary use of the *average* binding energies is to deduce whether a particular drug represents a good or bad match to its receptor". The predicted and observed binding affinities for our 3000 active compounds are compared on the same scales in Figure 3. A large percentage of the druglike leads have much less affinity than would be expected for molecules with this number of molecular features. In 10^6 screening determinations no compounds produced an IC_{50} of less than 10 nM. From Andrews' analysis 22% of compounds of this complexity would have been expected to have an AVERAGE pK_i of less than 10 nM.

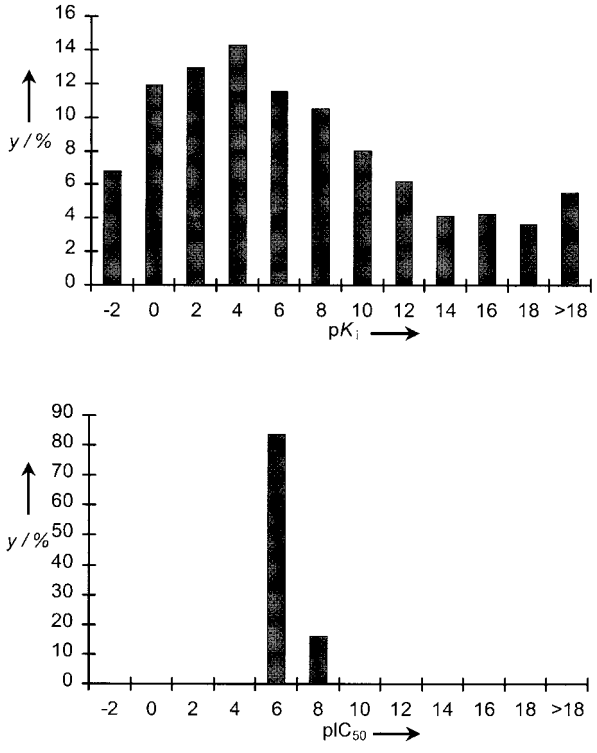

Figure 3. Comparison of pK_i values calculated by Andrews et al.[7] and observed IC_{50} values of active compounds from 10^6 high-throughout screening determinations. The ordinate (y) represents percentages of the total sample set in each abscissa bin.

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Another source of leads which are not very potent at the required receptor are those that are obtained by observing side effects in existing drugs (Table 1, entries 10–12). Here the same pattern of increasing molecular weight and lipophilicity is observed. Finally there are many recent examples where the lead originating from high-throughput screening of historical collections is elaborated by exploiting additional lipophilic interactions to produce molecules with druglike physicochemical properties and high affinity (Table 1, entries 13–18). Thus if it is anticipated that both molecular weight and lipophilicity will increase during the process of lead-to-drug optimization, and that orally active compounds are eventually required, there are clear implications for the design of libraries intended for lead discovery.

We propose that there is a great deal of precedent to suggest that libraries consisting of molecules with $M_r = 100–350$ and $\mathrm{clg}\,P = 1–3.0$ are greatly superior to those comprising druglike compounds. These libraries are intended to provide leads with μM affinity in high-throughput screens, but also to allow for the discovery and exploitation of additional interactions in the lead-optimization phase. This is illustrated graphically in Figure 4, where the molecular weight distributions of a library of leadlike molecules, all oral drugs from the Physicians Desk Reference (PDR),[26] and a typical combinatorial chemistry library are represented. Optimization of affinity for leadlike molecules produces a rightward shift into the druglike region.

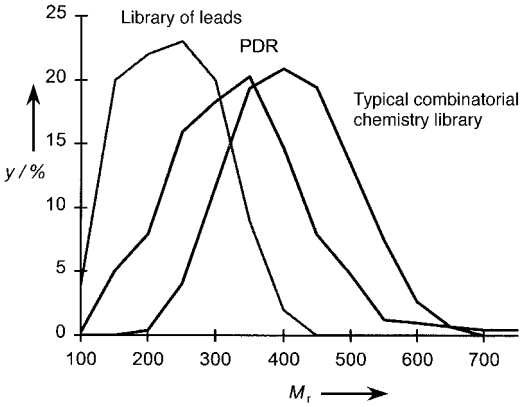

Figure 4. Distributions of M_r for a leadlike library, oral drugs (Physicians Desk Reference (PDR), 1994), and a typical combinatorial chemistry library.

Molecules with leadlike molecular weight and lipophilicity must still interact with a receptor to produce an IC_{50} in the 1–10 μM range if they are to be detected in a high-throughput screening determinations. This may account for the preponderance of leadlike molecules bearing a single charge at physiological pH values, since this provides for the possibility of a large binding affinity with little molecular weight penalty.

It is clear that small, polar molecules can also display sufficient selectivity in receptor binding assays. Thus, norepinephrine, dopamine, and histamine, for instance, display selectivity for their respective receptors, even though these receptors all belong to the G-protein-coupled receptor (GPCR) superfamily. Often receptor subtype selectivity, starting from one endogenous agonist, is obtained by the introduction of potency-enhancing, specific, lipophilic interactions. Small leadlike molecules have a better chance of binding to a receptor, because they can more easily find a binding mode than larger druglike molecules. Once a small polar molecule with affinity at μM levels has been found, more focused libraries can be rapidly improve upon it. This is often achieved by the introduction of lipophilic groups which simultaneously improve affinity and the pharmacokinetic properties of these molecules. However, if libraries of molecules of druglike size are used at the outset, this opportunity is lost.

An emphasis upon generating libraries consisting of low molecular weight, polar molecules, with the aim of obtaining leads with affinity at μM levels may justify a reexamination of the role of some combinatorial technologies. Large libraries generated by concatenating several monomers using multicomponent reactions or using several steps incorporating split-and-mix protocols may not be the most effective approach. Relatively simple one- or two-step elaboration of a wide variety of small templates is more useful in providing libraries of this type. The leads discovered are more easily elaborated into drugs with the required physical properties. In our experience the relative values of active compounds emerging from a high-throughput screen can usefully be assessed on the basis of biological activity per unit of molecular weight and lipophilicity. The selection of leadlike compounds for further optimization eases the pressure on subsequent and more labor-intensive parts of the drug-discovery process, such as obtaining suitable bulk properties together with an acceptable metabolic and pharmacokinetic profile.

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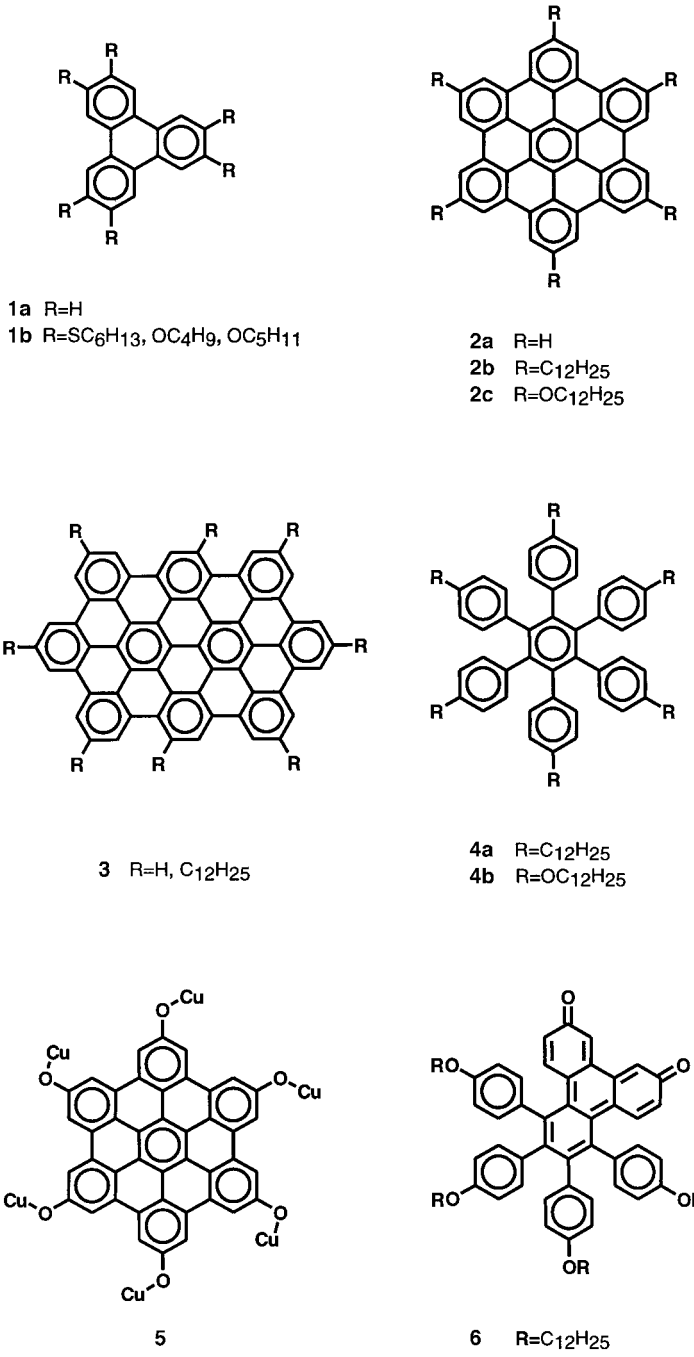

Scheme 1. Polycyclic aromatic hydrocarbons **1** – **6**.

Template-Mediated Synthesis of Polycyclic Aromatic Hydrocarbons: Cyclodehydrogenation and Planarization of a Hexaphenylbenzene Derivative at a Copper Surface**

Klaus Weiss, Gunda Beernink, Florian Dötz, Alexander Birkner, Klaus Müllen, and Christof H. Wöll*

Polycyclic aromatic hydrocarbons (PAHs) such as triphenylene (**1a**), hexa-*peri*-hexabenzocoronene (HBC, **2a**), and its higher homologue **3** (Scheme 1) form two- and three-dimensional superstructures that are attracting considerable attention in the field of charge transfer processes.[1–4] The deposition of monomolecular layers, a central step for using such disklike molecules in nanoelectronic devices, can be performed by evaporating PAHs in ultrahigh vacuum (UHV) and, in case of alkyl-substituted soluble derivatives, also by deposition from solution. However, both preparation procedures cannot be applied to larger PAHs which have recently been synthesized.[5–8] We therefore present a method to produce PAHs, for example, hexabenzocoronene, directly by a thermally induced cyclodehydrogenation route starting from a precursor molecule adsorbed on a Cu(111) surface. This new synthetic route is based on the following concept:

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