Alkyl Isosteres

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Ⓢ Supporting Information

ABSTRACT: By substituting an ER_3^- unit (E = Group 13 element) or $E'R_3^+$ (E' = Group 15 element) for CR_3 one gets to methyl isosteres, compounds analogous to alkyls and isoelectronic or iso-valence-electronic to them. The substituent charge can be used to stabilize countercharged aromatic systems; some compounds of this type are known. Nature makes available all kinds of escape routes to such formally zwitterionic species. Strategies for impeding the often facile reaction channels that open up can be designed. We construct what we believe are viable further examples of zwitterionic methyl isosteres based on 3-, 5-, 7-, and 8-membered rings. A similar strategy is laid out for dicationic and dianionic xylene isosteres.
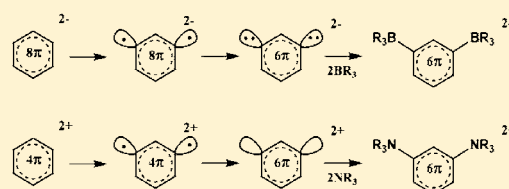
1. INTRODUCTION

In the course of stabilizing a hypothetical iodabenzene,[1] we came across a strategy for changing the electron count in a molecule by substitution of an H by a Lewis acid, such as BR_3, or a Lewis base, such as NR_3. An example will illustrate the unsophisticated thought process.

Consider an electronically unhappy 8 or 4 π-electron cyclic system, the dianion or dication of benzene (**1**, **2**, Scheme 1). These systems might in fact undergo severe geometrical distortions. Putting these for a moment aside, we remove two hydrogens from these molecules. We choose here a *meta* abstraction as an illustration; that choice is arbitrary. A formal diradical results. Take two electrons from the eight-electron π system of **1** and put them into the σ radical lobes. Or take the two radical σ electrons in the four π-electron system, **2**, and add them to the π system. Either way, you are left with a 6 π-electron aromatic system. Next, add two Lewis acids, say, boranes, in the first case, and two Lewis bases, say, NH_3 (or PH_3, CO, or a stabilized carbene), in the second case. You get what seem to be stable benzenoid systems (**3**, **4**, Scheme 1) for which reasonable, charged Lewis structures can be drawn. The ions **3** and **4** and *m*-xylenes are isosteres[2−5]—replacing the CH_3 in *m*-xylenes by isoelectronic BH_3^- or NH_3^+ would give the ions **3** and **4**.

Yes, one could have skipped the construction process and just written the final ionic Lewis structures. But we think the construction has heuristic value.

So far, this seems like paper chemistry. But not quite, for there is a recent report of the fascinating nucleophilic chemistry of $B(CN)_3^{2−}$, leading to a family of phenylborate anions, **5**,[6] closely related to the molecules of Scheme 1. **5** is an isostere of a substituted toluene. There are some other molecules that can be thought of in the same way, as we will see.

It must be said immediately that several components of this idea are not novel—the groups of Power,[7] Robinson,[8] Frenking,[9] Braunschweig,[10] and Bertrand[11,12] in particular have used Lewis acid/base ligand replacement strategies identical to or

Scheme 1. Hypothetical Construction of 6 π-Electron Aromatic Systems (3, 4) from Antiaromatic Benzene Dianion, 1, and Dication, 2
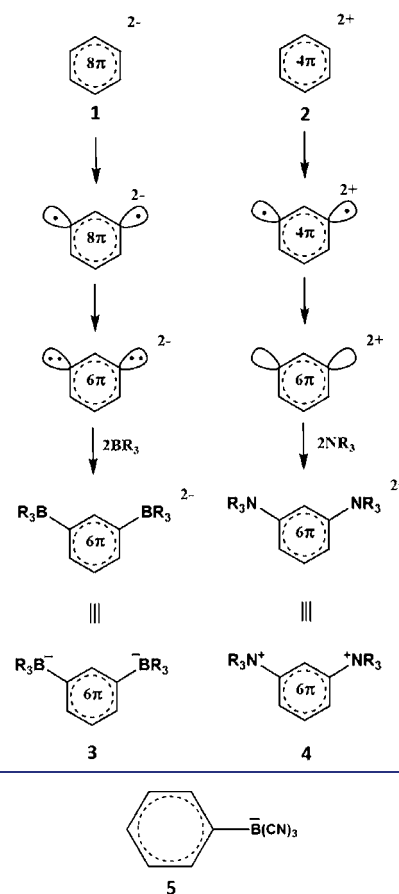
resembling the idea set out here. Wannere, Schleyer, and Schaefer et al. have already studied in detail, theoretically, the aromaticity of zwitterionic aromatic systems, including the ammonium-substituted ones to which we will return.[13] In this paper, playing with isosteres, we focus on the kinetic stability of borate-, aluminate-, ammonium-, and phosphonium-substituted zwitterionic aromatic systems. We do not discuss the wider class of stable zwitterions, be they amino acids or other organic examples; the reader can find a good survey of these in the Wannere, Schleyer, and Schaefer work.[13]

To get a feeling for whether this kind of substitution might in general result in realistic, viable compounds, we tried some calculations. The results we report are from DFT calculations at the M06-2X/Def2-TZVPPD level of theory, using the G09 program.[14−18] We chose the M06-2X method for our calculations, as there is evidence in the literature that this level does well for main-group thermochemistry and kinetics. For comparison, we add results from MP2 and PBE0 calculations as well in the Supporting Information (SI) for the smaller systems in each case.[19]

2. RESULTS AND DISCUSSION

2.1. Escape Routes: Take 1, The 1,2-H-Shift. We began with the isosteres of methyl-substituted monocyclic aromatic ions, specifically, methylcyclopropenyl cation, cyclopentadienyl anion, and cycloheptatrienyl cation (structures **6**, **7**, **8**, Scheme 2).

Scheme 2. Methyl-Substituted Charged Aromatic Systems (6, 7, 8), Corresponding Neutral Isosteres (9, 10, 11), and Their 1,2-H Shift Reaction[a]
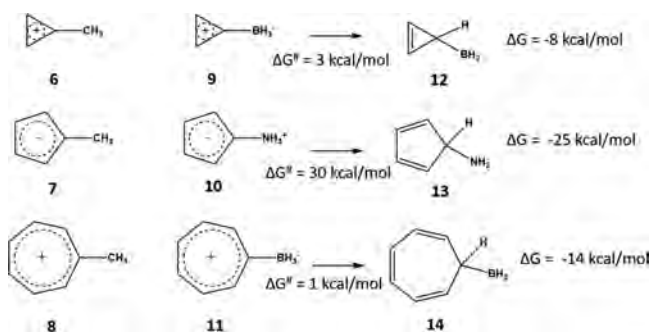
[a]Calculated Gibbs energies of activation ($\Delta G^{\#}$) and Gibbs energies of reaction (ΔG) are also shown.

Replacing the CH_3 in **6**, **7**, and **8** by isoelectronic BH_3^- or NH_3^+ moieties, so as to give neutral molecules, would give the isosteres **9**, **10**, and **11**. In computations, these emerge as local minima, with significant HOMO−LUMO gaps (8.0, 5.0, and 5.9 eV, respectively). But, in each case, there is an available hydrogen shift to a lower energy product, as shown in Scheme 2. The activation energy for the process is calculated to be 3, 30, and 1 kcal/mol, respectively, indeed very low for the BH_3-substituted cases. Still other isomers are then available by a sequence of sigmatropic shifts in the organic rings.

A general comment that can be made here is that we are seeing a working out of the information carried by a Lewis structure. The formal charges in a Lewis structure are not determinative, but they are indicative of the actual charge distributions in a molecule. And if there be a choice for a molecule between a Lewis structure that has charged atoms and an isomer where the Lewis structure contains no such charged atoms, the latter appears to be energetically favored, at least for simple structures.

For the cyclopentadienyl case (**10**), closely related derivatives are known experimentally, with phosphines instead of NH_3. The triphenylphosphonium cyclopentadienide is a familiar example.[20−22] Structures of type **10** are the cyclic analogues of the well-known ammonium ylides, which are the intermediates in the base-catalyzed Stevens rearrangement of quaternary ammonium salts (to which we will return).[23,24] Crystal structures are available for ammonium ylides stabilized by π-accepting groups.[23,25] The adducts of the immensely useful N-heterocyclic carbenes (NHCs) or cyclic (alkyl)(amino)carbenes (CAACs) with boranes are related to systems **9** and **11**.[26−38] Recently, an antiaromatic cyclopentadienyl molecule with a BF_3 substituent was detected in matrix isolation studies.[39] The recent synthesis of a zwitterionic 10π-aromatic system similar to **10** further emphasizes that the systems we consider are not far from reality.[40]

Note that the migration of a hydrogen from an ammonium to the ring has a much higher activation energy than that calculated for borates. There is a good reason for this, which we will explain.

It is clear that the general idea of methyl isosteres is a workable one. But, the hydrogen shift we have just discussed reveals an obvious escape channel, the first of several that we will uncover. This reaction channel must be inhibited if one wants a kinetically persistent isostere. Below we discuss our attempts to stabilize the Lewis-acid- or Lewis-base-coordinated aromatic systems of this type. We do not include the Lewis acid/base-substituted cyclobutadiene systems (which are analogues of cyclobutadiene dication and dianion) in our discussion, as none we have found quite reaches kinetic stability. See SI for discussion on these systems.

2.2. Borate Isosteres. *2.2.1. Borate-Substituted Analogues of Cyclopropenyl Cation.* The isomerization mechanism for the neutral, borate-substituted 2π-aromatic system, **15**, is shown in Scheme 3. We studied the energetics of this reaction by varying

Scheme 3. Isomerization of the Borate 2π Aromatic System, 15
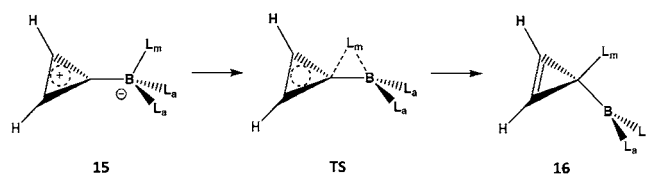
the migrating group (L_m) and the ancillary groups (L_a) at B; the results are tabulated in Table 1. Notice that in the reactant the electron deficiency is in the carbon ring, whereas in the product it shifts formally to boron, through its empty 2p orbital. This implies that electron-donating substituents on the carbon ring and electron-withdrawing substituents on B would stabilize **15**, and hence potentially increase the barrier to the ligand shift. We are fully aware of the ambiguity of making arguments about electron donation or acceptance, when ligands may carry both features. Thus, a chlorine substituent is a σ acceptor but a π donor. Notice the large barriers calculated for the migration of CN and F substituents (Table 1).

The large barriers calculated for F and CN migration do not imply that the corresponding zwitterionic structures are stable—if there are H atoms on B (see case 2, Table 1) there may be a low-barrier H migration available. The zwitterionic structure **15** would be kinetically stable only if all the substituents on B are "bad" migrating groups. Summarizing the barrier exploration, BF_3 and $B(CN)_3$ groups are best in stabilizing

Table 1. Energetics of the Isomerization of 15 As Shown in Scheme 3[a]

Case 1: L_m = H				
L_a	H	CH$_3$	CN	F	Cl
$\Delta G^{\#}$	3	0	12	4	7
ΔG	−8	−22	−1	−33	−19
Case 2: L_a = H				
L_m	H	CH$_3$	CN	F	Cl
$\Delta G^{\#}$	3	10	31	33	19
ΔG	−8	−6	10	24	16
Case 3: L_m = L_a				
L_m, L_a	H	CH$_3$	CN	F	Cl
$\Delta G^{\#}$	3	6	31	29	13
ΔG	−8	−18	9	16	9

[a]$\Delta G^{\#}$ and ΔG are the Gibbs energy of activation (G_{TS}–G_{15}) and Gibbs energy of the reaction (G_{16}–G_{15}), respectively, in kcal/mol. L_m and L_a denote migrating and ancillary ligands on B.

structure **15** (see case 3, Table 1). Hence, in subsequent calculations we will be using only these two groups as Lewis acids.

The mechanism shown in Scheme 3 is analogous to a cationic [1,2]-sigmatropic shift, which is symmetry-allowed; such rearrangements (and indeed, bridging hydrogens) are common in borane chemistry.[10,38] We have also looked at other possible reactions, such as a 1,3-shift to a more remote carbon. However, this process was always a higher activation energy path than the 1,2-shift (Table 2). Here and elsewhere in

Table 2. Barriers (kcal/mol) for the B(CN)$_3$- and BF$_3$-Substituted Aromatic Systems for the 1,2-Shift, 1,3-Shift, and C−B Cleavage Reactions

	B(CN)$_3$			BF$_3$		
no. of C atoms in the ring	1,2-shift	1,3-shift	C−B cleavage	1,2-shift	1,3-shift	C−B cleavage
3	31	68	−	29	50	−
3 (NH$_2$-substituted)	56	83	−	50	63	−
7	31	52	−	30	37	16
7 (NH$_2$-substituted at 3 and 5 positions)	45	63	−	42	47	−
8	3	−	1	−	−	−

the paper we report reaction barriers for 1,2- and 1,3-shifts. There are several factors affecting the relative barrier heights of these, which include the stability of the reactant, product, and transition state (TS), the charge distribution, and the structural distortion required to reach the TS. These deserve detailed consideration in future work; in the SI to this paper, we give a preliminary discussion.

The calculated structure of **15** with $L_m = L_a$ = CN is shown in **17**. One can provide further stability to these structures by substituting donors such as amino groups on the 3-membered ring, as in **18**.[41,42] The stabilization afforded in this way is so great that even a diamino-substituted cyclopropenium−triphenylphosphonium <u>dication</u> exists.[43]

The barrier for a 1,2-shift for **18** is 56 kcal/mol. We are now definitely in the range of easily isolable compounds—unless we have missed another reaction channel. Along with the 1,2- and 1,3-shifts, we also considered the possibility for dissociation of the borane moiety from the carbon ring. Table 2 lists the calculated barriers for all of these escape routes for the B(CN)$_3$- and

17

18
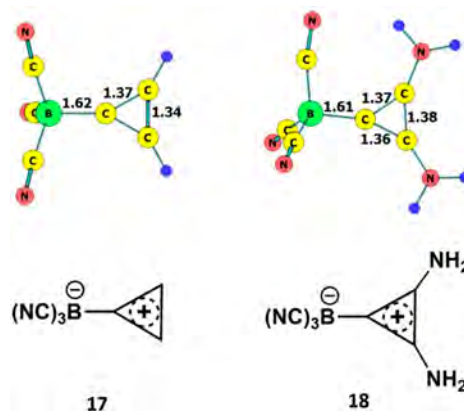
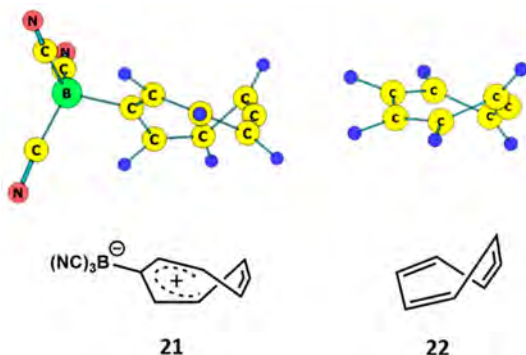BF$_3$-substituted cyclopropenium systems, with and without amino substitution on the carbon ring. We could not find the TS for the dissociation of the borane moiety from the 3-membered carbon ring; the scan of the potential energy surface along the dissociation coordinate showed no minimum, implying that the combination of the Lewis acid and base under discussion is a barrierless reaction.

2.2.2. Borate Derivatives of Larger Aromatic Systems. The calculated structures of B(CN)$_3$-substituted 7- and 8-membered aromatic systems are shown in **19** and **20**. For the 8-membered ring system, two borane substituents are required to achieve the Hückel count. There are other isomers for **20** which are higher in energy. Notice the bond length equalization in **19** and **20**.
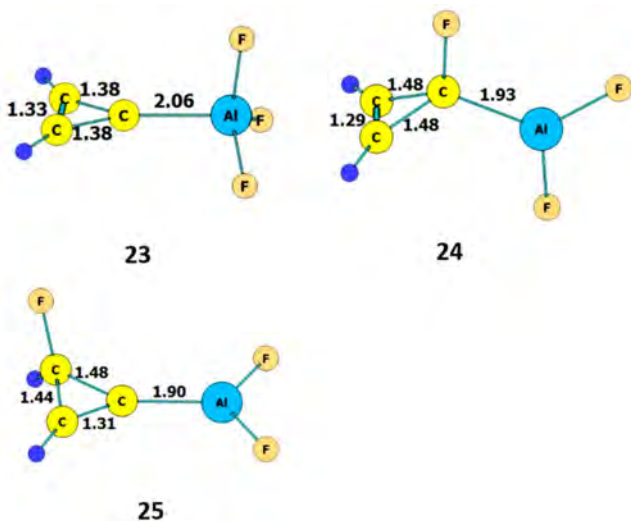

19

20
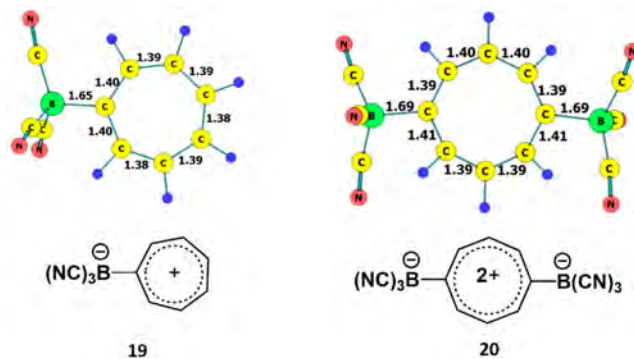
20 is nonplanar, similar to the structure of cyclooctatetraene dication ($C_8H_8^{2+}$) calculated at the same level of theory. The barriers for 1,2-shift, 1,3-shift, and C−B cleavage for **19** and **20** are listed in Table 2. The values for the corresponding BF$_3$-substituted systems are also indicated. Amino substitution enhances the stability of all the systems except the 8-membered ring system (Table 2). Throughout this paper, if substitution is explored on the carbon ring, we consider only those positions where the substituent on C and the substituent on B/Al/N/P do not interfere sterically/electronically with each other. Thus, for the 7-membered system, a 3,5-diamino-substituted system is discussed (the 3,6-isomer is slightly higher in energy), for the 8-membered ring substitution at the 3,7 positions, for the 5-membered ring substitution at the 3,4 positions, and for the 3-membered ring substitution at the 2,3 positions. The amino-substituted derivative of **20** converged to a bicyclic structure on optimization. A BF$_3$-substituted analogue of **20** was not a minimum. As evident from Table 2, we could find a TS corresponding to the dissociation of BF$_3$ or B(CN)$_3$ moiety (C−B cleavage) only for the B(CN)$_3$-substituted 8-membered ring and the BF$_3$-substituted 7-membered ring. The dissociation

products are shown in **21** and **22**. They could be viewed as an allene connected to a pentadienyl cation moiety and a butadiene, respectively—the Lewis structures drawn are just schematic. The geometrical and electronic structures of allenes in medium-sized rings have been studied in some detail.[44]

Table 3. Energetics of the Isomerization (1,2-Shift) of AlL$_3$-Substituted Cyclopropenium Analogue (C$_3$H$_2$-AlL$_3$)^a

	L				
	H	CH$_3$	F	Cl	NC
$\Delta G^{\#}$	6 (23)	13 (28)	49 (47)	38 (35)	26 (28)
ΔG	−14 (−26)	−9 (−20)	47 (38)	37 (29)	23 (12)

$^a\Delta G^{\#}$ and ΔG are the calculated Gibbs energy of activation and Gibbs energy of reaction, respectively, in kcal/mol. Numbers in parentheses correspond to 1,3-shifts.
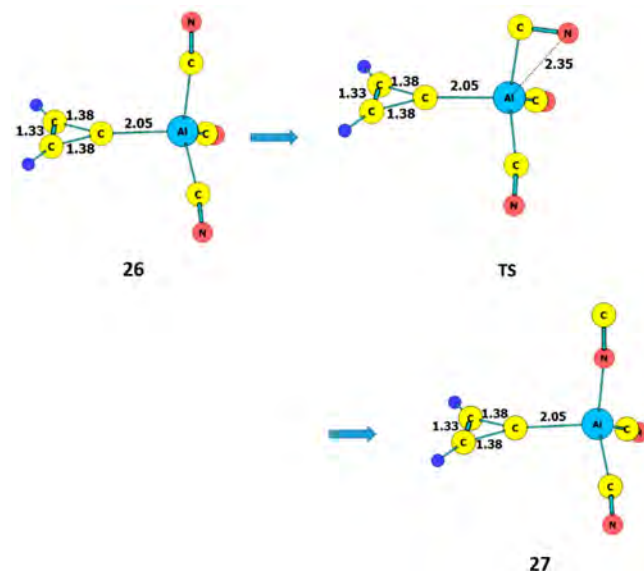
The strategy we employed is not the only way to get neutral analogues of charged aromatic systems. For example, to get a neutral analogue of cyclopropenium ion, one can replace a C atom in C$_3$H$_3$ by a B atom. Derivatives of such B-substituted aromatic systems are known experimentally.[45−52]

2.3. Aluminates: Diversity Rampant. We also tried the Al (aluminate) analogues of the borate aromatic systems discussed above. Table 3 shows the energetics for 1,2-shift of the substituent L for AlL$_3$ substituted in the 3-membered ring (C$_3$H$_2$-AlL$_3$). The values in parentheses correspond to 1,3-shifts. Computationally, C—Al cleavage is unlikely. Notice the significant kinetic stability of the F- and Cl-substituted aluminates. For these, the 1,3-shift has a lower barrier than the 1,2-shift. The 1,2-shift product is quite unstable in F and Cl cases and lies close to the TS. The AlF$_3$-substituted cyclopropenyl system and its 1,2- and 1,3-shift products are shown in **23**, **24**, and **25**, respectively.

Figure 1. Cyanide-to-isocyanide isomerization of Al(CN)$_3$-substituted 3-membered ring.

Figure 2. 1,2-Shift of Al(NC)$_3$-substituted 3-membered ring.

With CN substitution, we saw something unexpected—a cyanide-to-isocyanide isomerization (as shown in Figure 1) is calculated to occur with a very low barrier of only 12 kcal/mol. The Al(NC)$_3$-substituted structure was found to be more stable than the Al(CN)$_3$-substituted one by 10 kcal/mol. For Al(CN)$_3$, the isocyanide structure has already been shown to be more stable than the cyanide structure by calculations.[53] The barrier for 1,2-shift for the Al(NC)$_3$-substituted structure
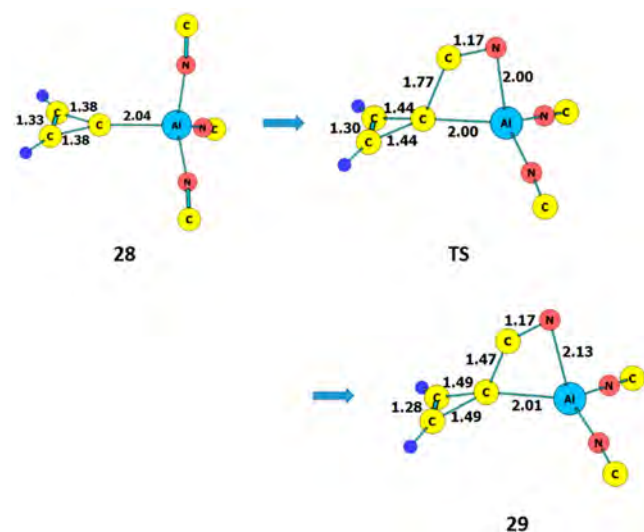
(**28**, Figure 2) is 26 kcal/mol; the TS in this case has a 4-membered ring, and the product is cyclic (**29**). For the unusual structure **29**, the one showing a 4-membered ring, computations at MP2 and PBE0 levels gave similar results (see SI for details). We will explore conditions for stabilizing these unusual four-membered rings separately.

One might wonder whether the cyanide-to-isocyanide isomerization as shown in Figure 1 can happen for the borate systems as well. The calculated barrier for this isomerization for

the boron analogue of **26**, i.e., structure **17**, is 35 kcal/mol—very high compared to that of **26** (12 kcal/mol).

From Table 3, it is evident that AlF_3 and $AlCl_3$ are best in stabilizing a zwitterionic aromatic structure. So, in further calculations we use only AlF_3 and $AlCl_3$. The barriers for 1,2-shift, 1,3-shift, and C−Al cleavage for the AlF_3- and $AlCl_3$-substituted 3- and 7-membered rings are listed in Table 4. The

Table 4. Barriers (kcal/mol) for the AlF_3- and $AlCl_3$-Substituted Aromatic Systems for the 1,2-Shift, 1,3-Shift, and C−Al Cleavage Reactions

no. of C atoms in the ring	AlF_3			$AlCl_3$		
	1,2-shift	1,3-shift	C−Al cleavage	1,2-shift	1,3-shift	C−Al cleavage
3	49	47	−	38	35	−
7	−	35	−	34	32	−

AlF_3- and $AlCl_3$-substituted 8-membered rings were not minima. One can increase the stability further by amino substitution on the carbon ring.

2.4. Shifts from Borate and Ammonium Substituents Are Fundamentally Different. We already saw that the shift of a hydrogen from the ammonium derivative of a cyclopentadienide anion is calculated to encounter a barrier of 30 kcal/mol, while the corresponding shifts from borate derivatives of cyclopropenium and tropylium ions have barriers of only 1 and 3 kcal/mol, respectively. This is a consequence of the fundamentally different electronic situation involved—the borate hydrogen shift is a two-electron 1,2-shift in a cation; the corresponding ammonium hydrogen shift is a four-electron 1,2-shift in an anion.

The left side of Scheme 4 shows the orbitals in the TS for a cationic 1,2-shift, illustrated for a methyl group, migrating in a suprafacial way. The orbitals for hydrogen migrating are qualitatively no different. The orbital symmetry conservation criterion is most generally fulfilled if the electrons in a TS occupy only bonding orbitals, whether simplifying symmetry is there or not.[54] This is certainly true for two electrons (Scheme 4, left). However, with four electrons (as in anionic 1,2-shift), one electron pair must enter an antibonding orbital. So the 1,2-shift of hydrogen in an anion is a forbidden reaction. A migrating methyl group (but not a hydrogen) in principle has another reaction path available to it, a 1,2-shift with inversion at the methyl. This is allowed, as the right-hand side of Scheme 4 shows (all four electrons in the TS are accommodated in bonding orbitals). However, the reaction is likely to have a large barrier, due to the poor overlap of critical orbitals in the TS.

The ammonium and phosphonium cases we will next examine provide consistent examples of large barriers to 1,2-shifts. From the perspective of stabilizing ionic isosteres, that seems like a welcome possibility. At the same time, as we will see, new reaction channels become available.

2.5. Ammonium-Substituted Aromatic Rings.
2.5.1. Radical Cleavage: A New Exit Channel Opens. With an ammonium ion coordinated to an aromatic anion, we come close to the well-known ammonium ylides (**30**), which are the intermediates in the base-catalyzed Stevens rearrangement of quaternary ammonium salts.[22,23] The zwitterionic formulation of **30** indicates that electron-donating substituents on N and electron-withdrawing substituents on the carbanion will stabilize the system.

As we described in a previous section, the isomerization of the ylide via a concerted pathway with retention of configuration at

Scheme 4. Schematic Reaction Paths for the Migration of a Methyl Group with Retention (Suprafacial, Left) and Inversion (Antarafacial, Right)[a]
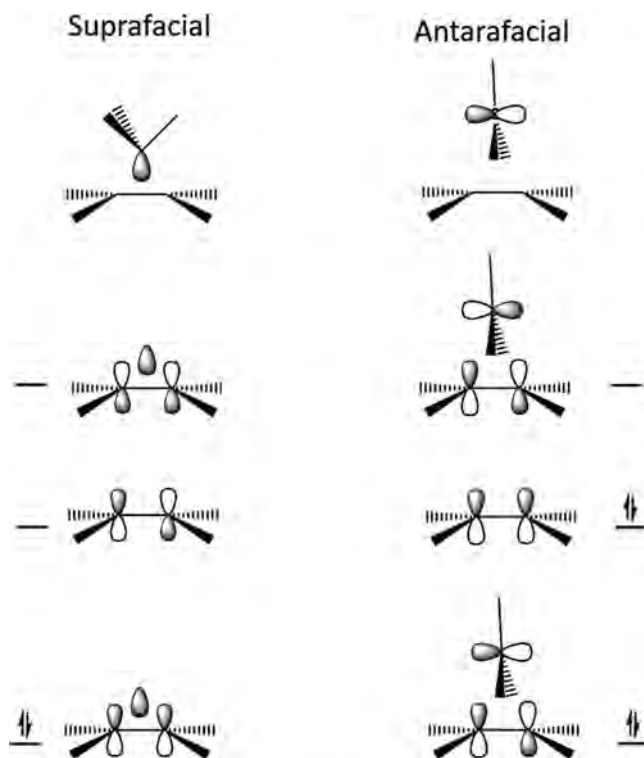
[a]The geometry of the transition state for each case is shown at the top. Below each TS are the three molecular orbitals primarily involved in the TS geometry, occupied by two electrons (at left, cationic shift) and four electrons (at right, anionic shift). Note that only bonding MOs are occupied for the two-electron case with retention and for the four-electron case with inversion.

the migrating group (as shown in Scheme 5 for **30** to **31**) is a symmetry-forbidden reaction, similar to an anionic 1,2-shift, and hence expected to have a large barrier.[55] A shift with inversion is difficult. Previous studies have shown that the Stevens rearrangement in fact proceeds via a radical mechanism.[56−61]

2.5.2. Analogues of Cyclopentadienyl Anion and Cyclooctatetraene Dianion. The radical fragmentation of ammonium ylides is a real escape channel, but no reason to give up the search for stable ammonium isosteres. The calculated structure of an NH_3-substituted 5-membered ring is shown in **32**. Notice the bond equalization, similar to that in a cyclopentadienyl anion. NMe_3 substitution also gives the same bond equalization. Calculations on NCl_3- and $N(CN)_3$-substituted systems did not give minima for similar structures. An NF_3 substituent gave a minimum with significant bond alternation, which can be better described as a $C_5H_4NF_2^+$ interacting with F^- (structure **33**). This is consistent with the significant elongation of one of the N−F bonds (1.68 Å) compared to the other two (1.33 Å). In agreement with these findings, the natural charge on the F atom of the elongated N−F bond is −0.48, whereas the other two F atoms have a charge of −0.13. Computations at the MP2 and PBE0 levels also gave similar results (see SI for details). In short, among the structures calculated, only NH_3 and NMe_3 substitutions gave structures analogous to the cyclopentadienyl anion. In the subsequent calculations on ammonium derivatives of aromatic systems, we will be using only NH_3 and NMe_3 groups.
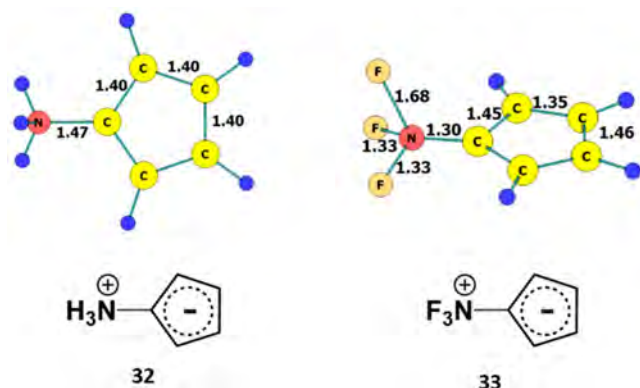
The barriers facing the various escape channels of ammonium-substituted aromatic systems are listed in Table 5. The radical dissociation refers to the reaction shown in Scheme 5

Scheme 5. Concerted and Radical Mechanisms of the Stevens Rearrangement of a Nitrogen Ylide
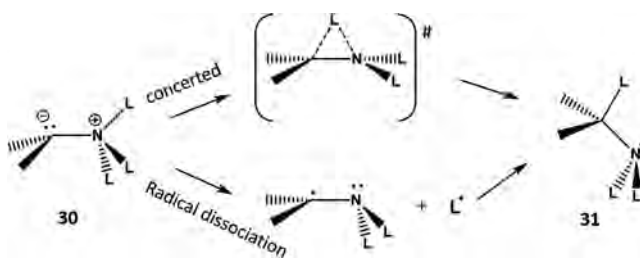
above. While the NH$_3$-substituted systems are reasonably stable, the NMe$_3$-substituted ones are prone to radical dissociation. Antarafacial TSs for methyl migration were unstable with respect to radical dissociation. We also calculated structures with CN substituents on the ring C atoms, in order to enhance their kinetic stability (see Table 5). For the 5-membered ring

Table 5. Barriers (kcal/mol) for the NH$_3$- and NMe$_3$-Substituted Aromatic Systems for the 1,2-Shift, 1,3-Shift, Radical Dissociation, and C−N Cleavage Reactions

	ring size			
reaction	5	5 (dicyano--substituted)	8	8 (dicyano--substituted)
	NH$_3$			
1,2-shift	30	37	28	36
1,3-shift	29	37	22	27
radical dissociation	27	39	23	34
C−N cleavage	−	−	15	16
	NMe$_3$			
1,2-shift	52	57	−	−
1,3-shift	−	−	−	51
radical dissociation	15	25	3	15
C−N cleavage	−	−	11	12

systems, we could not locate TSs corresponding to the dissociation of NH$_3$ or NMe$_3$ groups (C−N cleavage) from the ring. Additionally, we examined a variety of diammonium-substituted

four-membered rings (analogues of cyclobutadiene dianion); these are discussed in the SI.

Substitution of two H atoms in cyclooctatetraene (COT) by NL$_3$ groups results in a 10π-aromatic system. Several isomers are possible, and the most stable isomer is the 1,5-substituted one (others are closer in energy). The calculated structure of NH$_3$-substituted COT is shown in **34**; it is planar, similar to the calculated structure of the dianion of COT. This molecule was calculated previously by Wannere, Schleyer, and Schaefer.[13] The barriers for various reaction pathways for NL$_3$-substituted (L = H, Me) COT, with and without CN-substitution, are listed in Table 5 (CN substituents are introduced at the 3 and 7 positions of the ring, to avoid H transfer from NH$_3$ substituent to CN). Unfortunately for potential stability, radical dissociation can take place easily for the NMe$_3$-substituted systems. C−N cleavage is another low-barrier process, as can be seen from Table 5. The dissociation product, shown in **35**, can be viewed as an allene fragment connected to a pentadienyl anion moiety. Here again, the Lewis structure drawn is just schematic.
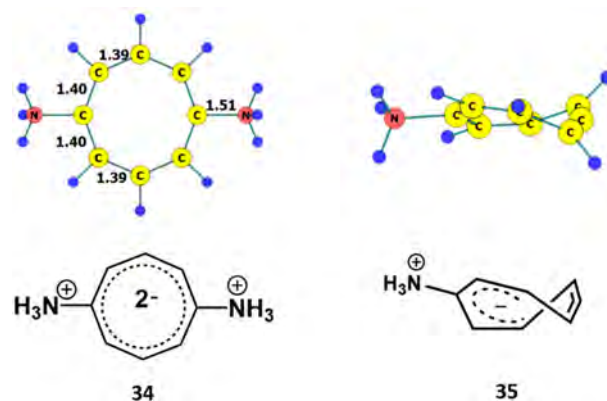
We had mentioned earlier the work of Wannere, Schleyer, and Schaefer on ammonium-substituted anions.[13] Among the ones they examined were acetylides, cyclopentadienides, pentalene, and COT derivatives. In general they did not examine escape channels except for a methyl 1,2-shift.

2.6. Phosphonium Isosteres. 2.6.1. Phosphonium-Substituted Aromatic Rings. The calculated structure of the PH$_3$-substituted 5-membered ring is shown in **36**. Unlike the case of the corresponding N analogue, bond length equalization is not pronounced in **36**. This could be due to contributions from resonance structures of type **38**, because of "negative hyperconjugation".[62] In molecular orbital (MO) language, the relevant interaction is between an occupied π orbital of the C-ring and the pseudo-π* orbital of the PL$_3$ fragment, as shown schematically in Figure 3A.[63] The actual MO calculated for **36** is shown in Figure 3B.

A natural resonance theory analysis is consistent with this way of thinking.[64−66] The summed contributions of the three
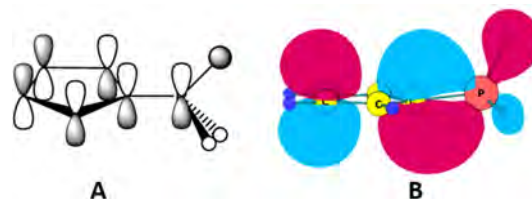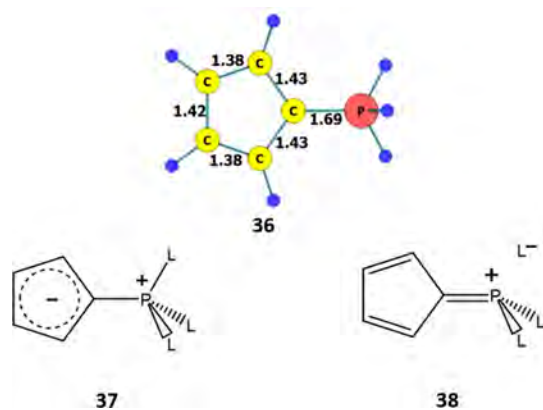

Figure 3. (A) Schematic representation of the negative hyperconjugation in phosphonium cyclopentadienide. (B) The corresponding MO calculated for **36**.

resonance structures of type **38** to the PH_3-, $P(CH_3)_3$-, PCl_3-, PF_3-, and $P(CN)_3$-substituted systems are 4, 3, 22, 31, and 24%, respectively. This indicates large C=P character for the PCl_3, PF_3, and $P(CN)_3$-substituted cases. The natural bond order values of C−P bonds in the PH_3-, $P(CH_3)_3$-, PCl_3-, PF_3-, and $P(CN)_3$-substituted systems are 1.09, 1.06, 1.34, 1.44, and 1.28, respectively. Resonance structure **38** will contribute more when L is an electronegative atom, as they can stabilize the negative charge better, to use valence bond language. Looking for better analogues of bond-equalized aromatic systems, we discuss here only the PH_3- and PMe_3-substituted ones. The calculated barriers for the various escape routes for the PH_3- and PMe_3-substituted 5-membered rings (phosphonium cyclopentadienides) are tabulated in Table 6. It is evident that these systems should have reasonably good kinetic stability.

Table 6. Barriers (kcal/mol) for the PH_3- and PMe_3-Substituted Aromatic Systems for the 1,2-Shift, 1,3-Shift, Radical Dissociation, and C−P Cleavage Reactions

		ring size	
		8	
reaction	5	1,5-isomer	1,4-isomer
PH_3			
1,2-shift	39	–	38
1,3-shift	38	28	34
radical dissociation	46	45	34
C−P cleavage	–	20	33
PMe_3			
1,2-shift	73	–	–
1,3-shift	–	–	–
radical dissociation	54	35	38
C−P cleavage	–	31	42

2.6.2. Phosphonium-Substituted Derivatives of Cyclo-octatetraene Dianion. The calculated structures of the 1,5- and 1,4-isomers of PL_3-substituted COT with L = H are shown in **39** and **40**. The PH_3 fragments are slightly out-of-plane; the structures calculated with PMe_3 groups have the P atoms in the plane of the carbon ring. The 1,4-isomer, **40**, is more stable than the 1,5-isomer, **39**, by 4 kcal/mol. However, the bond length equalization is better in **39**. The barriers for escape for both isomers are listed in Table 6. We can see that both the PH_3- and PMe_3-substituted systems have reasonable kinetic stability. The TS corresponding to the C−P cleavage could be found only for the 8-membered ring, as can be seen from Table 6. The disso-ciation product is similar to the corresponding N analogue (**35**).
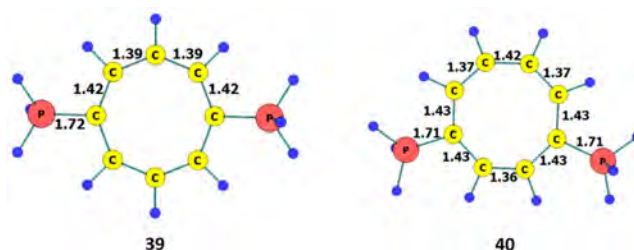

One could also construct diphosphonium-substituted cyclo-butadienes; these are discussed in the SI.

2.7. Escape Routes: Take 2. Throughout this paper, we have been careful to examine alternative pathways of reactions available to the methyl isosteres. In part, this is simply due diligence if one wishes to make realistic predictions of kinetic persistence. In part, it is just interesting to see the variety of ways in which a molecule can rearrange.

Scheme 6 collects most of the easy transformations we have seen.

Scheme 6. Escape Routes Explored for Lewis Acid/Lewis Base Substituted Aromatic Systems, Excluding Valence Isomerizations and Dimerizations
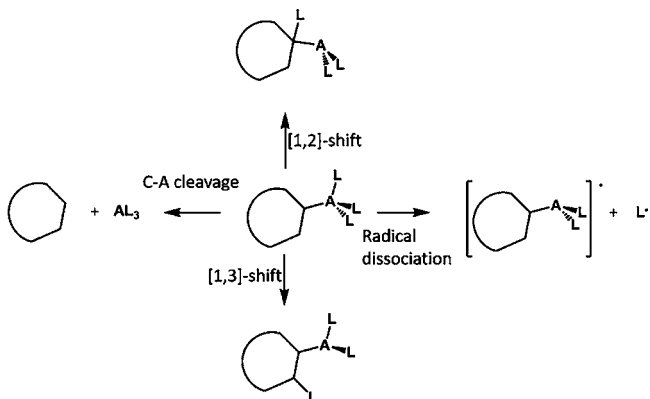
In addition to these reactions, we have also encountered (and do not show in Scheme 6) ligand isomerizations (for CN) and valence tautomerizations of an underlying cyclic skeleton.

The multitude of reaction paths is impressive. Note that we have not even broached bimolecular reactions, acid or base catalyzed, nor di- and oligomerizations. And we are well aware of the limits of our imagination—there might be other escape channels that we have simply not thought of.

2.8. A Sampler of Potentially Stable Molecules. With careful attention to potential reaction channels, and focusing on substituent patterns most likely to lead to stable molecules, we collect here (Figure 4) some of the molecules which emerge from the alkyl isosteres idea. These molecules are
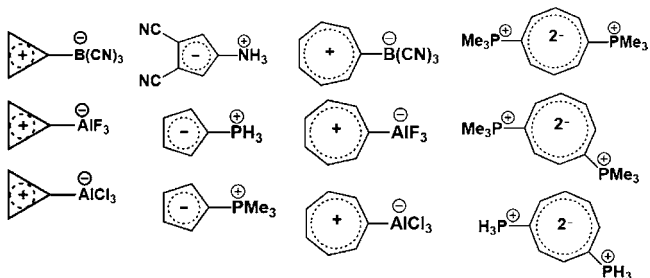

Figure 4. Candidates for synthesis.

calculated to be kinetically persistent, with computed barriers for the reactions considered >30 kcal/mol.

Still other viable structures may be obtained via amino substitution on the carbon ring for the borate and aluminate derivatives, and analogous acceptor substitution on the ring for ammonium and phosphonium aromatics. Also, though the aluminate derivatives seems to be very kinetically persistent in our study, the highly polar nature of the Al−Cl or Al−F bonds and the tendency of Al to hypercoordinate might result in acid−base reactivities we have not yet considered.

One final point needs to be made. The calculations reported here are without implicit or explicit consideration of solvent. One would naturally expect solvation to stabilize the zwitterionic side of any reaction. Exploratory calculations on the reactions of $BH_3/AlH_3/NH_3/PH_3$-substituted zwitterionic systems using the SMD solvation model confirmed this;[67] details are given in the SI.

2.9. Diammonium and Diborate Benzenes. Finally, we have not forgotten the pedagogically informed examples that began our investigation of methyl isosteres—the diborate and diammonium ions of benzene (**3**, **4**). In these, the hypothetical zwitterionic stabilization and the overall neutrality of the other ions we looked at earlier in this work are absent. In any escape channel for the benzene cases, one is going from a dication to another dication, etc., and any initial reaction away from the benzene faces a severe impediment—loss of aromaticity. Detailed discussion of these isosteres is relegated to the SI. In summary, we find that all the rearrangements from these xylene isosteres are energetically uphill. If one could find a route to these ions with suitable non-coordinating counterions, they should persist. Among the remarkable metastable products predicted to arise out of these doubly charged ions are diboracyclopropyl dianions and diiminium dications, some of them opening up the six-membered ring.

3. CONCLUSION

Computations indicate that neutral analogues of cationic aromatic systems can be formed by Lewis acid substituents, generating an exocyclic anion. Similarly, Lewis base ligands can provide neutral analogues of anionic aromatic systems. The zwitterions so constructed are formal methyl group isosteres. Isolated examples exist. We set out to design a general class of methyl isosteres, neutral zwitterionic aromatic systems, and of dicationic and dianionic substituted xylene isosteres.

A remarkable variety of escape channels (low activation energy processes) "resists" realization of the basic design of zwitterionic isosteres—a partial list includes 1,2-ligand shifts, 1,3-shifts, radical dissociation, and simple dissociation of the Lewis acid/base from the carbon ring. For the Group 15 isosteres, there is an orbital-symmetry-based greater barrier to the expected most common rearrangement mode, 1,2-shifts.

We persevere in the design of kinetic persistence, finding substituent sets that block the escape routes (E_a > 30 kcal/mol), for instance $(CN)_3$ or $(F)_3$ on B and Al and $(R)_3$ on P. At the end we have specific suggestions for synthesis involving 3-, 5-, 6-, 7-, and 8-membered carbon rings—and a design principle.

ASSOCIATED CONTENT

ⓈSupporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06141.

Coordinates and energies of the computed structures, discussion on the Lewis acid/Lewis base-substituted cyclobutadiene derivatives, diammonium- and diborate-substituted benzenes, relative preferences for 1,2- and 1,3-shifts, solvation effects on the zwitterionic structures, and additional figures and tables corresponding to calculations at different levels of theory (PDF)

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Notes

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